Radiography 24 (2018) 151–158

Contents lists available at ScienceDirect

Radiography

journal homepage: www.elsevier.com/locate/radi

Disuse osteopenia following leg fracture in postmenopausal women: Implications for HIP fracture risk and fracture liaison services

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ARTICLE INFO

Article history:
Received 30 September 2017
Received in revised form
1 December 2017
Accepted 8 December 2017
Available online 6 January 2018

Keywords:
Disuse osteopenia
Leg fracture
Function
Activity
Postmenopausal
Bone mineral density

ABSTRACT

Introduction: Disuse osteopenia is a known consequence of reduced weight-bearing and has been demonstrated at the hip following leg injury but has not been specifically studied in postmenopausal women.

Method: Bilateral DXA (GE Lunar Prodigy) bone mineral density (BMD) measurements were taken at the neck of femur (NOF), total hip region (TH) and lumbar spine in postmenopausal female groups comprising controls ($N = 43$), new leg fractures (#<3wks) ($N = 9$), and participants who had sustained a leg fracture more than one year previously (#>1yr) ($N = 24$). #>1yr were assessed at a single visit and the remaining groups at intervals over twelve months. Weight-bearing, function, 3-day pedometer readings, and pain levels were also recorded.

Results: The #<3wks demonstrated significant ($p < 0.05$) losses in ipsilateral TH BMD at 6 weeks from baseline 0.927 ± 0.137 g/cm^2, to 0.916 ± 0.151 g/cm^2 improving to 0.946 ± 0.135 g/cm^2 (n.s) at 12 months following gradual return to normal function and weight-bearing activity. The #>1yr scored significantly below controls in almost all key physical and functional outcomes demonstrating a long-term deficit in hip bone density on the ipsilateral side.

Conclusion: The clinical significance of post-fracture reduction in hip BMD is a potential increased risk of hip fracture for a variable period that may be mitigated after return to normal function and weight-bearing. Improvement at 12 months in #<3wks is not consistent with #>1yr results indicating that long-term impairment in function and bone health may persist for some leg fracture patients. Unilateral bone loss could have implications for Fracture Liaison Services when assessing the requirement for medication post fracture.

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Introduction

Alongside numerous lifestyle, hormonal and pharmacological factors affecting maintenance of bone health, skeletal mechanical loading is the key stimulus for bone remodelling and it follows that a reduction in weight-bearing will have a negative impact on the remodelling process. Reduced weight-bearing activity is an inevitable consequence of lower limb fracture and the condition of disuse osteopenia, characterised by reduced BMD and micro-architectural changes, may arise as a result.[1–5] The consequence of disuse osteopenia may be a reduction in the structural integrity of bones predisposing them to increased fracture risk either at the original injury site or secondary site that has also been subject to a bone density loss.[6–8] Prolonged immobility following lower limb fracture potentially results in either unilateral or bilateral loss in hip BMD.[9–17] Fractures of the hip, are more closely linked to BMD than other fracture types and have the most serious social and economic consequences due to high rates of subsequent morbidity and mortality.[18] As the rate of hip fracture increases exponentially with age, estimated to be a 17% lifetime risk from the age of 50 years in white females,[18,19] it potentially represents a major problem for post-menopausal women who are already losing bone systemically due to reduced oestrogen levels and may be at greater risk of not recovering bone following a period of disuse.

Jarvinen and Kannus[14] provide a comprehensive review of studies, up to 1997, of injuries to the lower extremities and their effect on bone density. The studies are grouped into knee injuries,

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https://doi.org/10.1016/j.radi.2017.12.005
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femoral shaft, tibial shaft and ankle fractures. It is evident from all of these studies that varying degrees of bone loss are associated with lower limb injury. This also includes bone density changes in the contralateral limb. Several studies include measurement of BMD changes in the proximal femur.[9–12,15,20] These studies, with one exception,[11] showed long-term bone loss in the ipsilateral proximal femur to a varying degree as a result of lower limb injury.

