Development of a novel imaging process to determine the clinical applicability of bone mineral density assessment of the osteoarthritic knee: a research proposal.

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Abstract

Osteoarthritis (OA) causes pain and reduced mobility. The primary outcome measure of radiography for knee OA is joint space narrowing (JSN), which occurs late in disease progression, often alongside increased patient reported symptoms, making radiography unsuitable for early diagnosis. Dual-energy X-ray absorptiometry (DXA), a measure of areal bone mineral density (aBMD), has the potential to be used as an earlier marker of OA-associated bone changes than radiographic imaging, thereby potentially also preceding increases in patient reported symptoms. Changes in aBMD may occur before JSN in patients with knee OA, but the accuracy with which aBMD represents OA pathogenesis is currently unclear. Measures of aBMD theoretically increase in proportion with bone depth, regardless of density, which means that osteoarthritis-associated changes in tibial bone depth may falsely elevate aBMD. This study aims to create an accurate estimate of volumetric bone mineral density (vBMD), and to explore the relationship between bone mineral density (BMD) and anthropometric measures. A population of 30 retrospectively, consecutively selected patients with Kellgren-Lawrence grade II-IV knee OA will be established from an existing research cohort. Previously collected knee DXA images will be co-registered with knee magnetic resonance imaging (MRI). Tibial bone depth will be calculated from MRI and each participantcipaBMD score will then be adjusted accordingly. The relationship between adjusted (vBMD) and unadjusted (aBMD) scores will be explored. Measuring bone changes early in the development of knee OA using DXA could be a relatively cheap, non-invasive and fast method for targeting preventative treatment, thus potentially minimising the pain and loss of mobility associated with progressive knee OA

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Introduction

Osteoarthritis of the knee causes pain and disability. Degeneration of the cartilage was traditionally considered to be the primary change associated with OA, but in recent years evidence has emerged to suggest that it is a disease of the entire joint, involving interactions between different tissues (Javaid and Arden, 2013).

Treatments to prevent, slow down or halt OA progression may help to prevent the associated pain and loss of function frequently reported by patients, and avoid invasive joint replacement surgery in the future. A recent study demonstrated that the drug Strontium Ranelate slowed down the progression of radiographic joint space narrowing associated with knee OA, as well as reducing pain in patients with knee osteoarthritis compared to those without the disease (Reginster et al 2013). Knee OA progresses at different rates in different people, so in some patients it never becomes severe and thus never requires joint replacement surgery. If preventative treatments are to be targeted to those that need it most, the use of diagnostic imaging is likely to be integral.

Radiographs are currently the most commonly used radiological imaging technique for the diagnosis and monitoring of knee OA, by identifying

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changes such as joint space narrowing (JSN), a radiographic manifestation of cartilage loss. These changes though, occur relatively late on during the disease, making radiography unsuitable for early disease detection (Bruyere et al, 2003). In addition, one study found that 15-81% of participants with radiographic knee OA experienced knee pain, and 15-76% of those with knee pain has radiographic evidence of knee OA. This suggests that knee pain is an imprecise marker of radiographic knee OA, and that radiography is inadequate for predicting the onset of OA-associated knee pain or disability (Bedson and Croft, 2008).

On the other hand, abnormalities detected by Magnetic Resonance Imaging (MRI) explain knee pain in osteoarthritis (Yusuf et al, 2011), making MRI a useful clinical utility in patients that present with clinical knee OA, but whose radiographs demonstrate no evidence of the disease. Bone marrow lesions have also been shown to predict disease progression (Driban et al, 2013), and changes in their volume are detectable by MRI within 6-12 weeks (Felson et al, 2012), whereas changes in cartilage structure are not detectable over a 6 month period (Hunter et al, 2010). This evidence supports the monitoring of bone marrow lesions to identify short-term structural changes in response to therapeutic intervention. On the other hand, MRI is currently expensive and time-consuming, which limits its universal application to a disease which is likely to grow in prevalence globally, as a consequence of an ageing population and obesity epidemic (Cross et al, 2013). Quantitative computed tomography (pQCT) is sensitive to certain disease changes, but is also expensive, not routinely available in clinical practice, and emits a high dose of ionising radiation, which can be harmful to patients.

