Retrospective analysis of eligibility for denosumab in patients presenting with osteoporotic fractures and renal impairment treated by orthogeriatric service at Middlemore Hospital

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ABSTRACT

BACKGROUND: Little is known about the prevalence of renal impairment in patients presenting with osteoporotic fractures contraindicating bisphosphonate use in New Zealand, and their eligibility to denosumab.

AIM: To assess the prevalence of renal impairment contraindicating bisphosphonate use in older adults presenting with osteoporotic fractures, differences in demographic variables between those with renal impairment and those who do not, and finally to assess eligibility for denosumab based on the current PHARMAC special authority criteria.

METHOD: All patients 65 years and older with osteoporotic fractures treated by inpatient orthogeriatric service (IOS) and the outpatient fracture liaison service (FLS) at Middlemore Hospital between 1 February to 31 April 2019 were assessed. Following data was retrospectively collected—age, sex, ethnicity, preadmission residential status, type of acute osteoporotic fractures, history of previous osteoporotic fractures, cognitive impairment and its severity, history of falls, previous dual-energy x-ray absorptiometry (DEXA) scan and the worst documented T-scores over total hip, neck of femur or L1-4 spine and previous funded anti-resorptive therapy use. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault formula based on the ideal body weight according to the recorded height and serum creatinine level at the time of patient's presentation. Patients with CrCl below 35ml/min were assigned to the renal group, and those with CrCl above 35ml/min to the non-renal group. Current PHARMAC criteria for denosumab was used to assess the eligibility in the renal group.

RESULTS: Total of 190 patients (102 IOS and 88 FLS) were assessed. Thirty-four patients (17.9%) had renal impairment with CrCl less than 35ml/min and were assigned to the renal group. There were no statistically significant differences in demographic variables between the renal and the non-renal group other than for age, where the renal group was significantly older (85.4 vs 77.5 years, P-value <0.0001). Two out of 34 patients were eligible for denosumab. Reasons for ineligibility to denosumab were as follows; not meeting the definition of severe established osteoporosis due to presenting with their first ever osteoporotic fracture (64.7%), no previous DEXA scans to quantify their bone mineral density (11.8%), measured bone mineral density T-score above -2.5 (5.9%); and no preceding treatment with a funded anti-resorptive therapy for at least 12 months prior to their osteoporotic fracture (11.8%).

CONCLUSION: Considerable number of patients aged 65 years and older with osteoporotic fractures also had renal impairment contraindicating the use of bisphosphonates. There were no significant differences in demographic variables between the renal and non-renal group other than for age. Majority of patients in the renal group were ineligible for denosumab based on the current special authority criteria. These results highlight the need for further review and revision of the current PHARMAC criteria to improve access to denosumab in older adults with renal impairment and osteoporotic fractures.

Osteoporosis is a disease characterised by low bone mass, micro-architectural disruption and skeletal fragility resulting in decreased bone strength and increased risk of fracture.[1] Presence of concurrent risk factors such as ageing and hormonal changes associated with menopause means that older adults are particularly affected. The patient-related and healthcare burden of the disease is significant, and in 2007 the combined cost of treating hip and vertebral fractures in New Zealand was estimated to be at least $118 million dollars per annum.[2] Hence, there is a compelling need to prevent fractures associated with osteoporosis. Along with measures to reduce falls risk, pharmacological therapies such as bisphosphonates have been shown improve bone mineral density (BMD)[3] and reduce the risk of osteoporotic fracture,[4] and bisphosphonates are currently used as a first-line therapy for osteoporosis in New Zealand.