Although ankle fractures are not considered to be a typical osteoporotic fracture, postmenopausal females frequently present with ankle fractures that often result from relatively minor trauma. Fracture Liaison Services (FLSs) aim to identify patients at increased risk of further low-trauma fractures due to bone fragility and routinely refer patients for DXA scans around 6 weeks post-fracture at a stage when bone loss may be at its peak. DXA scanning protocols may only include unilateral hip measurements, and a misleading assessment of BMD status may result where disuse-related bone loss has not been equal bilaterally. Effective and relatively inexpensive pharmacological interventions are available to mitigate bone loss[18] and prophylactic treatment, without prior screening, may be indicated for high risk groups immediately following injury, particularly when additional risk factors for osteoporosis are present. A FRAX® calculation is helpful in this situation.[21]

This study combined a prospective observational design with a cross-sectional study to investigate the extent of bone loss at the proximal femur as a result of mechanical unloading following leg fracture in a post-menopausal population. Factors that contribute to both loss and recovery of bone mass and quality were also evaluated with the aim of identifying participants who may be at heightened hip fracture risk following a protracted period of disuse.

Materials and methodology

Participants

The study recruited postmenopausal women over the age of 45 years. The groups comprised 43 controls with no history of leg fracture after the age of 21 years, 9 participants (#<3wks) who sustained a leg fracture within the previous 3 weeks, and 24 participants (#>1yr) who had sustained a leg fracture more than one year previously, post menopause and within the previous ten years.

Exclusion criteria for the #<3wks and #>1yr groups were treatment by external fixation and immobilization <6 weeks. Participants already on treatment for low BMD were not excluded as it was statistically probable that a high proportion of the study population would be in the osteopenic or osteoporotic range at baseline and already receiving treatment. It was expected that some participants would be diagnosed with low BMD during the study and would commence treatment within the study period. It was felt important to keep the patients in the study as close as possible to those seen in clinical practice to ensure that the results are generalisable to the wider population.

Patients were recruited from the Emergency Department and Fracture Clinic at the Princess Elizabeth Orthopaedic Centre (PEOC) at the Royal Devon &Exeter (RD&E) Hospital.

The project was approved by the Devon and Torbay Research Ethics Committee REC Ref:09/H0202/64. All participants provided informed consent.

Method

The #<3wks participants attended at baseline (visit 1) and following intervals of six weeks (visit 2), six months (visit 3) and twelve months (visit 4). As no changes were expected in the control group at six weeks, this group only attended follow-up visits at six and twelve months. The #>1yr group attended at a single visit at their own convenience.

At visit 1 participants completed the following:

- Questionnaire providing participants' medical and lifestyle history relating to bone health.
- A visual pain scale (pain VAS) with score range from 0 (no pain) to 100 (intolerable pain). This included pain due to any cause not necessarily related to their fracture.
- The Lower Extremity Functional Scale (LEFS).[22] A maximum score of 80 represents full functionality in all domains.

Height was measured (±0.01 m) using a stadiometer (Seca, Germany). Total weight was measured (±0.1 kg) using weighing scales (Seca 877, Germany). Relative left/right weight-bearing through the legs was measured using two sets of identically calibrated weighing scales (Seca 877, Germany) using the method described by Hopkins et al[23] All participants underwent DXA (GE Lunar Prodigy, Bedford, MA) scans of bilateral hips and lumbar spine, in accordance with the manufacturer's protocols.

Three-day pedometer readings, in the week following their visit, were provided by participants.

For the controls and #<3wks groups, baseline procedures (excepting the medical history/lifestyle questionnaire) were repeated at follow-up visits. As no changes were expected in the lumbar spine for any participants these measurements were not deemed necessary at the 6 week visit.

Statistical analysis

Data were analysed using SPSS v. 22. Differences at baseline between each fracture group and controls were compared using the two-sample t test for normally distributed variables, Mann–Whitney U test for skewed continuous variables and the Chi-square Test for categorical variables. The change between baseline and follow-up visit was compared using the two-sample (independent groups) t test.

Left and right side DXA measurements were re-designated as ipsilateral and contralateral sides; the left side was designated as the ipsilateral side for the control group.

Results

Figs. 1–3 show baseline differences between groups and changes over 12 months in BMD at the NOF, TH and lumbar spine. The #>1yr BMD measurements were significantly lower ($p < 0.05$) for all regions compared to controls excepting the contralateral TH.

