How do we improve assessment of fracture risk for individuals with type 2 diabetes?

Kara L Holloway-Kew[1], Pamela G Rufus-Membere[1], Muhammad A Sajjad[1], Lelia LF de Abreu[1], Mark A Kotowicz[1,2,3], Julie A Pasco[1,2,3]

1. Deakin University, Geelong, Australia; 2. Melbourne Medical School – Western Campus, Department of Medicine, The University of Melbourne, St Albans, Australia; 3. Barwon Health, Geelong, Australia

What is the problem?

Fractures are costly and debilitating. They are preventable with medications, however, these need to be targeted to those at high risk. The routine method of estimating fracture risk is to use dual energy X-ray absorptiometry (shown right). This measures bone mineral density, or the amount of bone present.

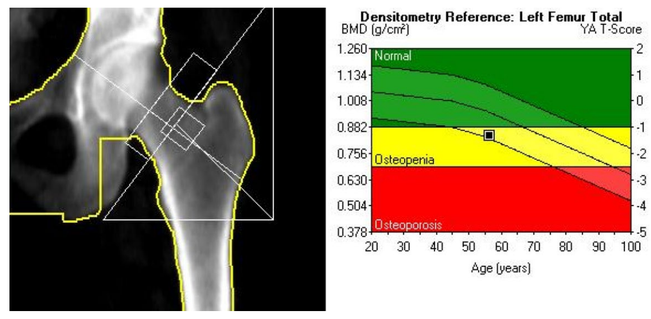
People with type 2 diabetes are at a higher risk of sustaining a fracture[1]. However, they have bone mineral density in the normal range, which is not reflective of their increased fracture risk[2]. This leads to the question: how can we better estimate fracture risk in people with type 2 diabetes?

What are the alternatives?

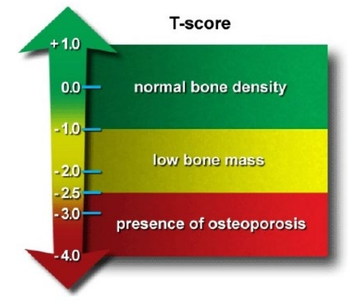
There are alternative methods for measuring bone, which measure properties that are not detected by dual energy X-ray absorptiometry. These include measurements of bone structure, turnover, strength and assessment of clinical risk factors. Results from the Geelong Osteoporosis Study for these alternative measures are shown below.

Dual energy X-ray absorptiometry is the routine method of assessing fracture risk.

Left: Dual energy X-ray absorptiometry machine



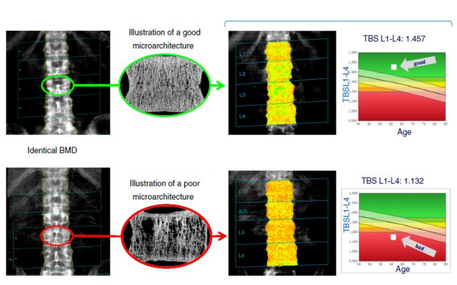
Above: Bone mineral density results from dual energy X-ray absorptiometry measurements at the hip. The software calculates a T-score, which is used to estimate risk of fracture.



Above: Diagram showing how bone mineral density results are used to estimate the risk of fracture. Even though people with type 2 diabetes are at a higher risk of fracture, they have bone mineral density T-scores in the normal (green) range.

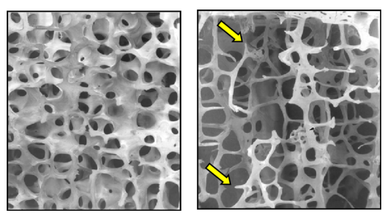
Images from
https://www.beyondphysio.com/dexa-bone-mineral-density-scan/
http://uisolutions.ca/amarhospital/detail.aspx?ref-id=4
https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/bone-densitometry

Trabecular Bone Score

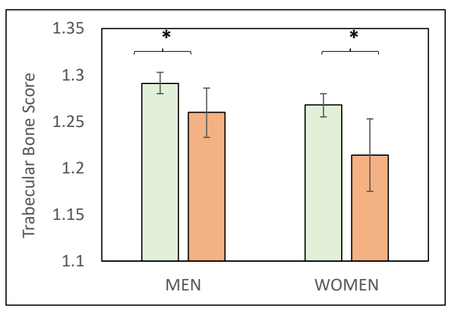


Trabecular bone score measures bone structure using spine scans obtained from dual energy X-ray absorptiometry. Bone mass and bone structure can differ. In the image[3] (left), the two patients have the same value for bone mineral density, but different trabecular bone scores.