However, bisphosphonates are primarily excreted by the kidneys and are contra-indicated in moderate to severe renal impairment with creatinine clearance (CrCl) below 30–35ml/min due to concerns about nephrotoxicity.[5] The limitation of its use in reduced renal function is particularly important in older adults where there is also a considerable co-prevalence of osteoporosis and chronic kidney disease (CKD). A longitudinal study[6] demonstrated that average estimated glomerular filtration rate (GFR) declined by 7.5 ml/min per decade of life. This age-related decline in GFR is further accelerated by commonly encountered comorbidities such as hypertension and diabetes; and high prevalence of CKD seen in older adults is therefore unsurprising.[7] CKD itself is also an independent risk factor for fragility fractures,[8] due to CKD-associated mineral bone disorder (CKD-MBD) arising from various mechanisms, including secondary hyperparathyroidism, vitamin D deficiency and increased oxidative stress.[9] While osteoporosis and CKD-MBD are distinctly separate disease entities which are difficult to distinguish clinically without a trans-iliac bone biopsy, it is nevertheless imperative to address metabolic abnormalities arising from CKD-MBD, which includes correction of calcium and phosphate balance, repletion of vitamin D levels and addressing hyperparathyroidism.[10]

In July 2018, Denosumab was made available as a fully subsidised treatment for osteoporosis in New Zealand. Denosumab is a fully humanised monoclonal anti-receptor activator of nuclear factor kappa-B ligand antibody which induces decreased osteoclast proliferation and bone resorption.[11] In contrast to bisphosphonate therapy, pharmacokinetic and pharmacodynamic properties of denosumab are not affected by renal impairment. Currently, the use of denosumab in New Zealand is regulated by the PHARMAC criteria. Notably, the existing criteria require that a patient has to have 'severe established osteoporosis', which is defined as having measured BMD below 2.5 standard deviation below the young adult mean (ie, T-score of less than -2.5) in the presence of one or more fragility fractures,[12] with severe renal impairment defined as creatinine clearance less than 35ml/min contraindicating the use of zoledronic acid, and "at least one symptomatic new fracture after at least 12 months' continuous therapy with a funded antiresorptive agent at adequate doses", which includes bisphosphonates such as oral risedronate and alendronate, intravenous zoledronate; and raloxifene, a selective oestrogen receptor modulator.[13] There are no studies to date which have evaluated the access to denosumab based on the current PHARMAC criteria in New Zealand.

Therefore in this study we first assessed the prevalence of renal impairment in patients 65 years and older presenting to Middlemore Hospital with osteoporotic fractures contraindicating bisphosphonates use; secondly assessed for any differences in demographic variables between those with renal impairment and those without, and thirdly assessed the eligibility of denosumab among the patients with renal impairment, based on the PHARMAC criteria.

Method

All patients 65 years and older presenting acutely with osteoporotic fractures treated by inpatient orthogeriatric service (IOS) and the outpatient fracture liaison service (FLS) at Middlemore Hospital between 1 February to 31 April 2019 were included. Patients with fractures due to high impact mechanism of injury or due to underlying pathology such as cancers were excluded. For the purpose of this study, World Health Organization definition of osteoporotic fracture was used, which defines it as *"a fracture caused by injury that would be insufficient to fracture a normal bone; the result of reduced compressive and/or torsional strength of bone."*[12] Severity of cognitive impairment was classified into nil, mild cognitive impairment (MCI) and dementia, with dementia being defined as having documented severe cognitive impairment affecting the instrumented activities of daily living (iADL) according to the Lawton iADL scale,[14] and MCI being defined as having milder cognitive impairment without evidence of direct impact on the iADLs. 'Renal impairment' and hence those in the 'renal group' were defined as patients with CrCl below 35ml/min, which is the generally accepted upper threshold for the safe use of bisphosphonates.[15]

Following data was retrospectively collected by reviewing the electronic hospital records, which included discharge summaries and clinic letters: age, sex, ethnicity, preadmission residential status (independent, rest home or private hospital), type of acute osteoporotic fractures defined by site [femur, humerus, wrist, neck of femur (NOF), rib, vertebral, multiple fractures or other]; previous history of osteoporotic fractures; documented history of cognitive impairment and its severity; history of falls within the preceding 12 months; previous dual energy x-ray absorptiometry (DEXA) scan and the worst documented T-scores over total hip, neck of femur or L1-4 spine; and the preceding use of funded anti-resorptive therapy (oral risedronate and alendronate, intravenous zoledronate and raloxifene) of at least 12 months' duration prior to the fracture. CrCl was calculated using the Cockcroft-Gault formula based on the ideal body weight according to their recorded height and serum creatinine at the time of the patient presentation. Patients were then assigned to the renal group (defined as having CrCl below 35ml/min) and non-renal group (defined as CrCl above 35ml/min). Descriptive statistical analysis and statistical tests including paired t-test, Fisher's exact test and chi-square test were used to assess for statistical difference in patient characteristics between the IOS and FLS group, and between the renal and non-renal group. PHARMAC special authority criteria for denosumab was used to assess eligibility in the renal group, and any reasons for their ineligibility were recorded.

