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Osteoporosis therapy initiation post-minimal trauma fracture

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ABSTRACT

Aim: To determine the proportion of patients admitted to a major tertiary teaching hospital in Australia aged 50 years and older with a confirmed neck of femur or vertebral minimal trauma fracture, who are commenced on specific anti-osteoporosis therapy by discharge, and to describe the agents prescribed. **Methods:** A retrospective analysis was conducted using patients' electronic medical files of patients admitted with a minimal trauma fracture of the hip or vertebra during a 6 month period. **Results:** A total of 407 patients were audited and 64 patients were included in the study; 37 were admitted for a fractured hip and 27 were admitted for a vertebral fracture. Of these 64 patients, a total of 14 (21.9%) patients were commenced on specific anti-osteoporosis therapy. Denosumab (71%) was the most commonly initiated treatment, followed by risedronate (21%) then alendronate (7%). **Conclusion:** Majority of patients presenting to hospital with a minimal trauma fracture were not commenced on anti-osteoporosis therapy in hospital. This is a missed opportunity for intervention that may place patients at a higher risk of subsequent fracture; therefore effective strategies should be implemented to address this treatment gap in the future.

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INTRODUCTION

Osteoporosis is a public health concern, both globally and in Australia (AIHW, 2014; Ebeling et al., 2007) with a total of 66% of Australians aged over 50 affected by osteoporosis or osteopenia in 2012 and a cost to Australia of over \$2.75 billion per annum (Watts et al., 2013). With the average life-expectancy of the Australian population increasing, the prevalence of osteoporosis and osteopenia is expected to rise and affect approximately 6.2 million people by 2022 (Watts et al., 2013).

Osteoporosis is a silent disease characterised by low bone mass and microarchitectural deterioration of bone tissue. As there are no noticeable symptoms, osteoporosis is often diagnosed after the first minimal trauma fracture (Panneman et al., 2004). A single minimal trauma fracture, which is defined as a

fracture occurring from low energy trauma such as falling from standing height or less (Gunathilake et al., 2016) can double the risk of a subsequent fracture, and that risk increases exponentially with future fractures (Barrack et al., 2009). Fractures carry a significant health burden due to the associated loss of independence, increased disability and mortality (Bliuc et al., 2009). Studies have shown that 40-60% of men and women will experience a subsequent minimal trauma fracture within 10 years of an initial fracture (Center et al., 2007).

Appropriate management of osteoporosis with drug treatments such as antiresorptive medications and supplements are shown to significantly reduce subsequent fracture risk (Therapeutic Guidelines, 2014).

Despite the availability of these evidence-based treatments, and the optimal position in the hospital setting to initiate secondary fracture prevention, the majority of patients presenting to Australian hospitals with a minimal trauma fracture are neither treated nor investigated for osteoporosis (Kimber and Grimmer-Somers 2008). Treatment rates of patients presenting with an osteoporotic fracture continue to remain as low as 20% and only 10% of patients have their fracture adequately investigated for the underlying cause (Teede et al., 2007).

This tertiary teaching hospital does not currently have a formal process for the initiation of anti-osteoporosis therapy, and anecdotal reports from clinical pharmacists suggest inconsistent practices for initiation between departments. Many patients are referred to their general practitioner for follow up, and some patients receive no instructions. Therefore, the main purpose of this study was to establish the proportion of patients discharged from the hospital with a minimal trauma fracture, who are commenced on, or have a plan to be commenced on specific anti-osteoporosis therapy and/or calcium or colecalciferol supplementation.

MATERIALS AND METHODS

Study design

This study was a retrospective inpatient file audit performed at a tertiary teaching hospital in Victoria, Australia. Data was collected by examining patients' electronic records. This study was designed to include patients who were admitted for a vertebral or hip fracture with a discharge date during the specified 6-month period.

Inclusion criteria

Patients who were discharged between 1st January 2016 and 30th June 2016 and diagnosed with a vertebral or hip fracture were retrieved from a central database and considered for inclusion in the study.

