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Tissue material properties and computational modelling of the human knee: A critical review

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Understanding how structural and functional alterations of individual tissues impact on whole-joint function is challenging, particularly in humans where direct invasive experimentation is difficult. Finite element computational models produce quantitative predictions of the mechanical and physiological behaviour of multiple tissues simultaneously, thereby providing a means to study changes that occur through healthy ageing and disease such as osteoarthritis. As a result significant research investment has been placed in developing such models of the human knee. Previous work has highlighted that model predictions are highly sensitive to the various inputs used to build them, particularly the mathematical definition of material properties of biological tissues. The goal of this systematic review is two-fold. First, we provide a comprehensive summation and evaluation of existing material property data for human knee joint tissues, tabulating numerical values as a reference resource for future studies. Second, we review efforts to model whole-knee joint mechanical behaviour through finite element modelling with particular focus on how studies have sourced tissue material properties. The last decade has seen a renaissance in material testing fueled by development of a variety of new engineering techniques that allow the mechanical behaviour of both soft and hard tissues to be characterised at a spectrum of scales from nano- to bulk tissue level. As a result there now exists an extremely broad range of published values for human knee tissues. However, our systematic review highlights gaps and ambiguities that mean quantitative understanding of how tissue material properties alter with age and osteoarthritis is limited. It is therefore currently challenging to construct finite element models of the knee that are truly representative of a specific age or disease-state. Consequently, recent whole-joint finite element models have been highly generic in terms of material properties even relying on non-human data from multiple species. We highlight this by critically evaluating current ability to quantitatively compare and model 1) young and old and 2) healthy and

osteoarthritis human knee joints. We suggest that future research into both healthy and diseased knee function will benefit greatly from a subject- or cohort-specific approach in which finite element models are constructed using material properties, medical imagery and loading data from cohorts with consistent demographics and/or disease states.

Tissue material properties and computational modelling of the human knee: A critical review

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Introduction

The knee joint is a primary component of the musculoskeletal system that aids the absorption and transition of weight bearing forces. As an integral part of biomechanical movement the knee joint is often subjected to injury or disease such as ligament rupture [Mullaji et al., 2008; Hill et al., 2005], meniscal tears [Lange et al., 2007] and osteoarthritis (OA) [Zhang & Jordan, 2008]. OA is one of the most common musculoskeletal conditions in the elderly population causing structural degeneration of tissues and ultimately leading to a decline in function [Rousseau & Garnero, 2012]. The most common type of OA exists in the knee joint which is the leading cause of locomotor disability [Zhang & Jordan, 2008]. The disease is encouraged by heredity influence, ageing, gender, obesity and trauma or injury to the affected joint [Manninen et al., 1996] and can often lead to joint replacement [Nigg & Herzog, 2006]. It is approximated that 40 % of adults over the age of 70 will be affected by OA of the knee in the United States of America [Punzi et al., 2010], with direct lifetime medical costs of $12,400 per person [Losina et al., 2015]. OA does not just present with direct joint degeneration but is intrinsically linked to other diseases and neuromuscular complications which can further exacerbate age-related issues such as sarcopenia and a loss of movement control. Individuals with OA have increased variability of gait spatial-temporal parameters [Kiss, 2011] which in turn can decrease locomotor stability and increase the risk of falls [Lord et al., 1996; Hausdorff et al., 2001; Owings & Grabiner, 2004; Brach et al., 2005; Hollman et al., 2007].

Typically, research surrounding OA focuses on the deterioration of articular cartilage; however recent research has highlighted the need to consider structural changes of subchondral bone in the progression of OA [Nigg & Herzog, 2006]. Significant relationships have been identified between changes occurring in different tissues specifically observing molecular crosstalk [Lories & Luyten, 2011; Mahjoub et al., 2012]. OA is therefore more recently seen as a disease of the entire joint with biochemical and biomechanical factors influencing the progression and status of the disease. Each tissue has a specific role and functionality within the knee joint in order to aid movement and stability. Individual tissues have a distinct structure and material properties that define its adaptive and responsive behaviour in accordance with the biomechanics of movement [Punzi et al., 2010]. Biochemical and mechanical changes naturally occur during ageing even in the absence of clinically defined injury or disease and these changes have been shown to modify form-function relationships at the knee joint [Hansen et al., 2006a]; however data is limited.

In order to fully understand the onset and progression of OA it is essential to comprehend the basic relationships between structure and function within a healthy human knee and how tissues age in the absence of disease. Understanding biomechanics of anatomically complex structures like the knee joint is challenging particularly in humans where experimental approaches must largely be non-invasive. The difficulty of achieving direct quantitative measures of tissue behaviour together with more widespread availability of imaging technology (i.e. magnetic resonance imaging (MRI), X-ray computed tomography (CT)) has led to an increasing use of computational approaches, notably finite element (FE) analysis, to study knee joint form and function [e.g. Pena et al., 2005; Pena et al., 2006; Wang et al., 2014]. Once suitably validated such FE models may potentially circumvent the issues surrounding direct invasive measurement

of tissue mechanics by producing quantitative predictions of the mechanical and physiological behaviour of multiple tissues simultaneously, thereby inherently calculating tissue interaction. This could be particularly useful in identifying tissue interaction that may occur during ageing and in the presence of disease.

Through use of parameterization, models can also be used in a predictive capacity to address questions that cannot ethically or even practically be asked by experimentation on humans or animals. Specifically, iterations of the same model can be generated where aspects of structure including gross anatomy and material properties, and loading behaviour are non-invasively manipulated to quantify the impact on function. In this way parameterization enables cause-effect relationships between anatomy and mechanics to be identified, whilst allowing the impact of individual and combinations of morphological characteristics to be isolated [Li et al., 2001]. Model manipulations can also be used for testing surgical interventions, treatment strategies and prosthetics [e.g. Baldwin et al., 2012; Tuncer et al., 2013].

Models are by definition abstractions of reality and their constituent parts or input parameters are typically tailored to address a specific research question or hypothesis. Consequently models of the same anatomical structure, such as the knee joint, may vary considerably between studies according to the research objective. One way to summarise this variation across studies is that models can either be conceptual and are therefore simplified, or generic inputs are chosen to give a more qualitative answer to a specific question (i.e. a yes or no answer; or “X is always higher than Y”); or models are highly analytical where more comprehensive or complex inputs are used to derive a highly quantitative answer (i.e. “during X the stress/strain = Y”; or “because of X the

stress/strain increases by Y%"). In the context of the human knee, for example, it is common for researchers to use models to answer questions on one specific tissue (e.g. ligament injuries under specific stress and strain) and as such effort and complexity is invested in these specific tissues while it is deemed sufficient to invest less towards input values for other tissues (i.e. therefore simplifying cartilage representation to a linear elastic material, or bone treated as a rigid-body). However, tissues within a joint inherently interact and behaviour of one is influenced by others, although to what extent to which tissues interact has not extensively been studied.