Result

Total of 190 patients were included (102 in the IOS group and 88 in the FLS group). Statistically significant differences were seen between the IOS and the FLS groups, with the former being older, having higher proportion of patients admitted from residential care, previous osteoporotic fractures, and higher rates of preceding cognitive impairment. Statistical inference was unable to be obtained for differences in specific type of acute osteoporotic fractures due to low frequency of certain fracture events; however, it is notable that NOF fractures occurred exclusively in the IOS group, and vertebral fractures in the FLS group. Mean CrCl and proportion of patients with CrCl below 35ml/min were similar between the two groups.

Thirty-four patients (17.9% of the study cohort) had CrCl of less than 35ml/min, and therefore were assigned to the renal group. Table 2 describes the comparison of demographic details between the renal and non-renal group. There were no statistically significant differences in demographic variables other than for mean age, where the renal group was significantly older (85.4 vs 77.52 years, p-value <0.0001).

Only two out of 34 patients were eligible for denosumab. As per Figure 1, majority of the patients (82.4%) were ineligible for denosumab as they did not meet the criteria for severe established osteoporosis.

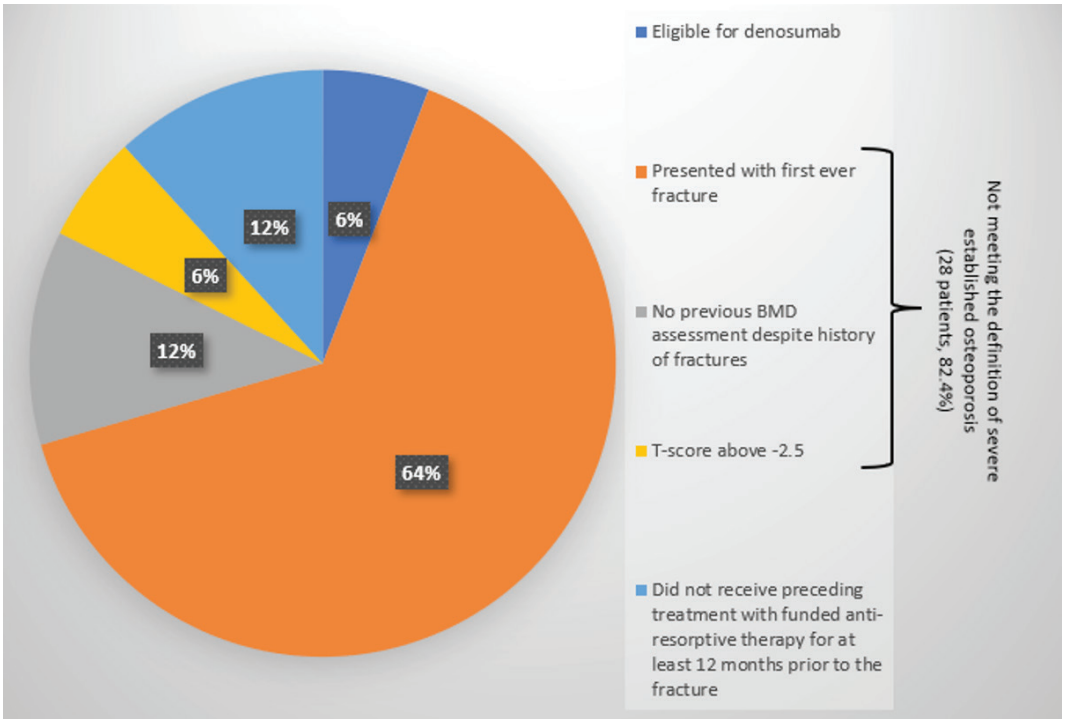
Table 1: Comparison of demographic variables between the IOS and the FLS group.

