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A study into post-traumatic and post-surgical disuse osteopenia and its short- and long-term effects.

Abstract

The aim of this study is to investigate the short and long term effects of disuse osteopenia (loss of bone density) resulting from immobilisation following lower limb fracture or total knee replacement. It will specifically look at effects on the hip as fractures at this site have the most significant consequences for patients in terms of loss of function and potential loss of life. The study will focus on post menopausal women over the age of 45 years as this group will be losing bone systemically and it is possible that immobilisation of a limb during this period may have the greatest long-term impact since the bone is least likely to fully recover.

Data will be used in a modelling study to infer structural changes and predict changes in fracture prevalence. This information may inform the potential use of therapeutic interventions such as drugs and exercises to restore bone density and reduce long term low trauma fracture risk in this population.

Aims

The aim of this study is to investigate the magnitude of disuse osteopenia at the clinically relevant fracture site of the hip in the following postmenopausal female populations:

•   Traumatic fracture in the lower limb treated with internal fixation.
•   Traumatic fracture in the lower limb treated with plaster of paris.
•   Post total knee replacement.
•   Age matched control group.

Methodology

150 patients will be recruited from the Orthopaedic Centre and the Royal Devon and Exeter Hospital immediately post treatment for traumatic fracture or prior to total knee replacement (TKR).   50 control participants will be recruited primarily by means of a poster and leaflet campaign. The study will focus on post-menopausal female patients aged 45 years and above. This age group will be losing bone systemically which is particularly accelerated in the 5 to 10 years post menopause, and it is possible that immobilisation of a limb during this period may have the greatest long-term impact since

the bone would be least likely to fully recover. This age group also frequently present with ankle fractures often resulting from relatively minor trauma, though ankle fractures are not considered at present to be an osteoporotic fracture.

Inclusion/Exclusion criteria

Included:-

Cases
Post menopausal women
> 45 years
Fractured lower limb within past 2 weeks or TKR

Controls
Post menopausal women
> 45 years

Excluded:-

Cases
Males
Pre-menopausal women
< 45 years
Treatment by external fixation

Controls
Males
Pre-menopausal women
< 45 years
Lower limb fracture or TKR post age 21 years.
Immobilisation of a lower limb for > 4 weeks within last 10 years or in post menopausal period.
Known knee osteoarthritis likely to result in a TKR within 1 year.
Corticosteroids >2.5mg for >3 months within last 5 years.

All patients will undergo a dual energy X-ray absorptiometry (DXA) scan of bilateral hips, lumbar spine and total body at each visit. Subgroups from the control and plaster of paris populations (with no contraindications) will also undergo MRI scans to look at cortical bone thickness.

An osteoporosis risk factor questionnaire will be completed at the first visit and any further fractures or changes in drugs or diseases known to affect bone metabolism will be recorded at subsequent visits. Periods of total immobility and partial immobility will be recorded at each visit and weight-bearing ability assessed using force plates.

To provide an objective assessment of weight-bearing activity we will measure habitual physical activity using an accelerometer. Data will be collected over a seven day period following visits at:

- Baseline
- 6 weeks post baseline
- 6months post baseline

In addition to this, a physical activity questionnaire will be used containing questions about types of activity, the intensity and duration of activity at the same time points as the accelerometer measurements. The activities will be graded to account for type and duration of weight-bearing activity.

The lower extremity functional scale developed by Binkley et al (1999) will be used on a weekly basis from baseline to the 6 weeks post baseline visit, followed by a monthly measurement for the rest of the study to assess functional recovery.

Quality of life and depression/anxiety questionnaires will be used to assess the social and psychological impact of fracture treatment and immobilization on the study participants.

The following visits are proposed:

Baseline:

Within 2 weeks of fracture or prior to surgery.
DXA: Lumbar spine, bilateral hips, total body.
MRI: T1, T2, STIR pulse sequences of bilateral hips (subgroups from plaster of paris and control groups only and no contra-indications to MRI).
Consent acquired.
Osteoporosis risk factor questionnaire, fracture / surgery history. Immobilisation recorded. Falls history.
Quality of Life questionnaire.
Depression and anxiety questionnaires.
Force plates to assess weight-bearing ability.
Accelerometer & instructions given.