Baseline differences between groups

All participants were of Caucasian ethnicity. The results show that participant characteristics (Table 1) were well matched at the baseline visit. There were no significant differences between groups in their history of medical conditions relating to bone health. Participants were asked about their own history of fracture (excluding their current injury where applicable) sustained at any age and due to any cause; the results showed significant differences ($p < 0.015$) between the groups with a median of 1 previous fracture for the #<3wks and #>1yr groups compared to zero for the controls.

With regard to medications known to impact on bone health, either positively or negatively, Tables 1 and 2 show that the groups were well matched with the notable exception of significantly ($p < 0.05$) higher use of bisphosphonate treatments and prescribed calcium supplements and lower use of multivitamins in the #>1yr group.

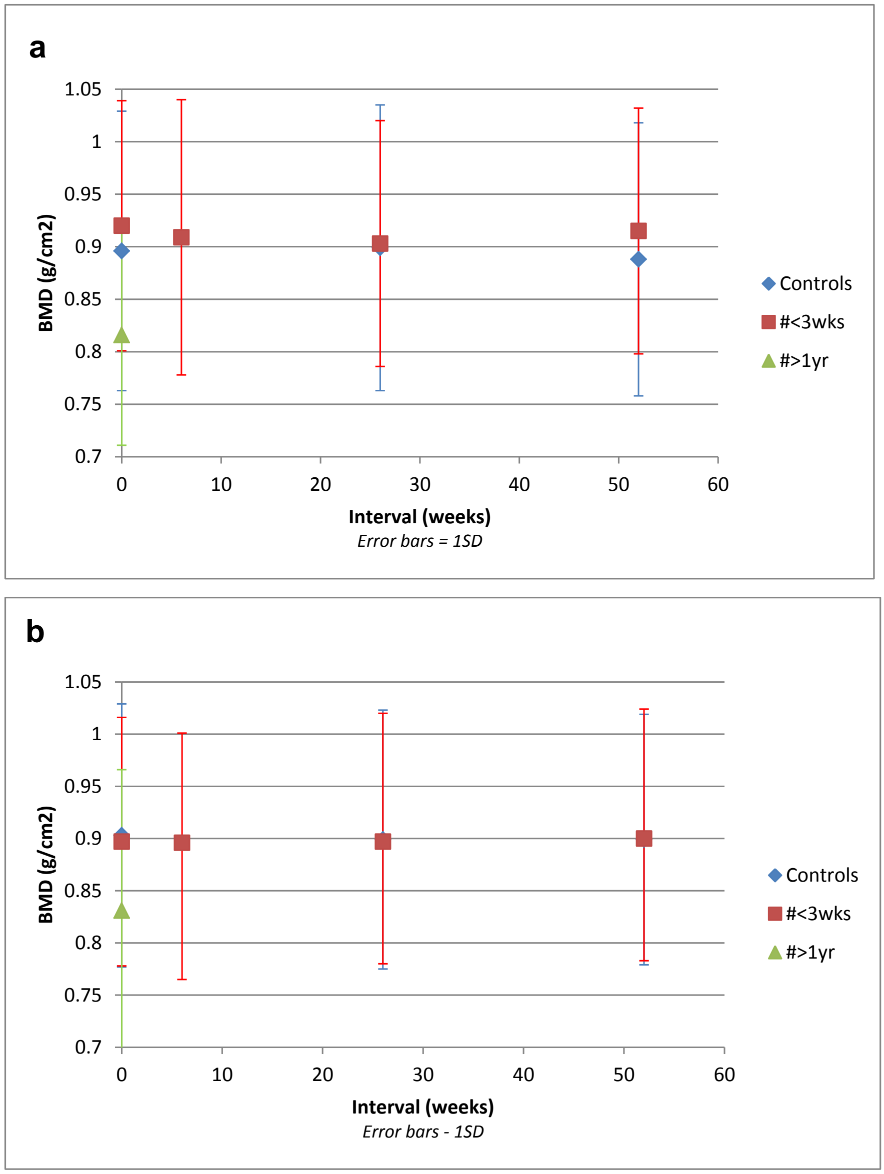


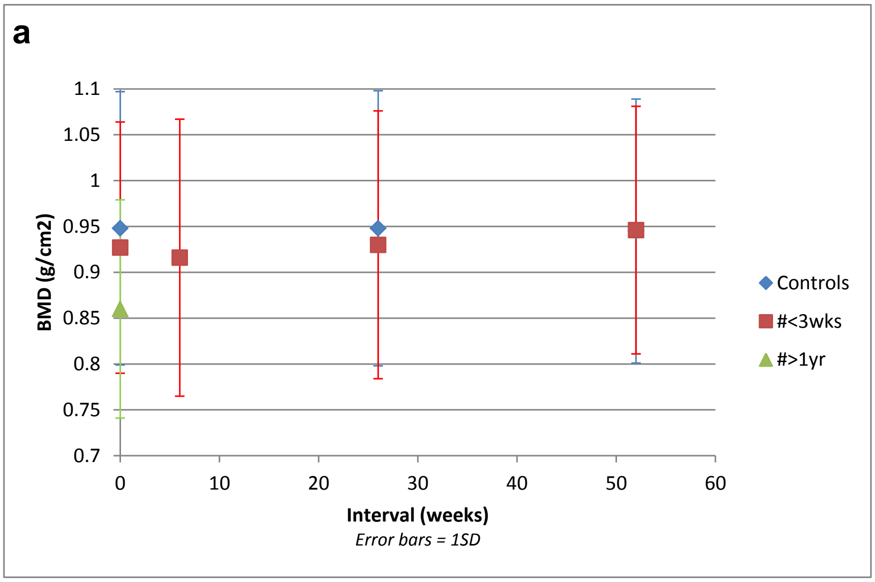
Figure 1. a. Changes in ipsilateral NOF BMD. b. Changes in contralateral NOF BMD.

The most marked differences between groups at baseline are evident in their levels of function. Whilst mean weight-bearing (Fig. 4.) on the ipsilateral leg was close to 50% for the controls and #>1year groups, it was obviously minimal (mean 23.7%) for the #<3weeks group who were all wearing a plaster cast at their first visit. Large differences were seen between levels of function measured by LEFS (Fig. 5.) which was indicative of the participants' ability to perform general daily activities. The control group mean score (73.7 ± 8.6) was close to the maximum of 80, whereas the #>1year result