Promising diagnostics for osteoporosis diagnosis and fracture risk prediction

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Introduction
Osteoporosis affects 200 million women worldwide, approximately 10% aged 60 and 67% aged 90. Within the UK, 50% of women and 20% of men will suffer a fracture after the age of 50 and annual rates are increasing. After a hip fracture, a high proportion of patients are unable to live without support as they cannot walk independently or perform other activities of daily living. Hip fractures are also associated with increased mortality; estimates of the relative mortality risk vary from 2 to >10 in the 12 months following a hip fracture. These issues are compounded by the asymptomatic nature of osteoporosis, which often remains undiagnosed until after a fracture occurs. It is widely recognised (eg by the National Osteoporosis Society and NICE) that accurate, low cost diagnostics that enable appropriate and individual patient management are required to significantly reduce this health burden.

As an engineering problem, one might compare bone mechanical functionality to that of an engineering structure such as a bridge. There are then three principal factors influencing mechanical performance: The architecture, the mass of construction material and the composition (quality) of the construction material. The first two of these are accessible through conventional imaging and bone mineral density (BMD) assessments determined by dual energy x-ray absorptiometry (DEXA).

However, it has been consistently demonstrated that BMD alone is a poor predictor of fracture; data from the Study of Osteoporotic Fractures (National Institutes of Health: results online) showed that 54% of new hip fractures occurred in women who did not have osteoporosis as determined by their BMD, while data from the National Osteoporosis Risk Assessment showed that 82% of post-menopausal women with fractures had bone of ‘normal’ BMD.

Enhancing risk assessment through the application of individual risk factors (eg WHO fracture risk assessment tool FRAX) is a relatively recent clinical tool but, to date, no diagnostic test is available for direct determination of bone quality characteristics.

Thus there has been some recent research effort to identify in vivo techniques that are able to provide complementary material information to support and augment conventional BMD measurement. Three such approaches are briefly described below.

1, Focal construct technology
It has been known since the discovery of x-rays that atomic and molecular material structures can be revealed through careful measurement of coherently scattered photons – this was how the structure of DNA was elucidated.

Unfortunately, although this scatter signature is always produced during radiographic imaging, it is several orders of magnitude smaller in intensity than the imaging photon component and thus specialist laboratory equipment is required for its measurement. Conventional data collections can be minutes to hours and reducing this time for dynamic studies has required increasingly powerful x-ray sources and detector efficiencies, all at significant financial cost. Medical diagnostics for disease such as breast cancer based upon coherent scatter have been developed previously but the requirement for large synchrotron x-ray sources has limited its use.

Recently a new approach has emerged that employs novel x-ray beam geometries to enhance the molecular signal intensity. Focal construct technology (FCT) employs hollow cones of x-rays to ‘focus’ the scatter signatures to single points thus enabling rapid data collections. The approach has recently been applied to the study of bone to augment conventional BMD assessments through the addition of bone quality information. In this case the target information has been characteristic of the bone mineral such as crystallite size, microstrain and chemistry.

Research by teams at Cranfield and Nottingham Trent Universities (led by Professors Keith Rogers and Paul Evans respectively) has recently shown significant differences in the coherent scatter from age-matched patients with hip fractures and those without (figure 1). Further, they have also demonstrated that FCT can be employed to measure these differences within ex vivo bone samples. A potentially useful additional discovery is that the beam topology of FCT enables depth resolved imaging simultaneous to the collection of coherent scatter. This presents the tantalising promise of a probe that simultaneously quantifies bone micro-architecture and material information.

The work has led to the design of a point-of-care instrument that could be utilised at primary care level, thus providing significant enhancement to individualised patient management (figure 2). This is being commercialised through Halo X-ray Technologies Limited, which aims to produce the first prototype within the next 24 months.

2, Raman spectroscopy
Another emerging technique with potential to diagnose osteoporosis non-invasively is a laser-based method, Raman spectroscopy. Although in its conventional form Raman spectroscopy is not capable of obtaining information below the surface of soft tissue, its recently introduced variant, spatially offset Raman spectroscopy (SORS), overcomes these limitations. Currently, the technique permits bone to be analysed non-invasively to depths of around 4-5mm but has a potential to reach even deeper with development in the near future. The method is currently being researched for bone disease diagnosis at several research centres worldwide including University College London/Science and Technology Facilities Council in the UK (team of Goodship, Parker and Matousek) and in the US by the University of Michigan, MI (team of Morris). Presently the technique is still in a research phase.