6 weeks: (excluding control group)

6 weeks post first visit (up to 8 weeks post fracture / surgery)
DXA: Lumbar spine, bilateral hips, total body.
MRI: T1, T2, STIR- bilateral hips (subgroups from plaster of paris and control groups only).
Update of medical history, remobilisation history and falls history.

Quality of Life questionnaire.
Depression and anxiety questionnaires
Force plates to assess weight-bearing ability.
Accelerometer & instructions given.

6 months:

6 months post first visit
DXA: Lumbar spine, bilateral hips, total body.
MRI: T1, T2, STIR- bilateral hips (subgroups from plaster of paris and control groups only).
Update of medical history, remobilisation history and falls history.
Quality of Life questionnaire.
Depression and anxiety questionnaires
Force plates to assess weight-bearing ability.
Accelerometer & instructions given.

12 months:

12 months post first visit
DXA: Lumbar spine, bilateral hips, total body.
MRI: T1, T2, STIR- bilateral hips (subgroups from plaster of paris and control groups only).
Update of medical history, remobilisation history and falls history.
Quality of Life questionnaire.
Depression and anxiety questionnaires
Force plates to assess weight-bearing ability.

Potential Impact
The current research available on disuse osteopenia, particularly long-term unilateral disuse osteopenia is limited. Correct diagnosis means patients can be monitored and treated, reducing their future fracture risk. Most research is focused on spinal cord injury, stroke patients, astronauts and bed-rest volunteers and may not be directly comparable to the effects of immobilisation of a single limb. This research aims to investigate long-term disuse osteopenia in a wider population, including the fracture prevalence, and possible therapeutic interventions to provide a reduction in long-term low energy trauma fracture risk. This is an important consideration for all healthcare teams caring for patients with long-term limb immobilization.

Outcomes
The longitudinal changes will be compared using parametric (or non-parametric equivalents) tests such as ANOVA. It is aimed that multi-level modelling will be applied

to the longitudinal data, which will be able to correct for potential confounders such as age, race, immobilisation differences, drugs and diseases. Future fracture data, should there be sufficient, will be calculated using a Cox proportional hazard analysis to calculate the relative risk.

Scores from the accelerometer, activity questionnaire, and functional scale will be included in the multi-level modelling as categorical or continuous variables as appropriate and can therefore be adjusted for as confounders within the data.

Mechanical modelling will be performed using data from the DXA and MRI scans to infer future fracture risk in this population based upon changes in bone density and cortical thickness. This will provide a better understanding of the potential of future fracture at the hip following lower limb fracture in the postmenopausal period.

Patients diagnosed with osteoporosis and put onto bone-sparing drugs will be analysed separately to investigate the impact of such therapeutic interventions in fracture healing and the reduction of disuse osteopenia.   Statistically, it is possible that approximately 50% of participants in this study will be diagnosed with osteoporosis and thus may receive treatment.

Evaluation and dissemination strategy
The results from the study will be written up and presented at national and international conferences such as the UK Radiological Congress, National Osteoporosis Society Conference and the American Society for Bone and Mineral Research. Newsletters will be distributed to participants in the study every six months. Presentations will be made to interested user groups and to local clinicians and healthcare staff. Finally a number of papers will be written up for peer reviewed international level journals.

Timetable
October 2009 to August 2011: Ethical approval & data collection.
September 2011 to December 2011: Statistical analysis.
January 2012 to A

Literature review and references
Disuse osteopenia or osteoporosis is a well recognised complication of immobilisation [1-4].   In the majority of patients there is reversal of the disuse osteopenia upon remobilisation [5].   However, stress fractures distal to the acute fractures have been reported in a small minority of patients post lower limb fracture upon mobilisation [6]. Low energy trauma fractures have been reported in the lower-limb long-bones of paraplegics [7,8] and in non-ambulatory children with congenital conditions [9], demonstrating that disuse osteopenia results in an increased fracture rate.