was significantly poorer (56.5 ± 16.4, $p < 0.01$), and the #<3weeks groups poorer still (17.8 ± 8.2, $p < 0.01$). Activity in terms of pedometer readings of average steps per day (Fig. 6.), showed a similar pattern with the controls achieving levels close to the 10,000 steps per day (9716 ± 3596) generally recommended for a healthy lifestyle.[24] Readings were significantly lower for the #>1year (6801 ± 3731, $p < 0.01$) and, as expected at this stage, extremely low, 1517 ± 830, $p < 0.01$ for the #<3wks group. The median pain scores were zero for the control group but similar for #<3weeks and #>1 year at 10/100 and 8/100 respectively.

Longitudinal changes

Significant changes compared to baseline occurred in all of the following parameters of recovery at varying intervals over the one year study period. Fig. 4 shows that the #<3weeks group return to 45.6 ± 4.2% ipsilateral weight-bearing at Visit 2 ($p < 0.01$) and are restored to the same levels as the controls by Visit 3 ($p < 0.05$). The LEFS scores (Fig. 5.) also followed the same trajectory with a progressive improvement in function returning to 66.9 ± 12.3, $p < 0.01$, just below control levels for the #<3weeks group at the final visit. This pattern was repeated for activity levels measured by pedometer (Fig. 6.) where #<3weeks participants returned to control levels at Visit 3 (n.s).

During the course of the study, numerous participants were diagnosed as osteopenic or osteoporotic and were prescribed a calcium with vitamin D supplement ± a bisphosphonate as a result. Table 3 shows a summary of participants receiving treatment for low bone density at baseline, and additional participants put onto treatment during the course of the study.