		IOS (102 patients) N (%)	FLS (88 patients) N (%)	P-value
Mean age (years)		80.7	77.0	0.002
Ethnicity	NZ European	76 (74.5)	58 (65.9)	0.086
	Asian	11 (10.8)	17 (19.3)	
	Pasifika	9 (8.8)	7 (8)	
	Māori	2 (2.0)	4 (4.5)	
	Other	4 (3.9)	2 (2.3)	
Sex	Male	30 (29.4)	24 (27.3)	0.744
	Female	72 (70.6)	64 (72.7)	
Residential care status	Independent	83 (81.4)	84 (95.5)	0.011
	Rest home	8 (7.8)	1 (1.1)	
	Private hospital	11 (10.8)	3 (3.4)	
Type of acute osteoporotic fracture	NOF	54 (52.9)	0	N/A
	Femur	5 (4.9)	2 (2.3)	
	Humerus	6 (5.9)	5 (5.7)	
	Wrist	7 (6.9)	18 (20.5)	
	Vertebral	0	49 (55.7)	
	Ribs	0	5 (5.7)	
	Multiple	10 (9.8)	2 (2.3)	
	Other	20 (19.6)	7 (8.0)	
Preceding history of osteoporotic fractures	Yes	34 (33.3)	15 (17)	0.017
	No	68 (66.6)	73 (83)	
Previous DEXA scan	Yes	20 (19.6)	22 (25)	0.372
	No	82 (80.4)	66 (75)	
Cognitive impairment	Nil	77 (75.5)	80 (90.9)	0.017
	MCI	8 (7.84)	3 (3.4)	
	Dementia	17 (16.7)	5 (5.7)	
History of falls over the preceding 12 months	Yes	15 (14.7)	13 (14.8)	0.990
	No	87 (85.3)	75 (85.2)	
Preceding anti-resorptive therapy use of at least 12 months duration	Yes	26 (25.5)	16 (18.2)	0.226
	No	76 (74.5)	72 (81.8)	
Estimated creatinine clearance (ml/min)	>35	83 (81.3)	73 (83)	0.93
	<35	19 (18.6)	15 (17)	
Mean CrCl (ml/min)		50.6	49	0.6

Table 2: Comparison of demographic variables between the renal and non-renal group.

		Renal (34 patients) N (%)	Non-renal (156 patients) N (%)	P-value
Mean age (years)		85.4	77.5	<0.0001
Ethnicity	NZ European	22 (64.7)	112 (71.8)	0.659
	Asian	6 (17.6)	22 (14.1)	
	Pasifika	4 (11.8)	12 (7.7)	
	Māori	0 (0)	6 (3.9)	
	Other	2 (5.9)	4 (2.6)	
Sex	Male	8 (23.5)	46 (29.5)	0.537
	Female	26 (76.5)	110 (70.5)	
Residential care status	Independent	28 (82.4)	139 (89.1)	0.51
	Rest home	2 (5.9)	7 (4.5)	
	Private hospital	4 (11.8)	10 (6.4)	
Type of acute osteoporotic fracture	NOF	11 (32.4)	43 (27.6)	N/A
	Femur	3 (8.8)	4 (2.6)	
	Humerus	0 (0)	11 (7.1)	
	Wrist	3 (8.8)	22 (14.1)	
	Vertebral	10 (29.4)	39 (25)	
	Ribs	1 (2.9)	4 (2.6)	
	Multiple	3 (8.8)	9 (5.8)	
	Other	3 (8.8)	24 (15.3)	
Preceding history of osteoporotic fractures	Yes	12 (35.3)	37 (23.7)	0.16
	No	22 (64.7)	119 (76.3)	
Previous DEXA scan	Yes	9 (26.5)	33 (21.2)	0.50
	No	25 (73.5)	123 (78.8)	
Cognitive impairment	Nil	25 (73.5)	132 (84.6)	0.26
	MCI	3 (8.8)	8 (5.1)	
	Dementia	6 (17.4)	16 (10.3)	
Preceding history of falls over 12 months	Yes	7 (20.6)	21 (13.5)	0.292
	No	27 (79.4)	135 (86.5)	
Preceding anti-resorptive therapy use of at least 12 months duration	Yes	12 (35.3)	30 (19.2)	0.065
	No	22 (64.7)	126 (80.8)	

Figure 1: Eligibility for denosumab under the current special authority criteria in the renal group.