Exclusion criteria

The patients were screened and excluded if one or more of the following criteria applied: Non-minimal trauma fracture; Less than 50 years of age during admission; Pre-admission specific anti-osteoporosis therapy; Palliative or for non-burdensome treatment

(defined as Goals of Care category C or D); Deceased during admission.

Outcome measures

The primary outcome was to determine the proportion of patients commenced on specific anti-osteoporosis therapy on or before discharge; and to describe the specific agents selected for those starting on specific anti-osteoporosis therapy on or before discharge.

Secondary outcomes were to determine the proportion of patients commenced on colecalciferol and/or calcium supplementation on or before discharge; proportion of patients not commenced on colecalciferol and/or calcium supplementation on or before discharge but had a documented plan to start therapy in the discharge summary; the proportion of patients not commenced on specific anti-osteoporosis therapy by discharge but had a documented plan to start therapy in the discharge summary; and the proportion of patients with "osteoporosis" mentioned in their final discharge summary.

Data collection

Data was obtained through the use of electronic systems, including electronic medical records, pathology system and dispensing software. A list of all patients admitted to the hospital with a fracture of the hip or spine during the period of 1st January 2016 to 30th June 2016 was compiled from hospital medical records. Each admission was examined by two auditors, and the data collection tool was completed accordingly. A third auditor then verified the data.

Data analysis

Results from the data collection tool were analysed manually and using pivot tables in Microsoft Excel. The data was analysed to obtain the number of patients commenced on specific anti-osteoporosis therapy (bisphosphonates, denosumab, raloxifene, strontium or teriparatide), the number of patients commenced on non-specific anti-osteoporosis therapy (colecalciferol and/or calcium), and the number of patients commenced on nil therapy. Of the patients not commenced on therapy, the data was analysed to determine how many patients received a referral to their general practitioner, received other instructions, or received no instruction at all. A three-tiered hierarchy structure of possible outcomes

enabled the allocation of patients to one outcome only: a patient being started on specific therapy took preference over being referred to a general practitioner for further investigations or follow up, and receiving nil instructions was at the bottom of the hierarchy. Secondary parameters analysed included the fracture type, age and gender of the patients. All parameter analysis was expressed as percentages.

RESULTS

Patient characteristics

There were 407 discharges for a fracture of the hip or vertebrae during the study period. Of those patients, 88 patients were admitted for a fractured hip and 319 for a vertebral fracture. Based on exclusion criteria, 67 patients were eligible for inclusion in the study. Three of these patients had insufficient information documented on their medical history, and were excluded from the study. This left a total of 64 patients to be included in the study. The main reason for exclusion was that the fracture was not due to minimal trauma, which accounted for 20 (22.7%) hip fracture patients, and 263 (82.4%) vertebral fracture patients. Basic characteristics were collected for each patient (Table 1).

Table 1. Patient characteristics (n=64)

Age	Median	IQR: 86-72 = 14
Sex	Male	21 (33%) *
	Female	43 (67%)
Fracture Type	Hip	37 (58%)
	Vertebral	27 (42%)
Osteoporosis related therapy before admission	Calcium	0 (0%)
	Cholecalciferol	18 (28%)
	Both	6 (9%)

* Percentages rounded up to the nearest percentage values

Treatment initiation

A total of 14 of 64 (21.9%) patients were commenced on specific anti-osteoporosis therapy during their stay at the hospital (10 hip fracture patients and four vertebral fracture patients) (Figure 1). This equates to 27% of hip fracture patients and 14.8% of vertebral fracture patients having received specific anti-osteoporosis therapy. Denosumab was the most commonly initiated treatment, being commenced in 10 of the 14 patients (71.4%). Risedronate was

commenced in three of the 14 patients (21.4%) and one of the 14 patients (7.1%) was commenced on alendronate. There were no other specific therapies commenced in this group of patients. Of the 50 patients not commenced on specific anti-osteoporosis therapy, 20 (40.0%) had a documented plan on their discharge summary for their general practitioner to commence therapy, 29 (58.0%) received no instructions regarding treatment and one patient did not receive treatment due to declining all treatment other than colecalciferol (Figure 2). Of the 20 patients who were referred to their general practitioner to commence therapy, some summaries had no further detail documented while other summaries had a plan for review before therapy initiation, such as a dental review (Figure 1).