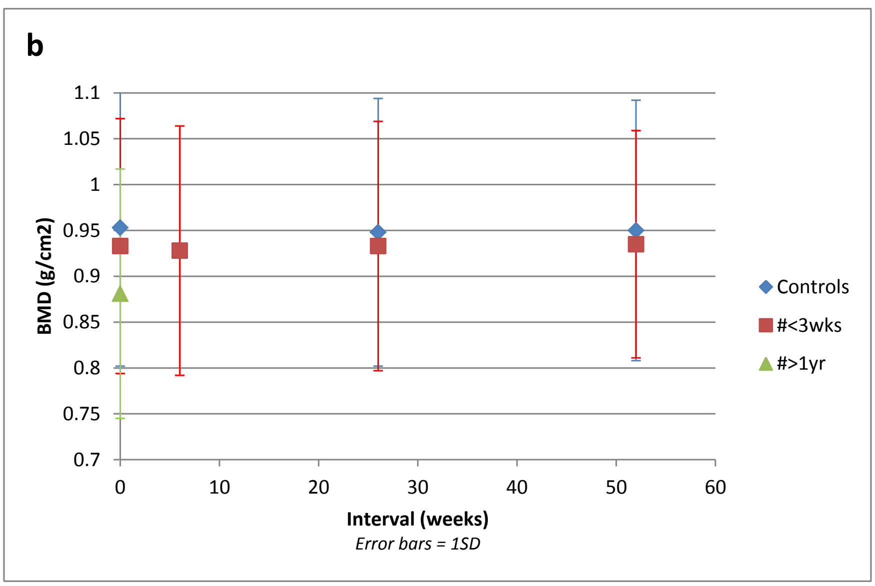


Figure 2. a. Changes in ipsilateral TH BMD. b. Changes in contralateral TH BMD.

Discussion

After the initial deterioration in general function at the time of injury, the #<3weeks group demonstrated good recovery at the end of the study in all physical and functional parameters. The results show an immediate and statistically significant loss of ipsilateral BMD at the total hip subsequently followed by recovery, returning to baseline values, or above, at the end of one year. TH improvement at 12 months to above baseline may possibly be explained by the delay (mean 20 days) in taking baseline measurements as participants may have sustained some post-fracture reduction in BMD before their baseline visit. Ipsilateral NOF measurement reduced (n.s) at 6 weeks and 6 months, improving at 12 months but not returning to baseline values. At 12 months there were no significant changes in contralateral NOF, TH or lumbar spine measurements for any of the groups.

The two fracture groups demonstrated comparable scores for previous fractures (median 1) compared to zero for the control group and this is consistent with previous studies which demonstrate that previous fracture, at any site, is a risk factor for subsequent fractures, independent of BMD.[25,26] It was expected that the levels of function for the #>1year group would be comparable, if not considerably better than for the #<3weeks patients at the end of the study. However the #>1yr group scored significantly below the control group in almost all key outcomes suggesting that a long-term impairment in function and bone health may persist following injury (although as a cross-sectional study, it is not possible to state categorically that these impairments are attributable to the consequences of the fracture) This group also demonstrated a long-term deficit in hip bone density on the ipsilateral side, which together with reduced levels of function and activity that inhibit restoration of BMD, may represent a heightened risk for future hip fracture. Given that the #<3weeks group returned to normal levels of function and activity at the end of the study, it is unclear why long-term impairments should remain in the #>1yr group. These findings may have implications for FLSs which routinely refer patients for DXA scans around 6 weeks post-fracture. Where scanning protocols only include unilateral hip measurements, a misleading assessment of BMD status may result if disuse-related bone loss has not been equal bilaterally i.e.

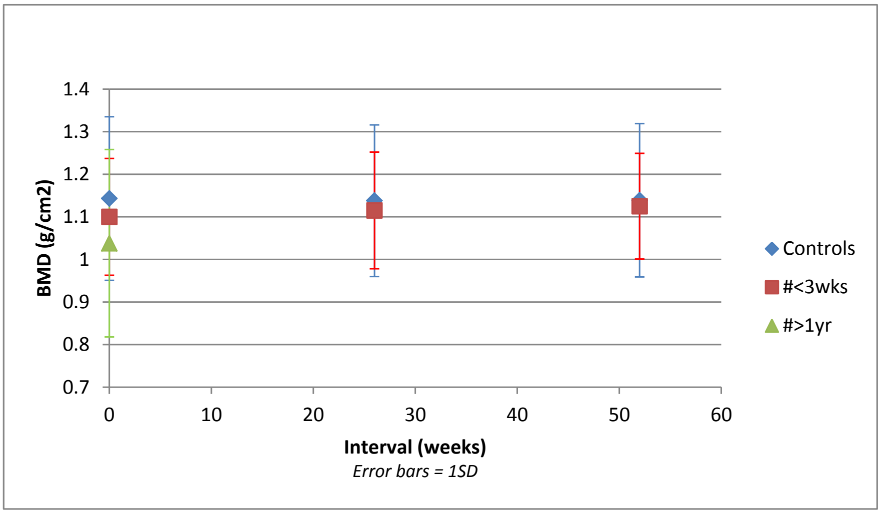


Figure 3. Changes in lumbar spine BMD.