Dual-energy X-Ray Absorptiometry (DXA) scanning estimates the strength of a selected area of bone by measuring its areal density, and therefore may be able to measure OA-associated changes in bone structure that occur prior to JSN. It benefits from being relatively fast, cheap, readily available in clinical practice and emits a significantly lower dose of ionising radiation than pQCT and radiography. On the other hand, the bone around the joint of an osteoarthritic knee expands. As DXA is only a two-dimensional (2D) measurement, it does not account for bone depth. Any significant increase in such may falsely elevate measurement, thus leading to an overestimation of bone strength in knee OA patients. The main aim of this study is therefore to determine the potential relationship between bone depth adjusted and standard BMD in patients with knee OA. A series of objectives are therefore as follows: to create an accurate estimate of vBMD, to explore the relationship between aBMD and vBMD, and to determine whether aBMD and vBMD are correlated with anthropometric measurements.

Literature Review

Osteoarthritis is a common, degenerative joint disease associated with pain and loss of function (Bijlsma et al, 2011). The societal and financial implications are also noteworthy (Litwic et al, 2013), whilst incidence is rising in line with an ageing population and the epidemic of obesity (Bijlsma et al, 2011). The eventual clinical outcome for many patients with knee and hip OA is total joint replacement (Dieppe et al, 1999). Although joint replacement manages symptoms and returns function for the majority, it is an invasive and expensive procedure that is only effective for a limited amount of time (Pelletier et al, 2013). This highlights the importance of effective diagnosis and treatment, with early identification being critical to clinical decision making and targeting of therapeutic intervention. This is particularly pertinent in light of the positive effects demonstrated by the drug Strontium Ranelate in a recent double-blind, randomised placebo-controlled trial (Reginster et al, 2013). In comparison to controls, participants given the drug experienced significantly less JSN. Those given 2g/day experienced greater reductions in pain sub-scores and negative health outcomes associated with OA, than those given 1g/day. This study illustrates that future knee OA treatment may be focused on prevention rather than surgical intervention, and highlights the importance for developing diagnostic imaging techniques to facilitate such.

In the majority of cases diagnostic assessment of OA involves the combination of clinical history, physical examination and radiographic imaging (Braun and Gold, 2012). For investigation of knee OA, imaging most commonly comprises radiographs in two planes: weight bearing antero-posterior (AP) and lateral (Chaisson et al, 2000). During the progression of OA, multiple boney changes may occur, including: osteophyte development, subchondral sclerosis, subchondral cysts and JSN (Braun and Gold, 2012). Several semi-quantitative methods have been developed for grading the severity of OA from a radiograph (Marshall et al, 2008; Hellio Le Graverand et al, 2009; Trivedi et al, 2010). The Kellgren-Lawrence (KL) grading system (Kellgren and Lawrence, 1957) is validated (Kijowski et al, 2006) and commonly used in clinical practice to determine the severity of OA at the tibio-femoral joint (Emrani et al, 2008).

Joint space narrowing is the most commonly used measure of disease progression detected by radiography (Emrani et al, 2008). In the cycle of knee OA, though, cartilage thickness initially increases, before decreasing as the disease progresses (Bet al, 2 et al, 1995). This makes radiography detected JSN unsuitable for early disease diagnosis. In addition, Kijowski et al (2006) reported sensitivity of JSN for the detection of cartilage degeneration in the medial tibio-femoral compartment as 67% (95% CI: 58-75), whilst sensitivity of other radiography detected bone changes ranged from 10-46%, and figures at the lateral compartment were lower for all measures. The study was open to selection bias as all participants in the study group were symptomatic and selected from a database of MRI knee examinations performed at the centre in the preceding years. Even so, use of cartilage degeneration by arthroscopy seems an appropriate reference gold standard, and the design was suitable for a diagnostic test study. The sensitivity of radiographic features to the presence of knee OA pathophysiology were sub-optimal, thus presenting a major limitation of radiography, and indicating room for advancement in the radiological diagnosis of knee OA.

Traditionally, breakdown of joint cartilage was thought to be the primary change associated with OA. In recent years, though, evidence has emerged suggesting that OA is a disease involving the entire joint (Javaid and Arden, 2013).

In 1986, Radin and Rose suggested that bone, in addition to cartilage, absorbs shock placed on joints by impact loading, and that high cortical bone mass may favour OA development, given the associated increased mechanical stress on cartilage. Indeed, in 1993 Dieppe et al used bone scintigraphy to demonstrate that bone changes occur very early on in the progression of OA, the first undetectable by radiography. Using a cohort study design over a five-year period, the authors were able to prospectively determine early risk factors for knee OA progression. Although internal validity is slightly limited by what is a relatively short follow-up period in the cycle of OA progression, the study is otherwise robust in design. The findings were reinforced by Buckland-Wright et al (1996), who found that changes in bone structure were strongly correlated with the degree of joint space loss in 90 osteoarthritic knees, and that the earliest change to subchondral bone was an increase in the thickness of horizontal trabeculae. This suggests that cortical bone nearest to the joint, and trabecular bone directly distal to it, increase in density during knee OA, warranting investigation of imaging techniques that could measure these changes.