Within the 64 included patients, 40 were on neither calcium nor colecalciferol at admission. Of those 40 patients, colecalciferol was commenced in 20 patients (50%), both calcium and colecalciferol was commenced in 1 patient (2.5%) and 19 patients (47.5%) were not commenced on either supplement. Of the 19 patients not commenced on colecalciferol four patients (21%) had replete Vitamin D levels (Figure 3). Calcium and/or colecalciferol supplementation was sole therapy for 13 patients. It was unable to be determined whether patients who were not commenced on supplemental therapy had a documented plan to start therapy after discharge due to insufficient data.

Other investigations

The term "osteoporosis" was mentioned in the discharge summary as a diagnosis, comorbidity, or future management plan in 26 of the 64 patients (40.6%). The presence of "osteoporosis" in discharge summary was correlated with a higher rate of intervention. Of the 26 patients, 10 (38.5%) received specific anti-osteoporosis therapy, 12 (46.2%) received referral to general practitioner for therapy or investigations, one (3.8%) declined treatment and three (11.6%) had nil instructions.

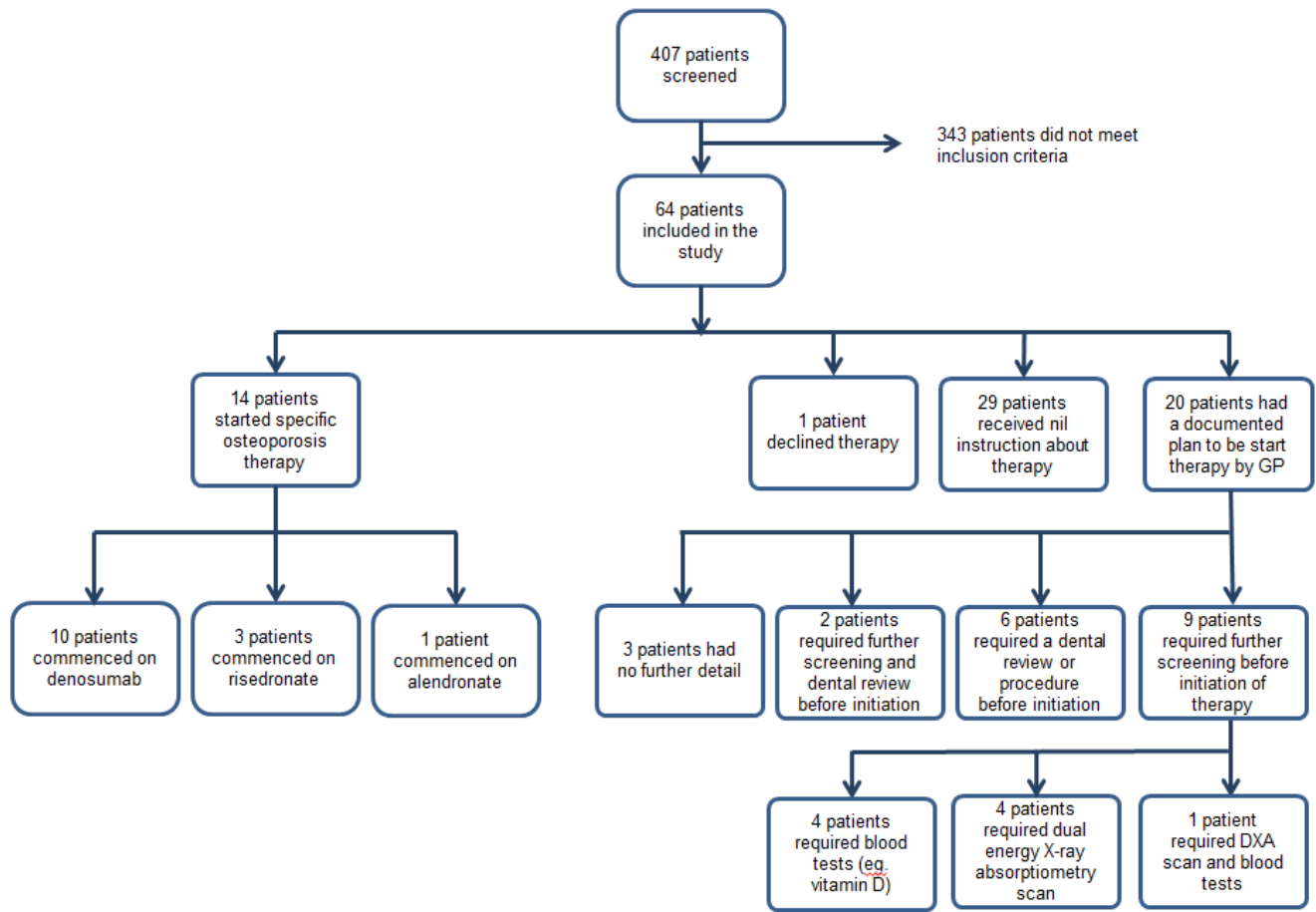


Fig. 1. Treatment Initiation Flowchart

DISCUSSION

The results of this study demonstrate that the treatment rates of osteoporosis post hip or vertebral minimal trauma fracture are low. These results are consistent with other Australian studies, which also reported a major treatment gap for patients with osteoporosis (Port et al, 2003). A study by Teede et al. conducted in 2003-2005 across 16 Australian hospitals found that only 8% of patients admitted with a minimal trauma fracture were commenced on a bisphosphonate (Teede et al, 2007), which compared closely to the 6.3% from this study. However, bisphosphonates were the treatment of focus as denosumab was not on the market at the time of that study.

Given their established efficacy, safety and low cost, bisphosphonates have been used widely for osteoporosis since the release of alendronate in 1995 (Therapeutic Guidelines, 2014). Despite this, results from this study have demonstrated that denosumab