Subject specific FE modelling is useful in the application of OA as it can investigate the true interaction between multiple tissues and how changes in one can lead to implications in an adjacent tissue, which may lead to disease initiation or progression. For example, ligament ruptures are histologically known to occur in the presence of OA [Mullaji et al., 2008], yet the impact or causative link to cartilage degeneration is unknown. Whilst efforts have been made to investigate this disease through computational approaches, it is indeed clear that there is a lack of baseline healthy measurements providing a foundation for comparative analyses. Research into the material properties of young healthy tissues surrounding the human knee is needed to compare to other cohort-specific groups. In the context of joint biomechanics this is crucial to understanding how, for example, component parts of the joint function so that corrective therapeutics can restore joint function to the normal baseline as per the healthy sample measurements. Baseline healthy measurements are also crucial for basic science contexts such as sports biomechanics, where increasing biomechanical function is directly linked to performance. The accuracy of computational modelling approaches in general has been shown repeatedly to rely on good input data [Guo et al., 2013; Kazemi et al., 2013; Freutel et al., 2014]. Direction of

115 future research towards understanding the influence of donor age and 'healthy' versus
116 pathological conditions on material properties with these new techniques has been cited as a key
117 goal [Lewis & Nyman, 2008], but it is presently unclear of extent to which this has been
118 achieved in the context of the human knee joint.
119
120 Evidently the human knee joint is crucial in biomechanical movement and function and has
121 therefore the relevant literature has been reviewed extensively in recent years. Specifically,
122 several reviews have discussed computational modelling of individual tissues of the knee joint.
123 For example, Wilson et al., [2005] reviewed articular cartilage representations of behavioural
124 and injury mechanisms, whilst Taylor & Miller, [2006] reviewed both micro- and macro-level
125 representation of cartilage tissue. Computational modelling of ligaments has also been reviewed
126 by Woo et al., [1993] and Weiss & Gardiner, [2003] focusing on viscoelasticity and one-
127 dimension to three-dimension representations respectively. Whole knee joint modelling has also
128 been reviewed in recent years by Pena et al., [2007], Elias & Cosgarea, [2007] and Kazemi et al.,
129 [2013]. Whilst these reviews focused on advances in modelling, to date no review paper has
130 critically evaluated the nature of material property available for human knee joint tissues and
131 subsequently how this data has been transferred to FE models, with particular reference to ageing
132 and OA.
133
134 The aim of this review paper is two-fold. First, to conduct a review of scientific literature to
135 understand what material property data currently exists for cartilage, bone and ligament samples
136 from the human knee joint in an attempt to understand alterations during healthy ageing and
137 disease status. Second, this paper aims to determine how this data has been subsequently applied

within biomedical engineering in the form of existing FE models of the whole human knee joint. In doing so we collate a comprehensive database of material properties of human knee joint cartilage, bone and ligaments to substantiate our critical review of recent advances and current limitations, whilst also serving as a resource for future research in this important area. The critical aspect of our review focuses on the question "how systematic or holistic is the material property data that exists for the human knee in terms of its ability to represent a specific human cohort or demographic"? To evaluate this question we focus on young healthy representation of material properties to understand the current baseline for accurate comparison to old OA representation.

Survey Methodology

Firstly, published scientific papers were sourced for review that contained material property data of soft and hard tissue from the human knee joint only. The selection criteria are outlined here. Literature search engines were used, including ScienceDirect, PubMed (NCBI), MedLine, SpringerLink and Wiley Online Library. Terminology including *cartilage, bone, ligament, human, knee, joint, femoral, femur, tibia, tibial, anterior, posterior, cruciate, medial, lateral, collateral, material properties, elastic modulus, Young's modulus, compression, tensile, indentation, FE, model, modelling, three dimensional,* and *computational* were used. All relevant studies meeting search criteria were included in this review.

For cartilage and bone material properties the research must have been on distal femoral and proximal tibia only (excluding patella samples). Studies must have also incorporated the use of

compression or indentation techniques for ease of comparison of testing techniques and data obtained (as opposed to tensile elongation, 3-point bending, 4-point bending or buckling techniques) to collate the elastic modulus, shear modulus or comparable parameters. For ligament material properties studies must have incorporated at least one of the following: anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), medial collateral ligament (MCL), and lateral collateral ligament (LCL) from the human knee tested using tensile techniques. Compression and tensile testing techniques have specifically been chosen to mimic primary biological *in vivo* mechanics.

Secondly, published scientific papers were sourced for review that incorporated a 3D FE model of a whole human knee joint. This included any study modelling the femoral and tibial bone and cartilage structures and the four main ligaments of the knee joint – ACL, PCL, MCL and LCL. Studies not including all these structures were excluded. Additionally models may or may not have included the menisci tissue, and studies of insoles or footwear, joint replacement or arthroplasty mechanics, meniscectomies and ligament reconstructions were also excluded. Included is an additional exploration into models representing OA.

Structure, composition and material property data obtained from human knee joints will initially be reviewed separately for cartilage, bone and ligament tissue (*Section A*), followed by a review of use of data within currently published human whole-knee joint FE models (*Section B*).

Section A - Material Properties

Articular Cartilage

Articular cartilage is a type of fibrous connective tissue composed of cells forming between 2-15 % of the net weight and an extracellular matrix (ECM) forming the remaining 85-98 %, of which 65-80 % is water. Its primary function is to maintain a smooth surface allowing lubricated, near-frictionless movement and to help transmit articular forces, thereby minimising stress concentrations across the joint. It is most commonly found within synovial and diarthrodial joints forming a 1-6 mm thickness and covering the epiphysis of bone. The knee joint is composed of both hyaline and fibrocartilage in the form of articular cartilage covering the end of bone and fibrocartilage forming the menisci [Martini, 2007].