There are few studies investigating disuse osteopenia in single limbs. Tandon et al. [10] reported reduced disuse osteopenia following external fixation of the tibia compared to

those placed in plaster of Paris, even though those who underwent external fixation had more severe fractures. Marchetti et al. [11] reported disuse osteopenia following shoulder surgery, which was partially reversed six weeks following remobilisation, whilst Rüegsegger et al [12] reported bone loss bilaterally post total hip replacement. One of the most frequently studied groups suffering disuse osteoporosis are astronauts following time spent in microgravity during space missions. Lang [13] reported that up to 15% of bone strength can be lost at the proximal femur over a 6 month flight. Rapid and severe bone loss has also been reported in patients suffering stroke [14] and in volunteers on bed-rest studies [15].

Studies of bed rest volunteers and spinal cord injury (SCI) patients have consistently reported an increase in markers of global bone resorption [15]. However, in most studies the markers of bone formation have remained unchanged, suggesting that there is no decrease in bone formation as a result of disuse osteopenia [15,16]. Maimoun et al. studied the effects of disuse osteopenia on osteoprotegerin (OPG) and reported that OPG was stimulated in SCI patients, whilst Receptor Activator for Nuclear Factor kB Ligand (RANKL) was inhibited. These results led them to hypothesise that OPG may provide a protective mechanism in the body. Whilst the OPG was deemed to have a protective role in this study, patients still lost bone and bone resorption markers were elevated, suggesting that the stimulation of OPG is insufficient to prevent osteoclastic proliferation and bone resorption [16]. Studies of bed rest volunteers have also reported increased urinary and faecal excretion of calcium coupled with increased serum calcium and decreased intestinal calcium absorption. Increased serum calcium results in low parathyroid hormone and vitamin D, a regulatory response to the increased bone resorption, which results in a decreased intestinal calcium absorption through the vitamin D mediated pathway [15,17-19].

Nutritional interventions have been reported to have a small influence of addressing the negative calcium balance in disuse osteopenia [20], and early remobilisation is the most important factor for the prevention of disuse osteopenia [7]. However, in patients where this is not possible, other therapeutic interventions may be required. The bisphosphonate Tiludronate has been demonstrated to be an effective treatment for disuse osteoporosis in paraplegic patients [21], whilst aldendronate has been demonstrated to be well tolerated and effective in non-ambulatory children [9]. In an animal study Ma et al [22] reported increases in trabecular bone in the tibiae of rats with continuously immobilised hind legs treated with 1,38 human parathyroid hormone (hPTH), suggesting this could be an effective treatment for disuse osteopenia. It is possible that non-pharmacological therapeutic interventions might improve disuse osteopenia such as weight-bearing exercise, or vibrating plates, both of which have been demonstrated to have positive effects on bone density [23,24].

In conclusion, the current research available on disuse osteopenia, particularly long-term unilateral disuse osteopenia is limited. Correct diagnosis means this patient can be monitored and treated, reducing her future fracture risk. Most research is focused on SCI, stroke patients, astronauts and bed-rest volunteers and may not be directly

comparable to the effects of immobilisation of a single limb. Further research is required to investigate long-term disuse osteopenia in a wide` population, including the fracture prevalence, and possible therapeutic interventions to provide a reduction in their long-term low energy trauma fracture risk. This is an important consideration for all healthcare teams caring for patients with long-term limb immobilisation and long-term future fracture risk and appropriate therapeutic intervention requires consideration.