is the most commonly prescribed medication at this hospital for osteoporosis. In Australia, denosumab was first listed on the Pharmaceutical Benefits Scheme (PBS) for secondary fracture prevention in women in December 2010, providing better financial accessibility and encouraging its use.

A potential reason for the shift in prescribing habits may be related an increased risk of atypical fractures with the use of bisphosphonates over 5 or more years, particularly in elderly patients (Abrahamsen et al., 2009). There have only been a few reported cases of atypical femoral fracture with denosumab therefore it is hypothesised that physicians may be more inclined to prescribe this agent. The practicality of denosumab as a subcutaneous 6-monthly injection compared to oral bisphosphonates, which require more frequent administration, may also contribute to its increase in prescribing, as less frequent dosing may increase patient medication adherence. A meta-analysis estimated the 12-month persistence of

denosumab to be 83% at 12 months, compared to 45% for oral bisphosphonates (Karlsson et al., 2015).

Many factors may contribute to the low uptake of osteoporosis treatment in hospital. From a physician perspective, this may include disjointed communication between various healthcare providers involved in the patient's care, and a lack of responsibility for ownership of osteoporosis management and treatment (Kelly et al., 2008). This is demonstrated by the transferring of responsibility of therapy initiation to a general practitioner as per the audit results.

A lack of awareness regarding the importance of initiating treatment in patient groups who are at a high risk of experiencing future fractures may also exist (Kelly et al., 2008). A study by Jachna et al. suggested that only patients who had multiple comorbidities were thoroughly reviewed by hospital consultants, and their other medical demands were seen as more important than the need for osteoporosis screening and therapy initiation (Jachna et al., 2003). Implementation of osteoporosis treatment algorithms alongside educational sessions for medical professionals has been shown to improve awareness of osteoporosis in the hospital setting (Banakh, 2011).