Material properties of articular cartilage have been widely reported giving compressive, tensile and shear forces at the macro- [Armstrong & Mow, 1982; Setton et al., 1999; Kleemann et al., 2005], micro- [Stolz et al., 2009; Desrochers et al., 2010] and nano-scale [Stolz et al., 2009] within the ECM of multiple species. Various techniques have been utilised including confined and unconfined compression [Kleemann et al., 2005; Silver et al., 2002; Hori & Mockros, 1976; Franz et al., 2001] and more recently AFM [Wen et al., 2012; Wilusz et al., 2013; Wang et al., 2013] and nanoindentation [Taffetani et al., 2014]. Custom made indentation instruments have also previously been used to measure articular cartilage stiffness during compression [Hori & Mockros, 1976; Kempson et al., 1971; Lyyra et al., 1995; Kiviranta et al., 2008] used to calculate dynamic modulus [Kiviranta et al., 2008], creep modulus [Kempson et al., 1971], shear, bulk and elastic modulus and Poisson's ratio [Hori & Mockros, 1976].

One of the first studies to explore human knee joint cartilage material properties utilised uniaxial confined compression on 20 proximal tibia samples. Age and gender of donors were not specified; however each sample was classified with a grade of OA using the Bollet system [Bollet et al., 1963 cited in Hori & Mockros, 1976]. Progressive compression loads were manually applied giving an elastic modulus between 1.3-10.2 MPa. When categorising elastic modulus to grade of OA averages were 6.82 MPa, 6.74 MPa, 4.76 MPa and 2.99 MPa for grades 0, 1, 2 and 3 respectively, although this correlation was not significant [Hori & Mockros, 1976]. Testing specifications and resultant data can be seen in Table 1 alongside information from all reviewed human knee joint cartilage material property research.

In more recent decades there has been considerable focus on micro-scale unconfined compression testing. In consecutive studies by Shepherd and Seedhom, [1997; 1999a], human femoral condyle and tibial plateau cartilage were tested. Earlier research utilised a total of five donors although no age or gender was specified. Results indicated an elastic modulus of between 2.6-18.6 MPa depending on physiological loading rate [Shepherd & Seedhom, 1997]. In the latter study 11 humans cadavers (three males and 8 females, aged 33 - 80 years) were tested giving an elastic modulus of 6.0-11.8 MPa (Table 1) across all cadavers with no correlation to age [Shepherd & Seedhom, 1999a].

Thambyah et al., [2006] tested cartilage from seven fresh frozen healthy human male tibias (62 – 70 years) using uniaxial tensile testing to compare articular cartilage from beneath the menisci to that independent from the menisci. Results showed an individual mean elastic modulus from all

seven cadavers between 2.13 and 5.13 MPa (Table 1) across varying testing locations. Hydration maintenance is not specified within the methodology.

Also utilising uniaxial compression testing Silver et al., [2002] obtained 39 femoral condyle samples from 21 females and 18 males with a mean age of 65 years. Samples were categorised according to degeneration and fibrillation of surface, which is indicative of OA, and hydrated cartilage was tested both parallel and perpendicular to the collagen fibres at the tidemark. Elastic modulus of healthy superficial articular cartilage perpendicular and parallel to the collagen fibres was 2210 MPa and 7000 MPa respectively, whilst elastic modulus of OA samples perpendicular to the collagen fibres decreased to 131 MPa in comparison (Table 1). Likewise collagen fibril length was decreased in OA samples suggesting the capability to store elastic energy was also decreased. OA grade and elastic modulus was not presented as a function of age.

Kleemann et al., [2005] explored the macroscopic composition of articular cartilage within 15 female and six male OA tibial plateau samples (70 ± 13 years). Research obtained architectural data from haematoxylin and eosin staining and elastic modulus by unconfined uniaxial compression. An inverse correlation was observed between the elastic modulus of the articular cartilage against the International Cartilage Repair Society (ICRS) grade [Brittberg & Peterson, 1998] seen in Figure 1 (Grade 1 0.50 MPa, Grade 2 0.37 MPa, and Grade 3 0.28 MPa (Table 1)). The research also suggested a relationship between changes in histology, structure and mechanics of the articular cartilage during all stages of OA degeneration although this was not compared with age of donor. Moreover Bae et al., [2003] found decreased indentation stiffness and an increased ICRS score was associated with degeneration of cartilage rather than with age

252 or cartilage thickness. This suggests that it is possible to reliably distinguish degeneration of
253 cartilage by microscopic histological analysis and macroscopic observations.
254
255 Franz et al., [2001] used a handheld indenter to collate the shear modulus of 24 human cartilage
256 samples (32 – 89 years) obtained from the medial and lateral femoral condyles. Shear modulus
257 was converted to elastic modulus (using the Poisson's ratio expressed in the original research)
258 for the purpose of this paper, which were 4.32 MPa and 4.88 MPa (Table 1) in the lateral and
259 medial femoral condyles respectively; however this was not correlated to the age of cadaver.
260 Cartilage samples were graded for OA using the Mankin system [Mankin et al., 1971] and results
261 indicated a positive correlation between a slightly roughened cartilage surface and stiffness at the
262 medial femoral condyle. However it should be noted that no samples presented with gross
263 fibrillation or surface irregularities. Sample shear modulus was however presented in age
264 categories with corresponding proteoglycan and collagen content which are known to adapt
265 during ageing and disease (Fig. 2).
266
267 The development of increasingly sophisticated testing techniques has further advanced our
268 understanding of cartilage material properties by allowing measurements to be made at the nano-
269 scale. With the use of nano-scale indentation stiffening of cartilage due to age-related influences
270 alongside stiffness differences in healthy and OA cartilage can be detected more accurately in
271 comparison to microindentation [Stolz et al., 2009]. It has been shown that microindentation is
272 either unable to detect such changes or produces a lower stiffness measurement when compared
273 to nanoindentation leading some to question its accuracy [Stolz et al., 2009; Stolz et al., 2004].
274 Additionally, stiffness is higher in articular cartilage collagen fibrils than in proteoglycans;

however when measured at micro-scale, this differentiation may not be detected [Loparic et al., 2010]. A change in the structure of proteoglycans, including a decline in density, often accompanies the process of OA along with reduced stiffness through loosening of the collagen network causing alteration to the material properties, further enhancing the need for testing at the nano-scale [Wang et al., 2013].

Thus incorporating nanotechnology, Wen et al., [2012] utilised AFM to test elastic modulus of tibial plateau articular cartilage fragments obtained from three female patients undergoing arthroplasty surgery. Samples from the surface, superficial middle, deep middle and bone-cartilage interface regions were graded for OA with the Outerbridge scoring system [Outerbridge, 1961]. Collagen fibres were obtained from the overlap zone from each layer which can be mechanically stiffer than collagen fibres in the gap region [Minary-Jolandan & Yu, 2009]. Results show there is a significant mechanical stiffening of individual human collagen fibrils between healthy (aged 35 years) and mild OA (aged 52 and 59 years), at the surface of articular cartilage (2650 – 3110 MPa respectively) through to the bone-cartilage interface (3700 – 5640 MPa respectively) (Table 1). It must be noted that tissue samples were dehydrated with ethanol prior to testing which will alter the true mechanical properties of cartilage; however the aim of this research was to identify the differences in elastic modulus of healthy and OA tissues where mechanical alterations would change simultaneously in both healthy and OA samples.

