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The inferomedial femoral neck is compromised by age but not disease: Fracture toughness and the multifactorial mechanisms comprising reference point microindentation

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ABSTRACT

The influence of ageing on the fracture mechanics of cortical bone tissue is well documented, though little is known about if and how related material properties are further affected in two of the most prominent musculoskeletal diseases, osteoporosis and osteoarthritis (OA). The femoral neck, in close proximity to the most pertinent osteoporotic fracture site and near the hip joint affected by osteoarthritis, is a site of particular interest for investigation. We have recently shown that Reference Point micro-Indentation (RPI) detects differences between cortical bone from the femoral neck of healthy, osteoporotic fractured and osteoarthritic hip replacement patients. RPI is a new technique with potential for in vivo bone quality assessment. However, interpretation of RPI results is limited because the specific changes in bone properties with pathology are not well understood and, further, because it is not conclusive what properties are being assessed by RPI. Here, we investigate whether the differences previously detected between healthy and diseased cortical bone from the femoral neck might reflect changes in fracture toughness. Together with this, we investigate which additional properties are reflected in RPI measures. RPI (using the Biodent device) and fracture toughness tests were conducted on samples from the inferomedial neck of bone resected from donors with: OA (41 samples from 15 donors), osteoporosis (48 samples from 14 donors) and non age-matched cadaveric controls (37 samples from 10 donoros) with no history of bone disease. Further, a subset of indented samples were imaged using micro-computed tomography (3 osteoporotic and 4 control samples each from different donors) as well as fluorescence microscopy in combination with serial sectioning after basic fuchsin staining (7 osteoporotic and 5 control samples from 5 osteoporotic and 5 control donors). In this study, the bulk indentation and fracture resistance properties of the inferomedial femoral neck in osteoporotic fracture, severe OA and control bone were comparable ($p > 0.05$ for fracture properties and $< 10\%$ difference for indentation) but fracture toughness reduced with advancing age (7.0% per decade, $r = -0.36$, $p = 0.029$). Further, RPI properties (in particular, the indentation distance increase, IDI) showed partial correlation with fracture toughness ($r = -0.40$, $p = 0.023$) or derived elastic modulus ($r = -0.40$, $p = 0.023$). Multimodal indent imaging revealed evidence of toughening mechanisms (i.e. crack deflection, bridging and microcracking), elastoplastic response (in terms of the non-conical imprint shape and presence of pile-up) and correlation of RPI with damage extent (up to $r = 0.79$, $p = 0.034$) and indent size (up to $r = 0.82$, $p < 0.001$). Therefore, crack resistance, deformation resistance and, additionally, micro-structure (porosity: $r = 0.93$, $p = 0.002$ as well as pore proximity: $r = -0.55$, $p = 0.027$ for correlation with IDI) are all contributory to RPI.

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Consequently, it becomes clear that RPI measures represent a multitude of properties, various aspects of bone quality, but are not necessarily strongly correlated to a single mechanical property. In addition, osteoporosis or osteoarthritis do not seem to further influence fracture toughness of the inferomedial femoral neck beyond natural ageing. Since bone is highly heterogeneous, whether this finding can be extended to the whole femoral neck or whether it also holds true for other femoral neck quadrants or other material properties remains to be shown.

1. Introduction

Osteoporosis and osteoarthritis are two of the most prevalent and impactful musculoskeletal disorders. However, the primary means of clinically assessing osteoporosis (Bone Mineral Density, BMD) has poor accuracy. BMD does not detect a high proportion of individuals who go on to fracture when used as a binary test (based on a t-score of −2.5) (Schuit et al., 2004; Siris et al., 2004). As a result, other differences in bone quality such as structure (e.g. cortical thinning, increased porosity or reduced trabeculae connectivity (Poole et al., 2010; Bell et al., 1999; Keaveny and Yeh, 2002)), composition and material properties may contribute to osteoporosis. This rationale has moved the definition of osteoporosis away from BMD alone towards a condition of compromised mechanical integrity and increased fracture risk (NIH, 2000). Osteoarthritis, however, is primarily a condition of joint degeneration, which causes considerable pain and disability. There is increasing evidence of changes to bone in osteoarthritis and not just cartilage including; stiffening of the trabeculae and subchondral bone, elevated BMD and deformities/altered biomechanics of the femoral head and neck (Baker-LePain and Lane, 2012; Bobinac et al., 2013; Arden and Nevitt, 2006; Sun et al., 2008). Therefore, both in osteoporosis and osteoarthritis there may be influence of changes of bone material properties. Of particular interest is the femoral neck site, which is in close proximity to the most clinically severe osteoporotic fracture and is also close to the affected joint in osteoarthritis. Although there is evidence for deterioration in bone material properties with age (Zioupos and Currey, 1998; Burstein et al., 1976; Nalla et al., 2006; Koester et al., 2011; Jepsen, 2003), a risk factor for both osteoporosis and osteoarthritis, there is surprisingly limited research whether these properties deteriorate as a function of these two pathologies.