scanning the ipsilateral hip may overestimate fracture risk in the short term and vice versa for the contralateral hip; this may have implications for treatment recommendations.

Limitations

The study had several limitations. The methods and some results reported here are part of a larger study[27] that included a group of knee replacement patients. The #<3weeks group was very difficult to recruit for the main study, in part due to the requirements to attend data collection sessions close to the time of injury, and participants were generally limited to those with a strong support network who could assist them with transport. Despite the small sample size, results were statistically significant for BMD change at the ipsilateral TH at the 6 week visit and these findings may add to the broader knowledge base on this topic. The pedometer results suggest that the controls were a relatively active group for their age range. Although the socio-economic status of participants was not investigated, many, particularly amongst the control group, appeared to have backgrounds of relative affluence and good education that are generally associated with healthier lifestyles. Participants may not therefore be fully representative of the broader population which potentially limits the generalisability of the results. The Hawthorne effect is a well-known phenomenon in research whereby participants adapt their behaviour as a result of being observed.[28] This may have affected participants in the

Table 1
Participant characteristics at baseline – Visit 1.

	Controls (N = 43)	#<3wks (N = 9)	#>1yr (N = 24)
Age (yrs), mean (SD)	64.7 (7.7)	62.6 (7.2)	65.3 (8.3)
Weight (kg), mean (SD)	68.3 (10.2)	71 (11.1)	74.3 (15.8)
Height (m), mean (SD)	1.6 (0.1)	1.7 (0.1)	1.6 (0.1)
BMI, mean (SD)	25.4 (3.2)	26.1 (3.8)	28.4 (5.5)*
BMI at age 21, mean (SD)	22 (2.6)	22.1 (3.1)	21.8 (3.7)
Menarche age (yrs), mean (SD)	12.9 (1.6)	12.1 (1.2)	13.3 (1.7)
Menopause age (yrs, mean (SD))	50.2 (4.8)	47.9 (6.2)	49.1 (4.9)
Previous Hormone Replacement Therapy use, %	48.8	66.6	37.5
Previous Oral Contraceptive Pill use, %	72.0	77.8	45.8
Alcohol consumption, %			
None	7.0	0	8.3
Social only	7.0	22.2	41.7
1–5 units per week	39.5	55.6	16.7
6–10 units per week	23.3	22.2	16.7
11–15 units per week	9.3	0	8.3
16–20 units per week	4.7	0	8.3
>20 units per week	9.3	0	0
Caffeine consumption, %			
None	14	0	4.2
1–5 cups per day	74.4	77.8	70.8
6–10 cups per day	7.0	22.2	24.0
>10 cups per day	4.7	0	0
Exercise 6 months pre-baseline, %			
None	2.3	0	4.2
<0.5 h per day	9.3	11.1	33.3
0.5–1.0 h per day	48.8	33.3	25.0
>1 h per day	39.5	55.6	37.5
Patients wearing plaster cast (%)	0	100	0
Current smoker (%)	0	0	4
Relative with hip/spine/wrist fracture (%)	37	11	38
Relative with other fracture (%)	35	44	46
Relative with osteoporosis (%)	19	11	21

*$p \leq 0.05$ when compared to control group.

Table 2
Participant history of medications and dietary supplements relating to bone health (percentages of group).