Wilusz et al., [2013] also used AFM on eight human femoral condyles (six female and two male) aged 53 – 83 years. Cadavers were graded for OA using the Collins System [Collins, 1939 & Collins, 1949 cited in Wilusz et al., 2013] giving four healthy and four OA samples grades 2 – 3.

Results indicate that elastic modulus of the pericellular matrix (PCM) decreased in OA samples (0.096 ± 0.016 MPa) when compared to healthy controls (0.137 ± 0.022 MPa), as well as the ECM elastic modulus which also decreased in OA samples (0.270 ± 0.076 MPa) when compared to healthy controls (0.491 ± 0.112 MPa) (Table 1); although this was only significant on the medial femoral condyle. In agreement, Wang & Peng, [2015] used AFM to quantify elastic modulus of 12 knee articular cartilage samples (age and gender not specified) in various grades of OA and found an increase in elastic modulus in the presence of mild and moderate OA but a decrease with severe OA, although actual values are not stated.

AFM has also been used to identify nanoscale adaptations at varying indentation depths in five human (age and gender not specified) femoral condyles obtained from healthy, mild and severe OA cartilage [Wang & Peng, 2013]. Cartilage samples were graded using the Outerbridge scoring system [Outerbridge, 1961] and exposed to PBS during testing to maintain hydration. Stiffness was higher at a lower indentation depth for all cohorts; however stiffness was highest with mild OA (0.61 MPa) and lowest with healthy controls (0.16 MPa) when comparing to severe OA (0.19 MPa) (Table 1) [Wang & Peng, 2015].

Bone

There are two different types of bone including cortical and trabecular material. The cortical material is found on the outside of bone and is highly dense in nature and the trabecular material is located inside of the bone and has a greater porosity. The low and high densities work in

coordination to absorb stresses through the rigid outer surface and strains through the spongy inner material in order to resist breaking or deformation [Nigg & Herzog, 2006; Martini, 2007].

Recent research has started to direct focus onto the relationship between cartilage and bone in the progression of OA. Research has observed abnormal remodelling of subchondral bone showing trabecular structure alters in density, quantity and separation, with the greatest proliferation in volume evident at the bone-cartilage interface [Kamibayashi et al., 1995; Bobinac et al., 2003]. This suggests a synergistic relationship between bone and cartilage during the progression of OA. The role of subchondral bone in OA appears to be an essential component in the initiation and advancement of the disease [Burr, 1998; Lajeunesse & Reboul, 2003; Madry et al., 2010]; however research is unclear as to whether disruption of subchondral bone remodelling occurs pre- or post- initiation of OA [Intema et al., 2010; Kuroki et al., 2011]. Kuroki et al., [2011] suggested that a more comprehensive understanding of the disease mechanisms of OA including material properties of all tissues involved could yield considerable progression in clinical practice and treatment methods.

In previous decades uniaxial compression testing of human femoral and tibial trabecular bone was carried out by several researchers in order to obtain macro-scale material properties. Behrens et al., [Behrens et al., 1974] tested both femoral condyle and tibial plateau trabecular bone samples from six females and four males (40 – 92 years) resulting in an elastic modulus of 158.9 - 277.5 MPa for femoral bone and 139.3 - 231.4MPa for tibial samples (Table 2). Testing only femoral condyle trabecular bone, Ducheyne et al., [1977] found a slightly lower elastic modulus of 1.9 - 166.1 MPa (Table 2) based on donors aged 43 - 77 years (four males, two females).

343

344 Testing tibial plateau samples by uniaxial compression, Carter & Hayes, [1977] tested 100
345 human trabecular bone samples (age and gender unspecified) and found an elastic modulus
346 between 56.6 - 83.7 MPa (Table 2). Also using uniaxial compression, Lindahl, [1976] tested four
347 female and four male human cadavers (14 – 89 years) showing a higher elastic modulus in males
348 (average 34.6 MPa) compared to females (average 23.1 MPa) (Table 2).

349

350 Interestingly, as well as differences between male and female cadavers, material properties also
351 vary according to anatomical location. Goldstein et al., [1983] utilised uniaxial compression
352 testing to determine the elastic modulus of trabecular bone from the tibial plateau from 5
353 cadavers (50 – 70 years) across varying depths of the joint. Results showed high variation across
354 cadavers and testing location (4.2 - 430 MPa (Table 2)) with the highest values at load bearing
355 sites. Utilising an alternative method, Hvid & Hansen, [1985], used an osteopenetrometer on the
356 tibial plateau of 12 healthy human donors aged 26 - 83 years (three female and nine male).
357 Medial samples had an elastic modulus of 13.8 - 116.4 MPa and lateral samples had a lower
358 elastic modulus of 9.1 - 47.5 MPa (Table 2) further evidencing high variability across the joint.

359

360 Burgers et al., [2008] obtained four male and four female human cadavers (totaling ten femurs
361 aged 45 - 92 years). Cylindrical trabecular specimens (n = 28) were tested using unconfined
362 compression. Results were separated into superior or inferior and medial or lateral samples
363 giving a pooled elastic modulus of 376 MPa ± 347 MPa (Table 2) with the greatest variation
364 apparent between superior and inferior femoral condyle samples.

365

Previous studies researching human knee bone material properties, specifically in OA, are abundantly missing; however one study by Zysset et al., [1994] explored human tibial material properties from six cadavers (61 - 91 years) with grades 1 - 3 OA, scored using the Ahlback system [Ahlback, 1968]. Compression tests were conducted on cuboidal specimens giving an axial elastic modulus of the subchondral trabecular bone between 31 and 1116 MPa which decreased with increasing grade of OA. Although epiphyseal and metaphyseal trabecular bone samples showed that elastic modulus increased with OA grade in the axial (range 102 – 1726 MPa) and coronal (8 – 287 MPa) planes (Table 2). Corresponding OA grade and elastic modulus values can be seen in Figure 3.

In more recent years, testing bone at the tissue level has proven to be more accurate [Nigg & Herzog, 2006] particularly for the inclusion of FE models; however this has rarely been applied to femoral or tibial human bone. Using nanoindentation Rho et al., [1997] explored the tissue level material properties of a single osteon and interstitial lamellae of two longitudinal human (57 and 61 years old) tibial cortical bone. Results presented an elastic modulus of 22500 MPa and 25800 MPa for osteon and interstitial lamellae samples respectively (Table 2).