Distal to these areas of increased density, evidence suggests that trabecular bone decreases in strength. Karvonen et al (1998) used DXA to measure periarticular regions of the knee in both postero-anterior (PA) and lateral projections, producing three-dimensional (3D) estimates of bone strength. Comparing a group of 62 patients with mild knee OA to a group of 62 without knee OA, they reported statistically significant decreases in aBMD in all subchondral regions. In addition, they compared bone mineral density (BMD) measured in one projection (2D), to BMD measured in two projections (3D). They found that the average BMD of the study group compared to the controls was 7.3% lower by 2D measurement, and 13.3% lower by 3D measurement. The OA group only had mild OA, limiting external validity to this group. Nevertheless, findings suggest that not only does BMD decrease in some regions of periarticular bone of the tibia with mild OA independent of osteoporosis at other sites, but also that 2D measurement is confounded by bone depth in this group. As tibial bone size appears to be positively correlated with OA progression (Ding et al, 2007), this effect could be more profound in the later stages of knee OA, meaning that bone changes measured by DXA could be inaccurate at present.

DXA is a bone densitometry scanning technique, whereby the density of a given area of bone is estimated (Bonnick, 2010), based on the amount of x-radiation absorbed in that region. With the ability to quantify bone density in almost every region of the body, DXA has many potential roles in clinical practice (Bonnick, 2010). When applied to patients with knee osteoarthritis, it has proven to predict radiographic joint space narrowing of the knee, indicating a potential role in monitoring early stage OA (Bruyere et al, 2003). DXA also offers many advantages over other densitometry techniques, such as peripheral quantitative computed tomography, in that it is faster, emits a lower amount of radiation, has a higher level of precision and is readily available in clinical practice (El Maghraoui et al, 2006).

Despite the benefits of DXA, though, it is limited by being a 2D imaging technique. It measures density within a given area of bone (width multiplied by height), thus the depth of a bone is not accounted for. Bone depth subsequently seems to influence aBMD measurement in populations where bone size changes, such as paediatrics (Cvijetit and Kord t, 2004). Some studies using DXA have reported that aBMD of the tibia increased in patients with knee OA (Bruyere et al, 2003; Clarke et al, 2004), whereas a study using the 3D technique pQCT found that volumetric bone size, not volumetric bone mineral density (vBMD), increased with knee OA (Abdin-Mohamed et al, 2009). It is possible, therefore, that the observed increase in aBMD amongst patients with knee OA in these studies is artifactual, caused by an increase in bone depth that is associated with OA (Ding et al, 2007), as opposed to an increase in density. One might initially consider this clinically relevant, because if aBMD is significantly higher in the bone of an OA-affected joint, then it could be used to differentiate patients with knee OA from those without. In reality, this is extremely undesirable. An increase in BMD measurement suggests a decrease in fracture risk (Unnanuntana et al, 2010), whereas evidence suggests that the opposite is true for OA patients- that they are at increased risk of fracture (Arden et al, 1996; Arden et al, 1999; Bergink et al, 2003). The relationship between OA, osteoporosis and fracture risk is complex (Javaid and Arden 2013). If DXA is to be utilised to facilitate early diagnosis of knee OA, it may also have an application for monitoring fracture risk in this population. If DXA is to be used to target therapeutic intervention to those at highest risk of OA and/or fracture, then a high degree of accuracy is vital.

Carter et al (1992) proposed an early method of accounting for bone size using DXA. Areal bone mineral density is calculated by dividing bone mineral content by the projected area of the bone being measured. The authors recognised that any region of bone being measured has an average depth, and that to know this factor would allow calculation of volumetric bone mineral density, and thus removal of any confounding influence of bone depth. It was therefore estimated by inputting factors that were expected to scale proportionally to it. Three methods were tested for calculating bone depth, each with a different assumption. The first was that bone width, length and depth are all proportional, or in other words, the bone is cuboid in shape. The second method assumed that the whole skeleton is geometrically similar, and that bone depth is proportional to height. The third method assumed that the average width of the bone is proportional to the average depth of the bone. Although these approaches seem to remove a dependence of aBMD on a patientientt bone width, length and depth are all proportional, or in other words, the bone is cuboid in shape. The second method assumed that the whole skeleton is geometrically similar, and that bone depth have not yet been applied to knee DXA scans in a population with knee osteoarthritis.