The key benefit of SORS lies in its ability to ‘see’ both the mineral and collagen components, unlike the current gold standard DEXA which visualises only the mineral constituent of bone. Since both the collagen and mineral components contribute significantly to the mechanical properties...
of bone, their individual assessment is critical and could lead to significant improvement of performance compared with DEXA if its potential is fully realised.

Conventional Raman spectroscopy relies on illuminating a sample with laser light and collecting a small fraction of (Raman) photons that changed colour due to interaction with the sample by transferring a part of their energy onto vibrations of individual molecules. In general, Raman spectroscopy provides exceptionally rich chemical information (chemical fingerprint). For bones one can simultaneously obtain information on both the mineral and collagen components of bone, a property which research is expected to translate into higher specificity and sensitivity of this technique in disease diagnosis. Data gathered from Raman can inform on mineral to collagen ratios, carbonate content of the mineral component, as well as on collagen quality.

SORS is a variant of Raman spectroscopy based on illuminating the sample at one location and collecting photons that changed colour (Raman photons) due to interaction with samples at locations away from the illumination point (eg 5-10mm away). In very simple terms, the larger the spatial offset, the deeper the zone the Raman signal originates from. Mathematical processing of data from the measurements at different spatial offsets can then yield pure chemical signature of bone and, as such, inform on the presence or absence of a disease/condition, which typically alters such chemical makeup.

The SORS bone research builds upon previous conventional Raman spectroscopy studies that have been used extensively in the analysis of bone matrix ex vivo. The arrival of SORS opens for the first time prospects of applying it in vivo at depth.

SORS was first applied to transcutaneous assessment of bone by attaining depths of a couple of millimetres through soft tissue both in animal and human cadavers. The technique was then advanced, accessing depths of around 4mm. Recently, the research moved on to in vivo trials on humans within the operating theatre, enabling researchers to perform a direct comparison, for the first time, of in vivo transcutaneous data with those obtained from in vivo exposed bone in surgery on the same patient. Good agreement was reached between the exposed and transcutaneous data. Specifically in the area of the diagnosis of osteoporotic conditions by SORS, further progress has been made very recently. Buckley et al. demonstrated the potential of SORS in this area, building on earlier advances by Morris’ group. Buckley et al.’s study showed that on average, bone fragments from the necks of fractured femora measured ex vivo have higher mineral content relative to collagen (by 5-10%) than (cadaveric) non-fractured controls. Both the mineralisation distributions of the two cohorts were found also to be considerably overlapped. SORS in vivo measurements (figure 3) indicated a potential of the presence of similar differences but these were as yet statistically not significant. The study also identified instrumental developments needed to reach the statistical significance level in future trials.

3. Reference point microindentation

Microindentation is a well-known laboratory technique for characterising material mechanical properties such as tensile strength. This quantitatively examines the indentations formed by a controlled load that produces plastic deformations in a material. A bone mineral strength index for cortical bone has been derived from such measurements. Recently this technique has been developed commercially for in vivo measurements (Biodent Hfe, ActiveLife Scientific). Reference point microindentation (RPI) has been applied to measurement of the tibia mechanical properties and has been shown capable of differentiating fracture and non-fracture patient groups. This has recently been extended to measurements of the femoral neck where RPI could distinguish controls from fracture cases independent of BMD and FRAX information. However, at this stage it is unclear which of the many potential nano-structural bone modifications is being directly or indirectly measured by RPI.

Conclusions

There is little doubt that with an ageing population and its consequent increasing health burden, science and medicine will strive to develop new tests for more accurate and point-of-care diagnostics. This is particularly important for osteoporosis where even a modest increase in fracture prediction accuracy would result in significant economic and health savings. Each of the techniques discussed here have the potential to achieve this and may even do so without the requirement to determine BMD. Each also has advantages and disadvantages and therefore a Darwinian process will occur to enable a single or combined technique to dominate this field of diagnostics in future.

References

Figure 2
The Halo fracture prediction instrument.

Figure 3
SORS instrument used at University College London/Science and Technology Facilities Council pre-clinical trials at RNOH Stanmore, UK. Custom developed by Cobalt Light Systems Limited (photo: STFC).