	Controls (N = 43) %	#<3wks (N = 9) %	#>1yr (N = 24) %
Glucocorticoids	4.7	0	4.2
Anticonvulsants	0	22.2	0
Diuretics	9.3	11.1	17.4
Chemotherapy	2.3	0	0
Immunosuppressive agents	0	0	0
Heparin	2.3	0	4.2
Thyroxin	9.3	0	17.4
Didronel	0	0	4.2
Alendronate	2.3	0	29.2*
Calcitonin	0	0	25*
Risedronate	0	0	16.7*
Teriparatide	0	0	0
Strontium	0	0	0
Pamidronate	0	0	0
Zolendronate	0	0	0
Ibandronate	0	0	0
Fluoride	2.3	0	0
Multi vitamin	23.8	22.2	4.5*
Calcium[a]	28.6	11.1	50
Vitamin D	19	11.1	40.9

*$p \leq 0.05$ when compared to control group.
[a] The questionnaire did not differentiate between calcium and calcium plus vitamin D.

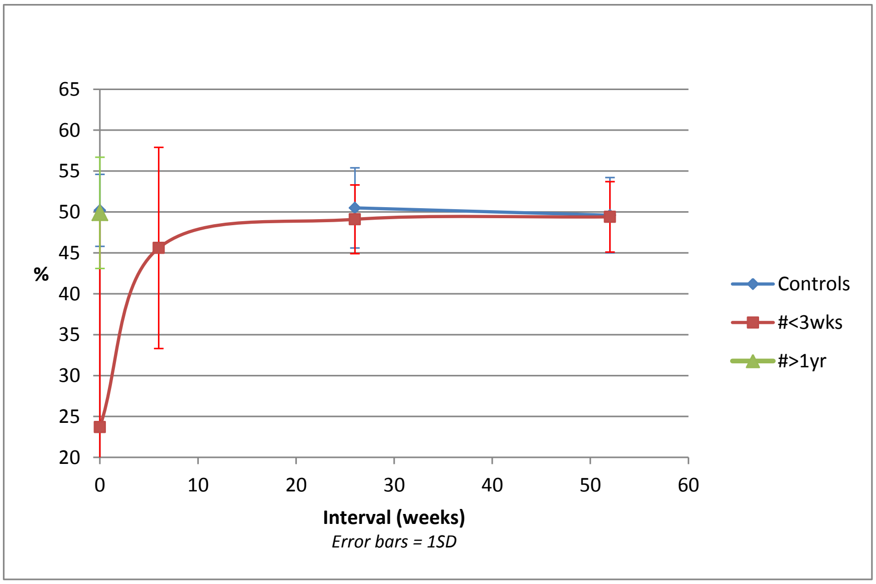


Figure 4. Changes in ipsilateral weight-bearing.

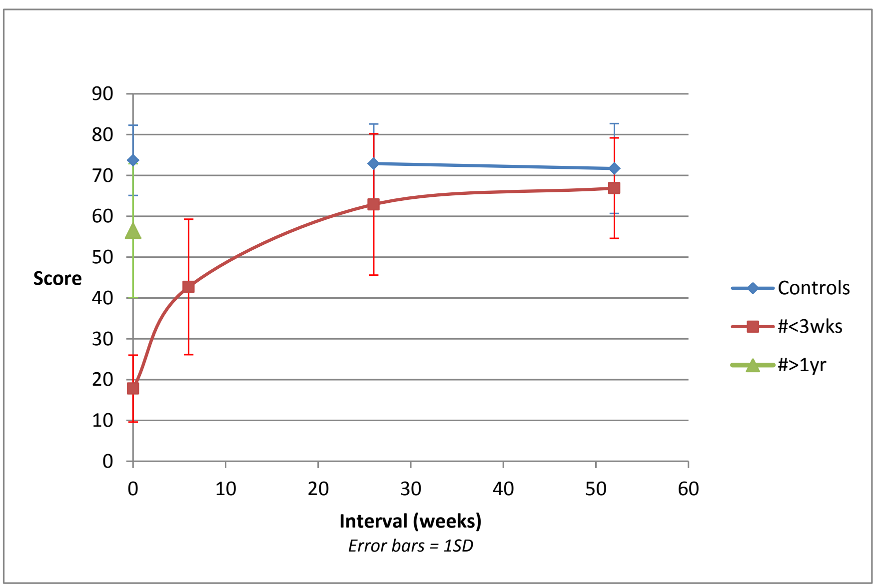


Figure 5. Changes in LEFS.

newly fractured group causing them to optimise their recovery. For this reason, it is possible that the results for this group are not typical of patients with leg fractures and results for the #>1yr group may be more representative of leg fracture outcomes. A potential confounder was the treatment for low bone density prescribed during the course of the study potentially mitigating bone loss in all groups.