Discussion

This retrospective study was conducted on patients aged 65 years and older presenting with osteoporotic fracture treated at Middlemore Hospital in South Auckland, New Zealand. The orthogeriatric service at Middlemore Hospital serves a large catchment population of over 500,000 patients within the Counties Manukau region and has two major arms. IOS consists of two full-time consultant orthogeriatricians and an orthogeriatric registrar based on the orthopedic ward who provide medical support and facilitate expedited transfer to the rehabilitation service for all inpatient orthopedic patients aged 65 years and above; and FLS liaises with the Middlemore Hospital radiology service and identifies all patients with osteoporotic fractures and coordinates investigations and treatment for osteoporosis as an outpatient basis. Distinctive roles of these two services explain the significant differences in the patient characteristics seen, as the older and frailer patients with hip fractures necessitates inpatient surgical management, while as those with fractures involving non-major sites such as the vertebra and upper limb can often be managed as outpatient basis. Both IOS and FLS group consisted predominantly of New Zealand Europeans and female sex, which is consistent with the observed demographic trend associated with osteoporosis in New Zealand.[2] A point of interest is that there were no significant differences in demographic variables between the renal and non-renal group other than for age, which would otherwise alter conventional approach in management of osteoporosis.

Thirty-four patients (17.9%) had severe renal impairment contraindicating the use of bisphosphonates. A previous study[16] assessing the prevalence of CKD in women with osteoporosis aged 50 years and older using the MDRD (Modification of Diet in Renal Disease) equation showed that around 3.59% had GFR of less than 35ml/min. Although not directly comparable, considerably higher prevalence of renal impairment in our study is most likely explained by older age of the screened population and the different methods of estimating the renal function.

Out of 34 patients, only two (6%) were eligible for denosumab. The most common reason for ineligibility to denosumab was not meeting the definition of severe established osteoporosis (having an osteoporotic fracture as well as having a documented T-score of -2.5 and lower). When the reasons for not meeting this definition was further

assessed, the most common reason (64%) was due to patients presenting with their first ever osteoporotic fracture (which meant that they did not have a preceding BMD assessment with a DEXA scan) followed by four patients (12%) who did not have a preceding BMD assessment despite having a preceding history of osteoporotic fractures, and two patients (6%) whose BMD severity was above the T-score of -2.5 threshold, therefore not meeting the definition of severe established osteoporosis. Four patients (12%) were ineligible for denosumab despite meeting the criteria for severe established osteoporosis as they did not receive at least 12 months of treatment with a funded anti-resorptive therapy prior to their new fracture.

In light of above findings, two important barriers in accessing denosumab on the current PHARMAC criteria will be discussed. Firstly, many of these patients would require a BMD assessment with a DEXA scan as a part of their assessment of eligibility for denosumab. Currently, Counties Manukau District Health Board has a single DEXA scan reported by two orthogeriatricians for its older adult catchment. DEXA scan is therefore a limited resource, being prioritised for those with documented osteoporotic fractures and risk factors for secondary osteoporosis, and routine DEXA scanning to assess the risk of osteoporosis in otherwise well subjects is currently not feasible. It is also important to mention that access to publicly funded DEXA scan is widely variable across New Zealand, and therefore mandatory BMD assessment is likely to be a greater barrier for some more than the others. Of note, over half of the patients in the renal group (27 patients, 58.9%) were 75 years and older and therefore would have qualified for funded treatment with bisphosphonates without the need for a DEXA scan if it were not for their renal impairment.[17] Secondly, the current denosumab criteria stipulates that their current fracture should have occurred after at least a 12-month course of a funded antiresorptive agent. However, various reasons including pre-existing reduced renal function and adverse drug reaction could have precluded the completion of treatment duration.