Another possible factor associated with the lack of therapy initiation may be concerns about medication adverse effects and their possible impact on the patient (Fraser, Ioannidis, Adachi, Pickard, Kaiser, Prior, et al., 2011). Furthermore, as denosumab can exacerbate hypocalcaemia, it is important to ensure correction of low vitamin D and calcium plasma concentrations prior to commencement of therapy (Therapeutic Guidelines, 2014). This may contribute to delays in initiating denosumab, as indicated by the proportion of patients referred to their general practitioner for consideration of treatment.

Bisphosphonates are considered to be first-line option (alongside the newer agent, denosumab) in the treatment of osteoporosis due to their good safety profile and efficacy in reducing future fracture risk; however, their use may be contraindicated in certain patient groups (Chen and Sambrook 2012). Due to their potential to cause upper gastrointestinal adverse effects, the use of oral bisphosphonates is not advised in those with dysphagia, other notable

gastro-oesophageal reflux symptoms or those unable to remain upright for 30 minutes after dosing.

Data relating to rates of incidence of adverse effects from osteoporosis therapy noted a common occurrence ($\geq 1\%$) of upper gastrointestinal adverse effects in patients using oral alendronate, risedronate and ibandronate (Rizzoli and Reginster, 2011). Once-weekly oral alendronate in patients with osteoporosis reported a 16% incidence of upper gastrointestinal adverse effects in bisphosphonate-naïve patients (Greenspan et al., 2002).

Conversely, intravenous administration of bisphosphonates should be avoided in those with substantial renal impairment, a condition frequently observed in ageing populations (Chen et al., 2002). These potential adverse effects as a result of the use of specific anti-osteoporosis therapy may be another reason for delaying treatment initiation.

The Australian Therapeutic Guidelines recommends that patients receive dental procedures and reviews before the commencement of anti-osteoporosis therapy, including both denosumab and bisphosphonates, due to the risk of a rare but serious condition osteonecrosis of the jaw (ONJ) (Therapeutic Guidelines, 2014). The prevalence of ONJ reported rates of 0.01-0.05% in oral bisphosphonates and 10-100 times greater in zoledronic acid and denosumab. The studies in that review were consistent in that the majority of the patients with ONJ had a recent dental procedure, thus placing this patient group at the greatest risk (Lazarovici and Yoffe, 2015). Results from this study found that multiple patients were not commenced on therapy due to the requirement of a dental review or procedure from a local health practitioner. However, the appropriateness of this recommendation given the low rates of ONJ cannot be determined from the results of this audit.

Majority of patients who were initiated on specific anti-osteoporosis therapy were commenced at discharge or after rehabilitation, as opposed to during admission. This delay in initiation of therapy could be related to the suggested association between anti-osteoporosis therapy and prolonged fracture healing time. Preliminary studies have

suggested weak to moderate clinical evidence supporting no significant increase in fracture healing time with early commencement of anti-osteoporosis therapy (Hegde et al., 2016).

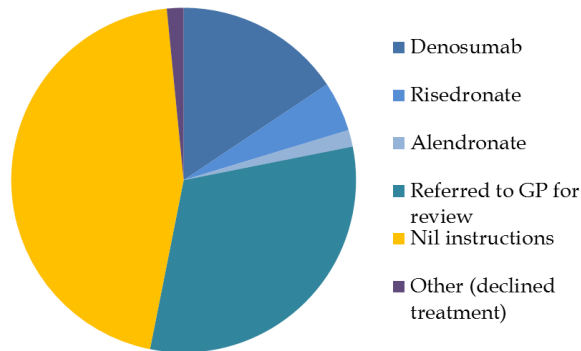


Figure 2. Specific anti-osteoporosis therapy initiation results. Data presented as frequency.

However, based on these limited conclusions, physicians should be aware of the benefits of early initiation of anti-osteoporosis treatment whilst also considering the risk of prolongation of fracture healing time. As no individual therapy is suitable for the entire patient cohort presenting with a minimal trauma fracture, treatment decisions should be individualized (Hegde et al, 2016) and the relative risks and benefits of specific anti-osteoporosis therapy accounted for. Aside from the adverse effects associated with therapy, a potential factor contributing to treatment initiation is the time required for fracture risk reduction to occur.