Additionally, in the picture below[4], the left image shows normal bone, while the right image shows where microarchitecture has been degraded (yellow arrows), resulting in weaker bones.



Normal bone Degraded bone structure



Above: Trabecular bone score in men and women with (**orange**) and without (**green**) diabetes. *p<0.05

Results from the Geelong Osteoporosis Study[5] (left) show that trabecular bone score is lower in people with diabetes compared to those without diabetes (normoglycaemia). This indicates that bone structure is negatively affected in type 2 diabetes, even though bone mass is not and this may lead to increased bone fragility.

Bone Turnover Markers

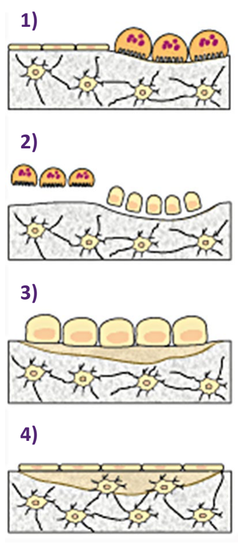


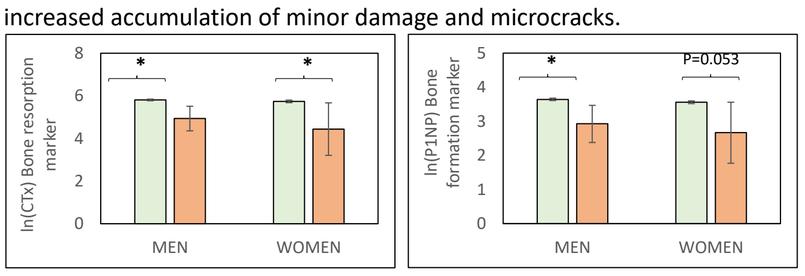
Image from:
https://www.iofbonehealth.org/introduction-bone-biology-all-about-our-bones

Bone undergoes constant renewal, repairing minor damage and microcracks which develop over time and can weaken the bone.

The image (left) shows the process of bone remodelling: 1) Osteoclasts remove damaged bone. 2) Osteoblast cells are recruited to the site and 3) deposit a layer of new bone. 4) Osteoblasts become bone lining cells on the new bone.

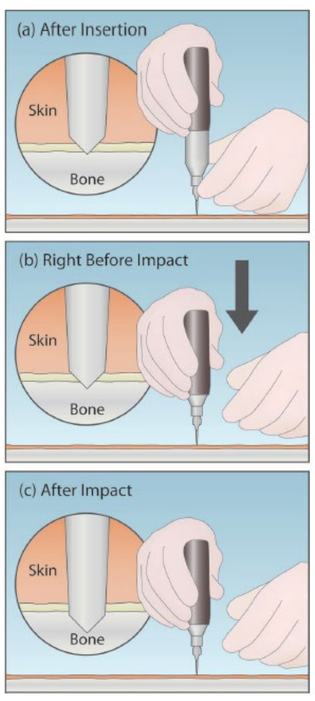
Bone remodelling can be measured using bone turnover markers in the blood. There are several, including C-terminal telopeptide of type 1 collagen (CTx) and Procollagen type 1 N propeptide (P1NP), which give an indication of bone resorption (step 1) and bone formation (step 3), respectively.

Results from the Geelong Osteoporosis Study are shown below[6]. People with diabetes have lower values of both bone resorption and formation markers than people without diabetes. This indicates that the bone fragility seen in diabetes may be related to a reduced bone turnover, resulting in increased accumulation of minor damage and microcracks.



Above: Bone resorption (left) and formation (right) markers in men and women with (**orange**) and without (**green**) diabetes. *p<0.05

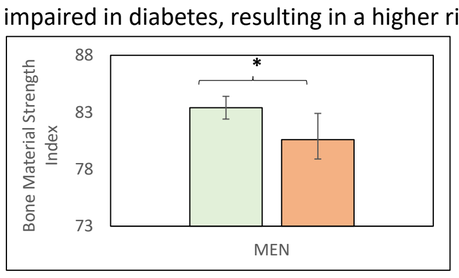
Impact Microindentation



Impact microindentation is a technique which allows the measurement of bone strength *in vivo*.
The steps for this technique are shown in the diagram[7] (left).