Ligaments

Ligaments are soft tissues that are fibrous in nature and composed primarily of collagen. They have a hierarchal structure of fibres, fibrils, subfibrils, microfibrils and tropocollagen but also contain water, proteoglycans and several glycoproteins. They function to guide and resist motion at a joint by connecting bone to bone. It has also been suggested that they act as a strain sensor to

restrict degrees of freedom in order to stabilise the joint and prevent excessive movement [Harner et al., 1995; Woo et al., 2006]. Ligaments have direct and indirect insertions into the bone and periosteum respectively allowing variation in fibre bundles to respond to different movements and resist loading during ranges of rotation at the joint. The entheses portion of the ligament is stiffer compared to the medial portion allowing decreased concentrations of stress and therefore reducing the opportunity for damage or tears at the bone-ligament interface [Woo et al., 2006].

When measuring material properties of knee ligaments (ACL, PCL, MCL and LCL) typical analysis includes tensile stress and strain at ultimate failure, tangent modulus and strain energy density, primarily obtained using a tensile testing machine. These parameters are tested *in vitro* by taking either a cross-section of the involved ligament [Quapp & Weiss, 1998] or more commonly a bone-ligament-bone sample (e.g. Fig. 4). During this process bone blocks are ordinarily embedded within polymethyl-methacrylate (PMMA) and the ligaments are wrapped in saline soaked gauze for protection [Harner et al., 1995; Butler et al., 1998; Momersteeg et al., 1995; Hewitt et al., 2001; Robinson et al., 2005; Bonner et al., 2015]. Additionally samples may be tested as a whole structure or divided into anatomical fibre bundles. Woo et al., [2006] suggests that the ACL has an anteromedial and posterolateral bundle and the PCL has an anterolateral and posteromedial bundle which are loaded differently. Ligaments therefore may need to be separated during tensile testing, in order to gain a true understanding of their unique material properties. A summary of the reviewed ligament material property research papers is provided in Table 3.

412 Harvesting a cross-sectional area of a ligament, Quapp & Weiss, [1998] explored the
413 longitudinal and transverse mechanical behaviour of the MCL from ten human cadavers (62 ± 18
414 years). Specimens were preconditioned and loaded to failure. Results included average tensile
415 strength (38.6 MPa and 1.7 MPa), average ultimate strain (17.1 % and 1.7 %) and average
416 tangent modulus (332.2 MPa and 11.0 MPa) for longitudinal and transverse specimens
417 respectively (Table 3).
418
419 Further research on the tensile properties of ligaments utilised the bone-ligament-bone method.
420 One of the first studies to explore ligament material properties harvested the ACL, PCL, MCL
421 and LCL from seven healthy human cadavers aged 29 - 55 years (gender not specified).
422 Ligaments were preconditioned over five cycles and loaded to failure at 100 % strain rate, which
423 is a change in strain equivalent to the initial length of the ligament. Stiffness was measured at
424 138.3 N/mm, 179.5 N/mm, 70.3 N/mm and 59.8 N/mm for the ACL, PCL, MCL and LCL
425 respectively, whilst failure load resided at 620.8 N, 658.0 N, 515.8 N and 376.6 N (Table 3)
426 [Trent et al., 1976].
427
428 Noyes & Grood, [1976] tested young (16 - 26 years) and old (48 - 86 years) anterior cruciate
429 bone-ligament-bone material properties, also at a 100 % strain rate, although excluded any
430 preconditioning. The research found a reduction in stiffness (129 and 182 N/mm), failure load
431 (734.0 and 1730.0 N), elastic modulus (65.3 and 111.0 MPa), maximum stress (13.3 and 37.8
432 MPa) and strain (30.0 and 44.3 %) when comparing older samples to younger samples
433 respectively (Table 3).
434

435 Butler et al., [1986] also tested young (21 - 30 years) ACL, PCL and LCL elastic modulus (278 –
436 447 MPa), maximum stress (30 – 44 MPa) and maximum strain (11 - 19 %) where ranges were
437 inclusive of all ligaments. Approximate values are given in Table 3 estimated from presented
438 graphs [Butler et al., 1986]. The ligaments were divided into their fibre bundles and tested to
439 failure at a 100 %/s strain rate (Table 3). Further research by Butler et al., [1992] looked at the
440 differences in seven human ACL (26 ± 4 years) divided into anteromedial, anterolateral and
441 posterior fibre bundles. Specimens were not exposed to preconditioning but were loaded to
442 failure at a 100 %/s strain rate. This resulted in anterior fibres having a higher maximum
443 modulus (284 MPa), stress (38 MPa) and strain rate (17.6 %) when compared to posterior fibres
444 (155 MPa, 15 MPa, 15.2 %) at failure (Table 3).
445 Race & Amis, [1994] and Harner et al., [1995] loaded to failure the anterolateral and
446 posteromedial fibres bundles of the human PCL. Race & Amis, [1994] obtained ten samples
447 from donors aged 53 – 98 years which resulted in higher stiffness (347.0 N/mm and 770 N/mm),
448 failure load (1620.0 N and 258.0 N), elastic modulus (248.0 MPa and 145.0 MPa) and maximum
449 stress (35.9 MPa and 24.4 MPa) for the anterolateral fibres in comparison to the posteromedial
450 fibres respectively (Table 3). Interestingly maximum strain was lower for the anterolateral fibres
451 (18.0 %) when compared to the posteromedial fibres (19.0 %). Harner et al., [1995] tested five
452 samples (48 – 77 years) and also found a higher failure load in the anterolateral fibres (1120.0 N)
453 in comparison to the posteromedial fibres (419.0 N) (Table 3) showing in both studies wide
454 variation depending on the location of the tissue.
455
456 A more recent study by Robinson et al., [2005] harvested three sections of the femur-MCL-tibia
457 complex from eight humans (77 ± 5.3 years), namely the superficial MCL (SMCL), deep MCL

(DMCL) and posteromedial capsule (PMC) based on fibre orientation and tested samples using the bone-ligament-bone approach. The SMCL is often used to define the overall MCL length; however it is thought that each section tenses and fully elongates under different loading axis or directions and functions to stabilise the knee joint in various ways. Samples were preconditioned and loaded to failure resulting in failure loads of 534 N, 194 N and 425 N for the SMCL, DMCL and PMC respectively (Table 3). The results indicated a bony avulsion in 75 % of tested samples after which the bone was removed and the end of the ligament was attached directly in the clamps and re-loaded to failure. Additionally mid-substance failure of the ligament as opposed to bony avulsion equated to 74 % higher maximum load.