Out of the currently funded anti-resorptive therapy options in New Zealand, raloxifene is an option for treatment of osteoporosis complicated by renal impairment. Clinical trials have shown that the blood levels of raloxifene and its metabolites were not affected by renal function in women with CrCl as low as 21 ml/min.[18] However, raloxifene has been shown to have only modest efficacy by reducing vertebral fracture risk without affecting the non-vertebral fracture risk[19] and was less effective than oral alendronate in improving BMD.[20] In comparison, FREEDOM trial demonstrated that denosumab improved BMD as well as reduce vertebral and non-vertebral fracture risk including hip fracture risk,[21] and denosumab was also shown to improve BMD over oral alendronate in a modest but statistically significant manner.[22] Post-hoc analysis of the FREEDOM trial also demonstrated that reduction in fracture risk and improvement in BMD did not differ significantly by the level of the kidney function.[23] It is worth keeping in mind however that FREEDOM trial only had 73 women with stage four CKD (estimated GFR of 15–29ml/min) with low rates of fracture events, and included no women with estimated GFR below 15ml/min. Severe hypocalcaemia is also a known adverse event more commonly associated with use of denosumab in reduced renal function,[24] which also needs to be taken into account.

This study is a first locally based study assessing the prevalence of renal impairment in patients presenting with osteoporotic fractures aged 65 years and above, and their eligibility for denosumab based on the current PHARMAC special authority criteria. It is appreciated that further research is needed to determine the long-term efficacy and safety of denosumab in CKD. However, these results raise the importance of ongoing discussion around the need to improve treatment options for older adults with osteoporosis complicated by renal impairment. While this study was not designed to look at the appropriateness of use of denosumab in the patients with renal impairment, baseline screening for concurrent CKD-MBD and wider consideration of patients' comorbid status and life expectancy still stands.

The main strength of this study lies in its clearly defined pre-study questions and inclusion/exclusion criteria for the study population, and inclusion of important variables such as residential care status and cognitive impairment, which are relevant in

a geriatric research setting. Main limitations include its retrospective study design, which lends itself to bias resulting from coding of diagnoses such as cognitive impairment and falls history. This study used Cockcroft-Gault formula to estimate the renal function, given that many of the drug dosing recommendations are still based on the Cockcroft-Gault formula on a historical basis,[25] and due to the perceived issue with acute kidney injuries in acutely admitted IOS patients preventing eGFR calculation using other methods such as the CKD-EPI equation. Limitations of estimating renal function using the Cockcroft-Gault equation is well appreciated,[26] and the prevalence of renal impairment in the study population may differ if the renal function was measured using gold standard markers such as inulin.

Conclusion

Prevalence of renal impairment contraindicating bisphosphonate use among patients 65 years and above presenting with an osteoporotic fracture was considerable. No statistically significant differences in demographic variables were seen between the renal and non-renal group apart from age. Majority of these patients were not eligible for funded treatment with denosumab based on the current special authority criteria. We identify a clear gap in access to treatment for older adults with renal impairment and osteoporotic fractures, and our study indicates that further review and revision of the current PHARMAC criteria is necessary in order to improve access to denosumab in this vulnerable cohort.

Competing interests:
Nil.

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REFERENCES:

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis and Therapy. Osteoporosis prevention, diagnosis and therapy. J Am Med Assoc. 2001; 285(6):785–795.
2. Brown P, McNeill R, Radwan E, Willingale J. The Burden of Osteoporosis in New Zealand: 2007–2020. 2007:1–52. http://www.iofbonehealth.org/sites/default/files/PDFs/white_paper_new_zealand_2007.pdf
3. Yates J. A meta-analysis characterizing the dose-response relationships for three oral nitrogen-containing bisphosphonates in postmenopausal women. Osteoporos Int. 2013; 24(1):253–262. doi:10.1007/s00198-012-2179-3
4. Murad MH, Drake MT, Mullan RJ, et al. Comparative effectiveness of drug treatments to prevent fragility fractures: A systematic review and network meta-analysis. J Clin Endocrinol Metab. 2012; 97(6):1871–1880. doi:10.1210/jc.2011-3060
5. Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. Kidney Int. 2008; 74(11):1385–1393. doi:10.1038/ki.2008.356
6. Lindeman RD, Tobin J, Shock NW. Longitudinal Studies on the Rate of Decline in Renal Function with Age. J Am Geriatr Soc. 1985; 33(4):278–285. doi:10.1111/j.1532-5415.1985.tb07117.x