Conclusion

The #>1year group exhibited distinct differences to both the controls and the #<3wk group, scoring significantly lower in almost all key outcomes suggesting that a long-term impairment in function, activity and bone health may persist following injury. They demonstrated a long-term deficit in hip bone density on the ipsilateral side, which together with reduced levels of function and activity that inhibit restoration of BMD, may represent a heightened risk for future hip fracture. It is not possible to state that these impairments were attributable to the consequences of the fracture but as these participants presented as a distinct group compared to the controls and the #<3weeks group, the reasons for the differences they exhibit merit further investigation.

Despite apparently conflicting results between the two fracture groups in terms of long term recovery, it is evident from the results for the #<3wk group that there is an immediate reduction in hip BMD following leg fracture. Transient disuse osteopenia on the ipsilateral hip means that a misleading diagnosis could arise either overestimating or underestimating fracture risk depending on which side has been scanned. The results may have implications for FLSs in the timing of DXA scans and emphasise the importance of bilateral hip assessment following leg fracture to take transient unilateral bone loss into account when considering treatment

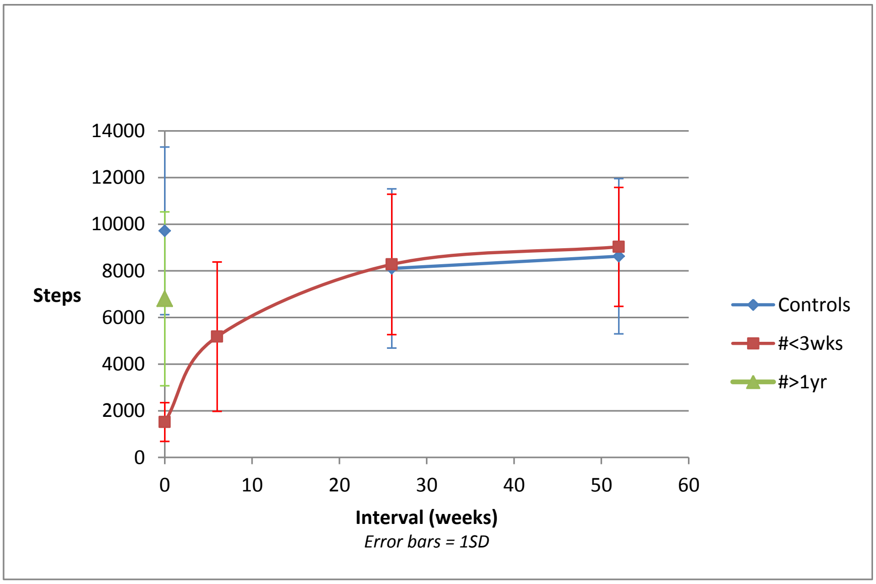


Figure 6. Changes in average daily pedometer reading.

Table 3
Changes in treatment (percentages of group).

	Controls (N = 43) %	#<3wks (N = 9) %	#>1yr (N = 24) %
Receiving prescribed calcium + vitamin D at Visit 1	0	0	12.5
Receiving prescribed calcium + vitamin D at Visit 2	–	22.2	–
Receiving prescribed calcium + vitamin D at Visit 3	7	22.2	–
Receiving prescribed calcium + vitamin D at Visit 4	9.3†	22.2	–
Receiving bisphosphonate and calcium + vitamin D at Visit 1	2.3	0	33.3*
Receiving bisphosphonate and calcium + vitamin D at Visit 2	–	0	–
Receiving bisphosphonate and calcium + vitamin D at Visit 3	14†	22.2	–
Receiving bisphosphonate and calcium + vitamin D at Visit 4	16.3†	22.2	–

*$p \leq 0.05$ when compared to control group.
†$p \leq 0.05$ when compared to baseline for the same group.

options for bone fragility. Further study on a larger sample would be valuable to validate the results from the #<3weeks group.

Conflict of interest

None declared

Acknowledgments

The project has received funding from the Society and College of Radiographers Industry Partnership Scheme (CORIPS).

We would like to thank Dr Adam Reuben for his assistance with recruitment and the participants for their time and input into this study.

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