Further variations in tensile properties can exist due to the angle of the femur in correlation to the tibia and the loading axis in correlation to ligament fibre loading direction. Woo et al., [1991] preconditioned and tested the ACL to failure along both the tibial and ligament axis and found higher stiffness values on the ligament axis with increasing extension angle when testing young and old cadavers. Significant variations in anatomical orientation failure load were apparent between age groups: 2160 N for 22 – 35 years (N = 9), 1503 N for 40 - 50 years (N = 9) and 658 N for 60 – 97 years (N = 9) (Table 3) as seen in Figure 5. However there was no correlation between age and orientation.

Interestingly, Chandrasekhar et al., [2006] found gender-based differences in tensile properties showing human female ACL (N = 9) (17 – 50 years) had 22.49 % lower elastic modulus and 8.3 % and 14.3 % lower maximum strain and stress respectively when compared to human male ACL (N = 8) (26 – 50 years) (Table 3). These differences can be partially accounted to the

physically smaller size of the female ACL [Anderson et al., 2001; Chandrashekar et al., 2005]; however when adjusted for covariates the tensile properties of the ACL are still lower. This may in turn be causatively linked to higher rates of ACL injuries in female athletes [Chandrasekhar et al., 2006].

Finally an analysis by Momersteeg et al., [1995] chose not to separate the fibre bundles but instead tilted the orientation of the loading axis at 5° increments (up to 25°) to recruit different fibres at varying angles to explore the changes in tensile properties during sub-ultimate testing. Bone-ligament-bone samples were harvested for the ACL, PCL, MCL and LCL of five human cadavers (63 - 81 years) and subjected to preconditioning before applying up to 7 % and 10 % strain rates for the collateral and cruciate ligaments respectively. Results indicate that strain levels were higher for cruciate ligaments than collateral ligaments and for every 5˚ of tilt there was a decrease in tensile stiffness (averages: -11.6 Nmm^{-1} ACL, -20.96 Nmm^{-1} PCL, -2.66 Nmm^{-1} MCL, -3.76 Nmm^{-1} LCL) (Table 3). The research suggests there is a greater decrease in stiffness for the cruciate ligaments as they have a shorter and wider morphology when compared to the long thin nature of collateral ligaments. These authors go on to conclude that ligaments are highly sensitive to a small change in orientation and therefore unidirectional tensile testing is not effective at defining ligament stiffness properties [Momersteeg et al., 1995].

Section B: FE Modelling

Freutel et al., [2014] presented a non-systematic review on the current research on FE modelling within soft tissues with a specific focus on the human knee joint and intervertebral disc. They

reviewed strategies for modelling various material properties, considering the interaction between soft tissues during contact and their sensitivity to changes in properties and environment (i.e. loading and boundary conditions). Their review concluded that inaccuracy or abstraction in each of these areas could manifest into important limitations in structurally complex models such as those of the human knee joint. Material property definition was cited by Freutel et al., [2014] and indeed by others [Gardiner & Weiss, 2003], as a research area with potential for significant improvement either through improved modelling approaches or *in vivo* inclusion of material properties particularly given the advances in techniques for characterising biological tissue behaviour in recent decades.

Following on from our review of available material property data for human knee joint tissues in *Section A* (above) we focus subsequently on the material property data that has actually been utilised in published whole-joint FE models of the human knee. It is our hope that clarifying the FE models that currently exist in the literature and their accuracy according to how they have obtained their material property data (i.e. primary data collection or from various data sets and donors) will help identify gaps within the knowledge and aid future directions for research.

Advances in FE modelling have allowed researchers to present cartilage as a non-linear anisotropic material with varying material properties as opposed to the traditional representation of a linear elastic isotropic material. This advance means cartilage can now be presented more closely to biological reality and therefore computational predictions of behaviour are more accurate. Whilst several authors have adopted this advanced approach in recent years [Tanska et al., 2015; Halonen et al., 2013], due to the complexity of such models and computational

527 expensive approach, individual tissues are often modelled in isolation, whilst other structures not
528 relevant to the research hypothesis are excluded. Whilst useful in particular applications
529 modeling tissues in isolation has its limitations when considering OA of the knee joint. It is now
530 well established that this is a disease of the entire joint with molecular crosstalk and changes in
531 subchondral bone structure [Lories & Luyten, 2011; Mahjoub et al., 2012], and histological
532 evidence of ligament structural changes [e.g. Mullaji et al., 2008]. Therefore when investigating
533 such disease it is now inherently clear that whole-joint representation is needed to fully
534 understand the implications of tissue interaction and disease progression on the knee joint.
535
536 When cartilage is modelled with linear elasticity it assumes an instantaneous response to stress
537 and strain; however nonlinear representation allows for viscoelastic or time dependent factors
538 such as those represented in Mononen et al., [2011] and Mononen et al., [2012]. It is now well
539 established that cartilage and ligaments are nonlinear and viscoelastic and material property
540 testing is starting to incorporate time-dependent testing by including a hold period, i.e. dynamic
541 nanoindentation of cartilage. This review is indented to analyse whole-joint representations only.
542 Studies presenting only singular tissues of the human knee joint with advanced modelling
543 approaches are outside the scope of this review, although they recent efforts in modelling
544 hyperelastic formulations of cartilage and efforts towards representing tissue anisotropy and
545 viscoelasticity are summarised below.
546
547 Modelling cartilage as a fibril reinforced poroviscoelastic tissue with multiple material
548 properties, Tanska et al., [2015] explored chondrocyte compression during walking, whilst
549 research by Halonen et al., [2013] explored cartilage deformation under large compression.

Further, work by Dabiri & Li [2013] also modelled cartilage with depth-dependent properties, made possible using a fibril-reinforced model to explore inhomogeneity within the tissue and analyses into fluid pressurization within the tissue. Meng et al., [2014] considered cartilage as a fibril reinforced biphasic material to explore knee joint contact behaviour under body weight. Other examples of research representing cartilage as a poroelastic or poroviscoelastic material include the work of Kazemi et al., [2011], Mononen et al., [2011] and Mononen et al., [2012]. These studies represented whole-joints and are therefore discussed in more detail below.

For the purpose of this review, research papers that have presented a FE model of a healthy human knee joint incorporating the femur, tibia, cartilage and four major ligaments each within a 3D form will be presented, addressing how and where these models have sourced material property data for their models. Following this, models that have included all these structures but most commonly represented them in a simplified form of one, two and 3D forms will also be reviewed. Finally the existing attempts to simulate the effects of OA within the knee joint using FE models will be discussed.