Another approach is to combine PA and lateral DXA scans of the region of interest (Duboeuf et al. 1994). Postero-anterior aBMD correlates significantly with height and weight at the 1% level, and body mass index at the 5% level (Jergas et al. 1995). By accounting for bone depth using the lateral scans, no significant correlation was found with any of these factors. This further suggests that PA aBMD is dependent on bone size. The extra time, cost and ionising radiation

exposure associated with performing an additional, lateral, projection limit the value of the potential application of this approach in clinical practice.

Two-dimensional medical imaging techniques, such as DXA, are able to measure the area of a bone: width multiplied (X) by height. Three-dimensional techniques, such as MRI, have the ability to measure the volume of a bone: width X height X depth. Whilst DXA benefits from being able to measure bone mineral density, it is limited by only being able to measure this within a given area of bone rather than within a volume. MRI is unable to measure bone mineral density, but it is capable of measuring bone volume. Combining a measure of volume from MRI, with a measure of density from DXA, offers a novel approach to estimating the volumetric density of bone, which is potentially more accurate than other estimates. To the author's knowledge there are currently no published approaches that co-register DXA images with a 3-dimensional imaging technique, such as MRI, to estimate vBMD. This study therefore aims to create an accurate estimate of vBMD, to explore the relationship between aBMD and vBMD, and determine whether aBMD and vBMD are correlated with anthropometric measurements.

Research Question

Are bone mineral density measurements of the osteoarthritic knee falsely elevated by anthropometric factors?

Null Hypotheses

1. Areal and volumetric bone mineral density measures of the osteoarthritic knee are uncorrelated
2. Areal bone mineral density is uncorrelated with height, weight and tibial length
3. Volumetric bone mineral density is uncorrelated with height, weight and tibial length

Proposed Design

This proposal uses existing data gathered as part of an ongoing epidemiological cohort study; the VIDEO trial. The VItamin D Evaluation in Osteoarthritis (VIDEO) trial is a randomised, double-blind, placebo controlled study of Vitamin D supplementation in the management of symptomatic knee OA. The study was conducted began in 2005 as a collaboration between the Medical Research Council Clinical Trials Unit (MRC CTU), Royal National Orthopaedic Hospital, Royal Free and University College London.

A retrospective cross-sectional design using a repeated measures analysis will be utilised to observe MRI and DXA images. To date, few studies of this nature have been reported, and as such sample size estimation was prohibited. A sample size of 50 patients was therefore pragmatically selected.

The target population is patients with osteoarthritis of the knee and a KL grade 2-3. DXA and MRI scans of their OA-affected knee must have been performed within 1 month of each other, to limit changes in bone structure between scans. Inclusion and exclusion criteria for this project are detailed in table 1.

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
KL-grade II-IV radiographic OA of the knee	Knee DXA scan incomplete/insufficient information
Had DXA and MRI of their OA-affected knee	Knee MRI scan incomplete/insufficient information
DXA and MRI scans performed within one month of each other	Knee DXA or MRI data unavailable