References

1.	Kleerekoper M, Siris E and McClung M. The Bone and Mineral Manual. A Practical Guide. 2nd Edition. London: Elsevier Academic Press.
2.	Uebelhart D, Demiaux-Domenech B, Roth M, Chantraine A. 1995. Bone metabolism in spinal cord injured individuals and in others who have prolonged immobilisation. A review. Paraplegia, 33(11),669-73.
3.	Joyce JM, Keats TE. 1986. Disuse osteoporosis: mimic of neoplastic disease. Skeletal Radiol,15(2),129-32.
4.	Armstrong P, Wastie M, Rockall A. Diagnostic Imaging. 5th Edition. Blackwell Publishing.
5.	Janes GC, Collopy DM, Price R, Sikorski JM. 1993. Bone density after rigid plate fixation of tibial fractures. A dual-energy X-ray absorptiometry study. J Bone Joint Surg Br, 75(6),914-7.
6.	Zlatkin MB, Bjorkengren A, Sartoris DJ, Resnick D. 1987. Stress fractures of the distal tibia and calcaneus subsequent to acute fractures of the tibia and fibula. Am J Roentgenol, 149(2),329-32.
7.	Elias AN, Gwinup G. 1992. Immobilization osteoporosis in paraplegia. J Am Paraplegia Soc, 15(3),163-70.
8.	Mulsow J, O'Toole GC, McManus F. 2005. Traumatic lower limb fractures following complete spinal cord injury. Ir Med J, 98(5),141-2.
9.	Sholas MG, Tann B, Gaebler-Spira D. 2005. Oral bisphosphonates to treat disuse osteopenia in children with disabilities: a case series. J Pediatr Orthop, 25(3), 326-31.
10.	Tandon SC, Gregson PA, Thomas PB, Saklatvala J, Singanayagam J, Jones PW. 1995. Reduction of post-traumatic osteoporosis after external fixation of tibial fractures. Injury, 26(7),459-62.
11.	Marchetti ME, Houde JP, Steinberg GG, Crane GK, Goss TP, Baran DT. 1996. Humeral bone density losses after shoulder surgery and immobilization. J Shoulder Elbow Surg, 5(6),471-6.
12.	Rüegsegger P, Seitz P, Gschwend N, Dubs L. 1986. Disuse osteoporosis in patients with total hip prostheses. Arch Orthop Trauma Surg, 105(5),268-73.
13.	Lang TF. 2006. What do we know about fracture risk in long-duration spaceflight? J Musculoskelet Neuronal Interact, 6(4),319-21.
14.	Poole KE, Warburton EA, Reeve J. 2005. Rapid long-term bone loss following stroke in a man with osteoporosis and atherosclerosis. Osteoporosis Int, 16(3),302-5.
15.	Ziambaras K, Civitelli R, Papavasiliou SS. 2005. Weightlessness and skeleton homeostasis. Hormones, 4(1),18-27.

16. Maïmoun L, Couret I, Mariano-Goulart D, Dupuy AM, Micallef JP, Peruchon E, Ohanna F, Cristol JP, Rossi M, Leroux JL. 2005. Changes in osteoprotegerin/RANKL system, bone mineral density, and bone biochemicals markers in patients with recent spinal cord injury. Calcif Tissue Int, 76(6),404-11.

17. Heer M. 2002. Nutritional interventions related to bone turnover in European space missions and simulation models. Nutrition, 18(10),853-6.

18. Sato T, Yamamoto H, Sawada N, Nashiki K, Tsuji M, Nikawa T, Arai H, Morita K, Taketani Y, Takeda E. 2006. Immobilization decreases duodenal calcium absorption through a 1,25-dihydroxyvitamin D-dependent pathway. J Bone Miner Metab, 24(4), 291-9.

19. Schneider VS, McDonald J. 1984. Skeletal calcium homeostasis and countermeasures to prevent disuse osteoporosis. Calcif Tissue Int, 36 Suppl 1,S151-44.

20. Iwamoto J, Takeda T, Sato Y. 2005. Interventions to prevent bone loss in astronauts during space flight. Keio J Med, 54(2),55-9.

21. Chappard D, Minaire P, Privat C, Berard E, Mendoza-Sarmiento J, Tournebise H, Basle MF, Audran M, Rebel A, Picot C, et al. 1995. Effects of tiludronate on bone loss in paraplegic patients. J Bone Miner Res., 10(1), 112-8.

22. Ma YF, Jee WS, Ke HZ, Lin BY, Liang XG, Li M, Yamamoto N. 1995. Human parathyroid hormone-(1-38) restores cancellous bone to the immobilized, osteopenic proximal tibial metaphysis in rats. J Bone Miner Res.,1 0(3),496-505.

23. Gusi N, Raimundo A, Leal A. 2006. Low-frequency vibratory exercise reduces the risk of bone fracture more than walking: a randomized controlled trial. BMC Musculoskelet Disord, 30;7:92.

24. Rector RS, Rogers R, Ruebel M, Hinton PS. 2008 Participation in road cycling vs running is associated with lower bone mineral density in men. Metabolism,57(2), 226-32.