3D FE Models of Healthy Human Knee Joints

Our review reveals that FE models most commonly use previously published data for material properties; however there is usually a lengthy referencing chain when tracing these material properties to their original and primary data research article. Material properties are likely to vary with age, gender and disease status [e.g. Kleeman et al., 2005; Lindahl, 1976; Woo et al., 1991; Chandrashekar et al., 2006] and therefore donor demographics in previously published

material property studies will undoubtedly impact upon the quantitative results obtained in FE analyses. Our review highlights a wide spectrum of matches in this respect to the extent that the absence of appropriate data has in some cases led to the use of non-human material properties in FE models of the knee. Material property sources from reviewed FE models are summarised in Table 4.

Wang et al., [2014] attempted to estimate cartilage stress under forces incurred during kneeling in a young healthy male (26 years), using primary MRI data to create their FE model (Fig. 6). The referencing chain starting from Wang et al., [2014] follows up to five secondary references until the original research article is cited. Original demographics include human tibial plateau and femoral neck samples for bone [Rho et al., 1993; Zysset et al., 1999], human femoral condyle and tibial plateau samples for cartilage [Shepherd & Seedhom, 1999a], human [Tissakht & Ahmed et al., 1995] and bovine menisci [Skaggs et al., 1994] and human ACL, PCL, LCL, quadriceps tendon and patella ligament samples for ligament material properties [Race & Amis, 1994; Woo et al., 1991; Staubli et al., 1999; Blankevoort et al., 1988; Brantigan & Voshell, 1941]. Where human samples were used for bone material properties the original research articles either do not state donor age [Rho et al., 1993] or donor age was 53-93 years [Zysset et al., 1999]. Human cartilage ranged from 33 - 80 years old [Shepherd & Seedhom, 1999a] whilst menisci was either 29 - 45 years old [Skaggs et al., 1994] or information was not available. Human ligament samples had an average age of 24.9 years [Staubli et al., 1999], an age range of 53 - 98 years [Race & Amis, 1994], 43 - 74 years [Blankevoort et al., 1988], or it stated that donors were ‘young’ [Butler et al., 1986] or it was unspecified [Brantigan & Voshell, 1941]

595 (Table 4). The specific material properties used within Wang et al., [2014], can be found in the
596 Table 5 alongside the material properties from other FE modelling studies reviewed.
597
598 Consecutive studies by Pena et al., [2005; 2006] carried out FE modelling of a healthy knee joint
599 using CT and MRI data of a healthy male volunteer (age not specified) to generate a model that
600 included bone, ligaments, tendons and articular and meniscal cartilages using previously
601 published material property data. The aim of these studies were to compare healthy human knee
602 biomechanics to meniscal tears and meniscectomies [Pena et al., 2005] and to analyse the non-
603 uniform stress-strain fields that the menisci and ligaments encounter during loading of the human
604 knee joint [Pena et al., 2006]. The referencing chain starting from Pena et al., [2006] also follows
605 up to four secondary references until the original research article is cited. As bone was modelled
606 as rigid this requires no material property input; cartilage material properties could not be traced;
607 menisci material properties were based on canine meniscal material properties [LeRoux &
608 Setton, 2002] and ligaments on human ACL, PCL, MCL and LCL material properties with ages
609 specified as 38 years [Butler et al., 1990], 37 - 61 years [91], 43 - 74 years [Blankevoort et al.,
610 1988] or simply denoted as 'young' [Butler et al., 1986] or unspecified [Brantigan & Voshell,
611 1941]. Pena et al., [2005] used the same original sources for cartilage and menisci material
612 properties and adopted ligament material property data from a review article [Weiss & Gardiner,
613 2001], summarised in Table 4.
614
615 Guo et al., [2009] created a 3D human knee joint model from a CT scan on a 45 year old healthy
616 female to understand the contact pressures on the femoral and tibial cartilages during different
617 phases of the gait cycle. Material properties were referenced from previous FE modelling papers;

618 however the referencing chain provides information that menisci data was originally presented
619 by LeRoux & Setton, [2002] based on canine meniscal properties. Unfortunately, bone, cartilage
620 and ligament material property sources cannot be traced back to a primary data collection
621 reference (Table 4).
622
623 A recent FE study explored misalignment differentiation of the knee joint to understand how this
624 influences contact pressure [Mootanah et al., 2014]. An MRI of a 50 year old cadaveric male was
625 used for geometry and validation of the model through mounting the knee joint and matching
626 loading and boundary conditions. Mootanah et al., [2014] obtained material properties from the
627 literature with a referencing chain going back through three other research papers to the original
628 primary research article. Bone material properties were based on human femoral condyle and
629 tibial plateau samples aged 45 - 68 years [Hobatho et al., 1991] whilst cartilage was based on
630 ages stated as 33 - 80 years [Shepherd & Seedhom, 99997; Shepherd & Seedhom, 1999b]. It is
631 unclear how the meniscal material properties were obtained. Ligament material property data
632 was obtained through primary data collection of the ACL, PCL, MCL and LCL giving validated
633 values for the geometry of the FE model (Table 4).
634
635 Kazemi et al., [2011] used a MRI scan of a healthy 26 year old male to construct an FE model to
636 understand the differences in creep behaviour of intact knee joints that have undergone
637 meniscectomies. Subsequent research by Kazemi & Li, [2014] similarly used an MRI of a
638 healthy 27 year old male, and modelled structures with the same modelling theories as Kazemi et
639 al., [2011], although marginally adapted these material property inputs in order to understand the
640 poroelastic response of soft tissues in the knee joint under large compression forces. Original