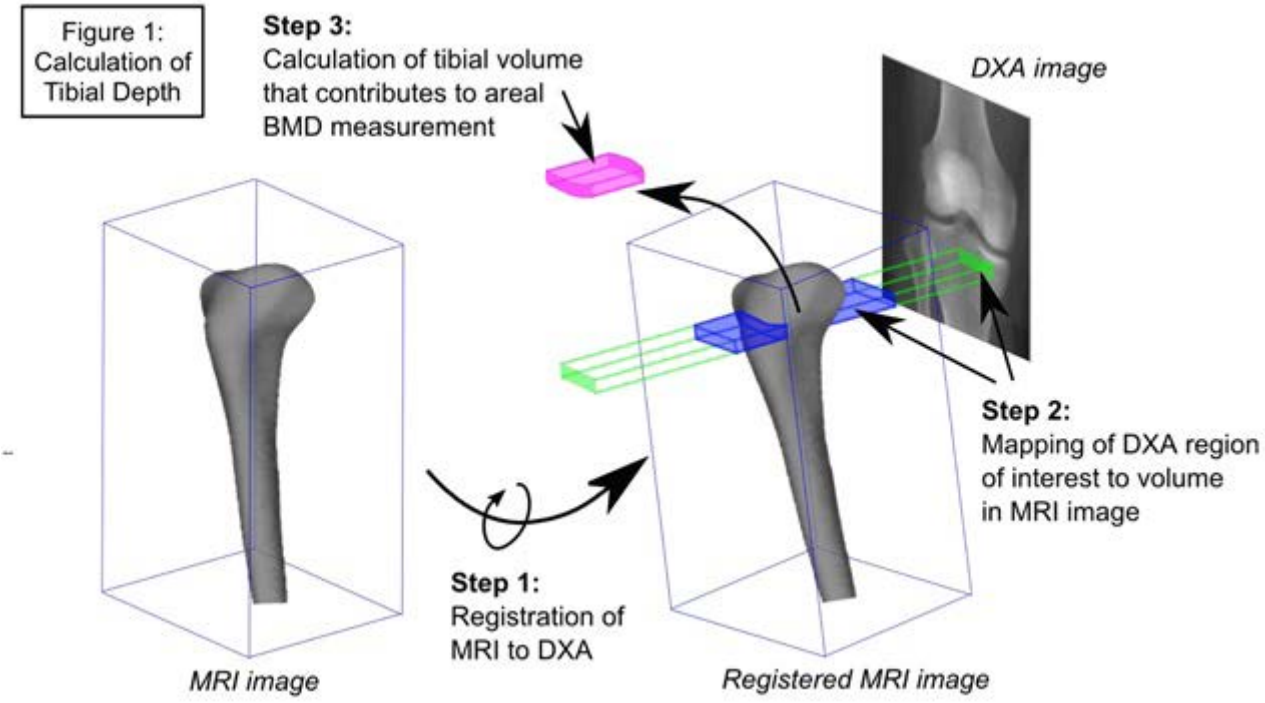
Data Analysis

The first step of data analysis will be to identify two regions of interest (ROI 2-3. DXA and MRI scansaBMD and vBMD. Femoral and tibial cartilage degeneration occurs at a similar rate and stage in the presence of knee OA, but measuring the bone of the distal femur with 2D imaging techniques like DXA is limited by the superimposition of the patella, the position of which is highly dependent on the position of the patients knee during the scan (Cicuttini et al, 2001). Consist with previous studies, and to maximise reproducibility, only the proximal tibia will be analysed during this study. Current evidence suggests that aBMD of cortical bone at the proximal tibia increases in the presence of knee OA (Clarke et al, 2004), whereas aBMD of the trabecular bone distal to it may decrease in density (Karvonen et al, 1998). Other osteoarthritis-associated changes that affect aBMD, such as osteophytes, are most common nearest the joint - where cortical bone is abundant (Nagaosa et al, 2002). To minimise confounding variables, regions that incorporate solely trabecular bone have been selected. Structural changes to bone associated with knee OA differ between the medial and lateral compartments (Lo et al, 2006), so two regions will be created: one medial and one lateral. Hologic DXA software will be used to apply the ROIthe ROIolely trabecular bone have been selected. Structural changes to bone associate

The image files for the analysed knee DXA scans, the whole-body DXA scans and knee MRI scans will be exported. Software will then be created to co-register DXA and MRI data, a process that is summarised in figure 1. The average depth of the tibia at the previously determined regions of interest on the DXA image will then be calculated. This process will be repeated for intra-rater agreement analysis. Volumetric BMD will be calculated by dividing BMC by the average depth of the tibia.

Statistical Analysis

All analysis will be conducted using IBM SPSS (version 21). The distribution of aBMD and vBMD scores will be analysed by observing a histogram. Assuming normality, two tests of intra-rater agreement will be performed using a two-way mixed intra-class correlation model: one of applying the ROI's to the knee DXA image, one of calculating average tibial depth. A Pearson correlation test, or Spearmanearmansts of intra-rater agreement will be performed using a two-way mixed intra-class correlatationship between aBMD and vBMD. The same test will then be used to determine whether aBMD and



vBMD are correlated with height, weight and tibial length (estimated from whole body DXA scans).

Ethical Considerations and Approval

All participants of the VIDEO study provided written informed consent for their participation. The study protocol received approval from the Scottish Main Research Ethics Committee (MREC), and Local Research Ethics Committee (LREC) approval was obtained at each site of participant recruitment.

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