7. Barrett Bowling C, Inker LA, Gutiérrez OM, et al. Age-specific associations of reduced estimated glomerular filtration rate with concurrent chronic kidney disease complications. Clin J Am Soc Nephrol. 2011; 6(12):2822–2828. doi:10.2215/CJN.06770711
8. Sprague SM. Renal function and risk of hip and vertebral fractures in older women: Is it always osteoporosis? Arch Intern Med. 2007; 167(2):133–139. doi:10.1001/archinte.167.2.115
9. Nitta K, Yajima A, Tsuchiya K. Management of osteoporosis in chronic kidney disease. Intern Med. 2017; 56(24):3271–3276. doi:10.2169/internalmedicine.8618-16
10. West SL, Patel P, Jamal SA. How to predict and treat increased fracture risk in chronic kidney disease. J Intern Med. 2015; 278(1):19–28. doi:10.1111/joim.12361
11. Miyazaki T, Tokimura F, Tanaka S. A review of denosumab for the treatment of osteoporosis. Patient Prefer Adherence. 2014; 8:463–471. doi:10.2147/PPA.S46192
12. World Health Organization. Guidelines for Preclinical Evaluation and Clinical Trials in Osteoporosis.; 1998. http://apps.who.int/iris/handle/10665/42088.
13. Application for subsidy by special authority: Denosumab. 2018:1-2. http://www.pharmac.govt.nz/2019/10/01/SA1777.pdf
14. Lawton M, Brody E. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969; 9(3):179–186.
15. Miller PD, Jamal SA, Evenepoel P, Eastell R, Boonen S. Renal safety in patients treated with bisphosphonates for osteoporosis: A review. J Bone Miner Res. 2013; 28(10):2049–2059. doi:10.1002/jbmr.2058
16. Lubwama R, Nguyen A, Modi A, Diana C, Miller PD. Prevalence of renal impairment among osteoporotic women in the USA, NHANES 2005-2008: Is treatment with bisphosphonates an option? Osteoporos Int. 2014; 25(5):1607–1615. doi:10.1007/s00198-014-2645-1
17. Application for subsidy by special authority: Zoledronic Acid. 2019. http://www.pharmac.govt.nz/2019/01/01/SA1187.pdf
18. Authority NZM and MDS. New Zealand Datasheet for Evista. 2015:1–21. http://www.medsafe.govt.nz/profs/Datasheet/e/evistatab.pdf
19. Delmas PD, Ensrud KE, Adachi JD, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: Four-year results from a randomized clinical trial. J Clin Endocrinol Metab. 2002; 87(8):3609–3617. doi:10.1210/jcem.87.8.8750
20. Johnell O, Scheele WH, Lu Y, Reginster JY, Need AG, Seeman E. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2002; 87(3):985–992. doi:10.1210/jcem.87.3.8325
21. Cummings SR, Martin JS, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009; 361(8):756–765. doi:10.1056/NEJMoa0809493
22. Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: A randomized, blinded, phase 3 trial. J Bone Miner Res. 2009; 24(1):153–161. doi:10.1359/jbmr.0809010
23. Jamal SA, Ljunggren Ö, Stehman-Breen C, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. J Bone Miner Res. 2011; 26(8):1829–1835. doi:10.1002/jbmr.403
24. Block GA, Bone HG, Fang L, Lee E, Padhi D. A single-dose study of denosumab in patients with various degrees of renal impairment. J Bone Miner Res. 2012; 27(7):1471–1479. doi:10.1002/jbmr.1613
25. Food and Drug Administration U. D of H and HS. Guidance for Industry - Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and impact on Dosing and Labeling. 1998;(May). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072127.pdf
26. Raman M, Middleton RJ, Kalra PA, Green D. Estimating renal function in old people: an in-depth review. Int Urol Nephrol. 2017; 49(11):1979–1988. doi:10.1007/s11255-017-1682-z