Bisphosphonates require a minimum duration of six months of treatment before improvements in bone mineral density are noted (Ross et al., 2003). In this study, 51.6% of patients were aged 80 or over, so whether their expected lifespan would be sufficient to gain benefit from therapy would have been determined by the treating team, and could be a possible reason why treatment in some of these patients was not initiated.

Limitations

There were several limitations to the study. Firstly, only a small sample size was eligible for inclusion. The majority of the patients excluded from the study were admitted to this hospital for a high impact vertebral fracture, often as a result of a motor vehicle

accident. Therefore, collecting data retrospectively from patients who were admitted for a hip fracture over a longer period of time would provide a larger sample size and more significant results. With this in mind, the inclusion of vertebral fracture patients has added value to the results. For example, it has been identified that there are lower treatment initiation rates and documentation of osteoporosis risk on vertebral fracture patients' discharge summaries, compared to the patients admitted for hip fractures. If vertebral fracture patients were initially filtered to exclude those admitted for a moderate or high impact trauma fracture, more time would have been available to audit an extended retrospective period. This may have resulted in a greater proportion of fracture patients that were ultimately included in the study.

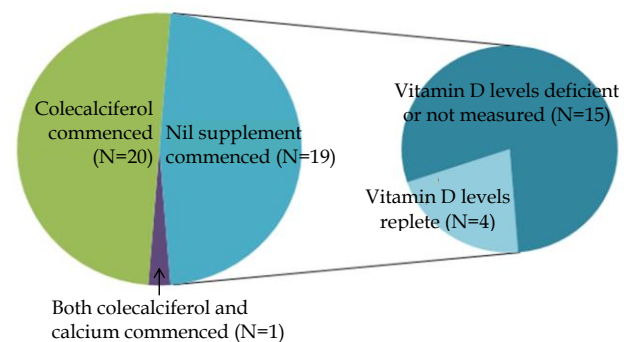


Figure 3. Calcium and colecalciferol supplement therapy initiation results and related vitamin D levels

Fractures of the wrist due to minimal trauma are the most common symptomatic fracture related to osteoporosis (Majumdar, Rowe, Folk, Johnson, Holroyd, Morrish et al., 2004). Patients admitted to this hospital for a wrist fracture were not included due to time limitations available for auditing. In addition, these patients are often assessed by the Emergency Department and not admitted as inpatients. Therefore, the short length of stay for these patients resulted in an inability to capture sufficient data for the purposes of the study.

Secondly, the study design is retrospective and therefore some assumptions were made, particularly regarding the inpatient information available. Scanning of medical records was recently implemented at this hospital, and as a result, there were incomplete patient medical information on the system. Additionally, when a pre-admission

medication history was not uploaded to a patient's file, the medication list and past medical history on the discharge summary was used as an alternative source to obtain information regarding patients' medical history prior to their admission. This resulted in some inconsistencies in the sources used to obtain information between patients. The discharge summary information was assumed to be accurate and provided to the patient's general practitioner for review upon discharge.

Lastly, the interpretation of whether the patient's fracture was due to a minimal trauma was assessed on an individual basis based on the medical admission notes. At times, the extent of the impact of trauma was unclear, and this resulted in difficulties determining whether or not the fracture met the predetermined definition of a minimal trauma fracture. To reduce bias during this process, all data was analysed together by pairs of auditors, and independently validated by a third auditor.

CONCLUSIONS

This audit has identified that treatment initiation rates following an osteoporosis-related minimal trauma fracture were suboptimal at this tertiary teaching hospital, as 29 out of 64 patients received nil instructions regarding treatment initiation and only 14 received specific anti-osteoporosis therapy by discharge.

Further research and effective strategies may be required to address the various factors that are contributing to this treatment gap, to ensure that all patients receive the best quality evidence-based treatment.

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