With ageing, there may be deteriorations to bone quality including the susceptibility to microcracks and microdamage. The ability to withstand propagation of existing cracks and, ultimately, the resistance to fracture, is therefore a valuable material property to consider. This property in particular, relating to fracture resistance and toughness, deteriorates with age (by 2.9–18.9% per decade (Nalla et al., 2006; Koester et al., 2011; Granke et al., 2015; Brown et al., 2000)) but it is unclear whether it is further compromised with osteoporosis or osteoarthritis, particularly at the femoral neck, the most clinically relevant fracture site. It may be fairly logical to assume that fracture toughness, the ability to resist fracture, is compromised with osteoporosis. Additionally, the discussed influence of osteoarthritis on bone mechanics also warrant investigation into further material properties including fracture toughness. However, there are surprisingly few studies that directly compare OA or osteoporotic bone to non-diseased controls. A small number of studies have investigated properties including, but not limited to; microhardness (Dall'Ara et al., 2011), energy absorption (Dickenson et al., 1981), ultrasound stiffness (Li and Aspden, 1997), and reference point indentation properties utilising the cyclic indentation technique of this study (the Biodent™) or a sudden impact indent proposed for clinical use (the Osteoprobe™) (Jenkins et al., 2016; Malgo et al., 2015; Diez-Perez et al., 2010; Gueerri-Fernandez et al., 2013; Milovanovic et al., 2014; Coutts et al., 2016). However, the comparison between either discussed disease and a control is still limited, particularly if considering cortical bone. Therefore, beyond the effects of ageing, the influence of both OA and osteoporosis on the material properties of bone demands further exploration. This is of particular importance in terms of fracture toughness and considering the femoral neck where the authors are not aware of any published research.

Reference Point micro-Indentation (also referred to in the literature as RPI, microindentation and Reference Point Indentation) is a technique that has been proposed for measuring the material properties of bone in vivo with the aim to supplement BMD (Jenkins et al., 2016; Malgo et al., 2015; Diez-Perez et al., 2010). This aims to overcome limitations of current fracture risk assessment techniques by introducing assessment of mechanical properties. The technique, which uses a reference probe to establish the surface and a test probe to cyclically indent into the bone, has shown some ability to discriminate osteoporotic (Jenkins et al., 2016; Malgo et al., 2015; Diez-Perez et al., 2010; Gueerri-Fernandez et al., 2013; Milovanovic et al., 2014) and osteoarthritic (Coutts et al., 2016) bone from non-diseased controls. Notably the technique has also been applied in vivo at the tibia, discriminating individuals who have fractured from non-fractured controls and reporting no complication (Diez-Perez et al., 2010; Gueerri-Fernandez et al., 2013). Further studies also investigate the Osteoprobe RPI method, also reporting no complications (Randall et al., 2013), yet this uses a different loading regime (one single impact cycle). *In vivo*, neither technique can be used directly at the site of interest, the most significant fracture site, the femoral neck, so in vitro studies are required to study this important location.

RPI has also been suggested to be distinct from conventional indentation testing (such as nanoindentation), in that the imprints are associated with microdamage (Diez-Perez et al., 2010; Beutel and Kennedy, 2015; Schneider et al., 2013) and it has therefore been purported to assess fracture resistance properties to varying extents (Granke et al., 2015; Diez-Perez et al., 2010; Katsamenis et al., 2015; Carriero et al., 2014). Specifically, RPI properties have shown high correlation with fracture toughness (Diez-Perez et al., 2010) but also a higher degree of independence (Granke et al., 2015; Katsamenis et al., 2015) as well as complete lack of correlation (Carriero et al., 2014). Furthermore, RPI has also shown correlation with elastoplastic resistance to deformation such as strength and toughness (Granke et al., 2015; Gallant et al., 2013) so it is still unclear what property this technique is assessing. Additionally, we have demonstrated that indentation properties vary with location (Coutts et al., 2015) and machining of the femoral neck (Jenkins et al., 2015). Though other indentation techniques are better understood for measuring the localised properties of bone (e.g. the established relationship between elastic modulus derived from nanoindentation), it is the clinical potential of RPI that makes it of particular interest in this study. Further, both osteoporosis and OA likely influence the RPI properties of the bone, including the surface properties of the femoral neck. However, it is still unclear how the indentation properties of the bulk of the femoral neck are influenced by disease or what (material) property or properties is/are being assessed by the technique.

In terms of RPI, or the development and interpretation of any clinical fracture risk assessment technique, it is critical to understand both the bone properties influenced by the disease state and how the technique may assess these deteriorations in properties. Therefore, this study, investigates two research questions: 1) what are the differences in selected bone material properties between osteoporosis, OA and controls and 2) what properties are being assessed by reference point microindenation?