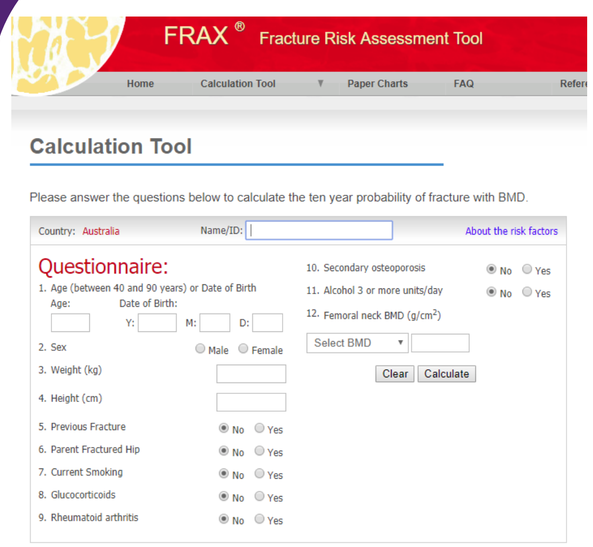
a) Following sterilisation and administration of local anaesthetic, the probe tip is inserted through the skin to rest on the bone surface.
b) The operator slides the outer housing of the device downwards, and the device generates a force of 40 Newtons.
c) The distance travelled by the probe tip is calculated and the software then converts this into a value called bone material strength index, or BMSi. The higher the BMSi, the more resistant the bone is to fracture.

Results from the male cohort of the Geelong Osteoporosis Study are shown below[8]. BMSi is lower in men with diabetes compared to those without diabetes. Other studies have also shown similar results in women[9-11]. These results indicate that bone strength may be impaired in diabetes, resulting in a higher risk of fracture.



Above: Bone material strength index values for men with (**orange**) and without (**green**) diabetes. *p<0.05

FRAX fracture risk assessment tool

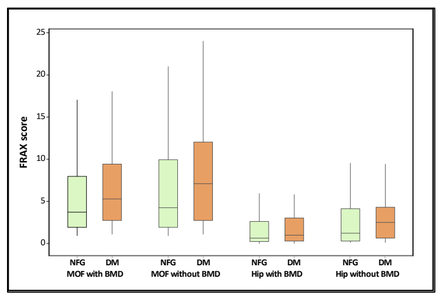


Right: Figure showing results of calculating FRAX scores for women with (diabetes mellitus (DM), **orange**) and without (normal fasting glucose (NFG), **green**) diabetes. MOF refers to the major osteoporotic fracture sites (hip, spine, forearm, proximal humerus). *p<0.05

The FRAX tool is a method of estimating the risk of hip or major osteoporotic (hip, spine, forearm, proximal humerus) fracture using clinical risk factors[12] (shown left). These calculations can be done with or without bone mineral density (bone mass).

It has been shown that FRAX underestimates the risk of fracture in people with diabetes[13].

Results from the female cohort of the Geelong Osteoporosis Study[14] (below) show that calculating FRAX without bone mineral density results in higher values, which is more reflective of the increased fracture risk in people with diabetes (DM) compared to those without diabetes (normal fasting glucose, NFG).



Conclusion

Although measurements of bone mineral density using dual energy X-ray absorptiometry are not effective at determining fracture risk in people with type 2 diabetes, other measurements of bone and fracture risk may prove useful. It is important to assess the utility of these measures in a clinical setting, and to investigate their ability to successfully predict fractures in longitudinal studies.

References

1. de Abreu LLF et al. Calcif Tissue Int 2019;104:262–72.
2. Holloway-Kew KL et al. Osteoporos Int 2019;30(9):1799-1806.
3. Ulivieri FM et al. Endocrine 2014;47:435–48.
4. Ström, O. et al. Arch Osteoporos 2011, 6: 59.
5. Holloway KL et al. Calcif Tissue Int 2018;102:32–40.
6. Holloway-Kew KL et al. Calcif Tissue Int 2019;104:599–604.
7. Bridges D et al. Rev Sci Instrum 2012;83:44301.
8. Holloway KL et al. Osteoporosis International, 29: S343.
9. Nilsson AG et al. J Bone Miner Res 2017;32:1062–71.
10. Furst JR et al. J Clin Endocrinol Metab 2016;101:2502–10.
11. Farr JN et al. J Bone Miner Res 2014;29:787–95.
12. University of Sheffield UK. FRAX ® WHO Fracture Risk Assessment Tool 2011.
13. Giangregorio LM et al. J Bone Miner Res 2012;27:301–8.
14. de Abreu LLF et al. Bone Reports 2019;11:100223.

IMPACT CENTRE FOR INNOVATION IN MENTAL AND PHYSICAL HEALTH AND CLINICAL TREATMENT

DEAKIN UNIVERSITY

GOS Geelong Osteoporosis Study

Barwon Health