641 data collection for material properties used within both studies was derived from bovine humeral
642 head cartilage [Langelier & Buschmann, 1999; Woo et al., 1976] and human tibial plateau (29 -
643 45 years) along with human menisci [Tissakht & Ahmed, 1995]. However ligament material
644 properties, specifically toe region fibril data, were based on previous studies of the human patella
645 tendon aged 29 - 93 years [Hansen et al., 2006b; Johnson et al., 1994] and human calcaneal
646 (Achilles) tendon aged 57 - 93 years [Louis-Ugbo et al., 2004]. The non-fibril ligament material
647 properties can be traced back to a theoretical modelling paper [Ault & Hoffman, 1992a], whose
648 results are represented in a companion paper with experimental work carried out on a rat tail
649 tendon [Ault & Hoffman, 1992b]. Ligament initial strains used within Kazemi et al., [2014] can
650 be traced back to Pena et al., [2006] which as discussed previously are originally sourced from
651 human specimens aged 43 - 74 years [Blankevoort et al., 1998], 53 - 98 years [Race & Amis,
652 1994], or ages are described as 'young' [Butler et al., 1986] or unspecified [Brantigan & Voshell,
653 1941] (Table 4).
654
655 *Simplified FE Models of the Healthy Human Knee Joint*
656
657 For computational simplicity FE models of a human knee joint often make adjustments to their
658 model including representing ligaments as non-linear one dimensional springs [e.g. Li et al.,
659 2001; Blankevoort & Huiskes, 1991; Blankevoort et al., 1991; Li et al., 1999; Donlagic et al.,
660 2008], bones as rigid bodies lacking material properties [e.g. Li et al., 2001; Li et al., 1999;
661 Bendjaballah et al., 1995; Jilani et al., 1997; Shirazi et al., 2008] or exclusion of particular
662 structures such as the menisci [e.g. Blankevoort & Huiskes, 1991; Blankevoort et al., 1991] or
663 ligaments [Guess et al., 2010; Donahue et al., 2002; Donahue et al., 2003].

Models that have been highly simplified but still integrate all the main structures of the knee joint include studies by Blankevoort et al., [1991] and Blankevoort & Huiskes, [1991] who created mathematical models of the knee joint, developed originally by Wismans et al., [1980], specifically focusing on the articular contact and interaction between ligaments and bones. Utilising the previously developed modelling theories [Blankevoort & Huiskes, 1991; Blankevoort et al., 1991]. Li et al., [1999; 2001] used a MRI of a 65 year old male cadaver to create a 3D model of the knee joint and conducted a sensitivity analysis varying input parameters to assess the effect on joint contact stresses. In continuation, Yang et al., [Yang et al., 2010] also utilised the work proposed by Blankevoort et al., [1991] and Blankevoort & Huiskes, [1991] to define MRI scans from three young volunteers (21 - 23 years) to determine cartilage contact stress during gait; however noticeable differences between studies include the representation of the menisci within Yang et al., [2010].

Within these corresponding studies ligaments were modelled as ‘bars’, which are one-dimension (1D) non-linear tension-only elements with just two nodes, although material properties are still assigned. It should also be noted that Li et al., [2001] states that ligament stiffness was optimised for the model, which is used to ensure numerical stability and model convergence. Blankevoort et al., [1991], Blankevoort & Huiskes, [191], Yang et al., [2010], Li et al., [1999] and Li et al., [2001] sourced ligament material properties from human ACL, PCL and LCL samples aged ‘young’ [Butler et al., 1986] or aged 43 - 74 years [Blankevoort et al., 1988]. Unfortunately, cartilage material properties were ambiguous due to multiple references available in the cited sources [Kempson, 1980; Mow et al., 1982] making the origin of the input data unclear.

687 Additionally, the menisci were modelled within Yang et al., [2010]; however the original data
688 collection reference could not be traced. Referencing information from these FE studies are
689 summarised in Table 4.
690
691 As well as simplifying anatomical geometry it is also common for investigators to reuse medical
692 image data sets to create different models. In sequential studies CT data of a 27 year old female
693 was used to construct a FE model of the human knee joint to explore contact pressures
694 [Bendjaballah et al., 1995], varus and valgus alignment [Bendjaballah et al., 1997], axial rotation
695 [Jilani et al., 1997], anterior-posterior forces [Bendjaballah et al., 1998], ACL and PCL coupling
696 [Moglo & Shirazi-Adl, 2003] and cartilage collagen fibril response to compression [Shirazi et al.,
697 2008]. Figure 7 illustrates the model created within these studies and highlights the difference in
698 comparison to Figure 6 in mesh generation and inclusion of all structures in 3D form. When
699 tracing the material properties assigned to structures within these corresponding FE models
700 cartilage primary data was ascertained from human tibial plateau samples aged 48 - 70 years
701 [Hayes & Mockros, 1971], ligaments from human ACL, PLC, and LCL samples, referenced with
702 ages of 53 - 98 years [Race & Amis, 1994], or from samples described as 'young' [Butler et al.,
703 1986]. Menisci material properties were based on human meniscal samples aged 29 - 45 years
704 [Tissakht & Ahmed, 1995] alongside additional data which could not be traced (Table 4).
705
706 Another simplified FE model was developed by Beillas et al., [2004] who modelled the whole
707 lower limb of a 30 year old male and coordinated this with *in vivo* kinematics of a one-leg hop.
708 However, this model was simplified with a 1D representation of the ligaments. Bone material
709 properties were originally obtained from proximal femur and mid femur human samples aged

either 28 - 91 years [Lotz et al., 1991], or age was unspecified [Reilly & Burstein, 1975], or bovine samples were used [Mente & Lewis, 1994]. Cartilage material properties can be traced to human tibial plateau samples although age was not specified [Repo & Finlay, 1977] and some further cartilage information was untraceable. Menisci data also came from human samples although again age was not specified [Fithian et al., 1990]. Finally, ligament material properties were based on human ACL, PCL, MCL, and LCL data obtained from donors aged 16 - 86 years [Noyes & Grood, 1976], 29 - 55 years [Trent et al., 1976], and 22 - 97 years [Woo et al., 1991] (Table 4).

Incorporating some of the material properties presented by Beillas et al., [2004], Donlagic et al., [2008] utilised a patient specific approach to derive geometry and loads for their FE model using an MRI of a 22 and 52 year old male alongside primary kinematic data of flexion and extension locomotion. However additional material property sources were also used for the representation of the cartilage including bovine and porcine femoral condyle and tibial plateau samples [Laasanen, 2003] (Table 4).

FE Models of OA Human Knee Joints

It was discussed previously (*Section A*, above) that changes in tissues structure during OA progression can result in changes in material properties. This in turn would correlate with a change in the response to loads and biomechanics of the whole knee joint. With this in mind, FE modelling has the potential to analyse such alterations in the presence of OA, assuming that tissue material properties representative of diseased tissues are incorporated into models.

733 Although some FE studies have attempted to investigate contact stresses to understand how OA
734 can initiate and progress [Pena et al., 2007; Dong et al., 2011; Moninen et al., 2011; Mononen et
735 al., 2012] or how arthroplasty procedures can affect the knee joint [e.g. Baldwin et al., 2012;
736 Tuncer et al., 2013] there is only a handful of research papers that utilise a whole knee joint FE
737 model based specifically on healthy versus OA material properties.
738
739 One of the first studies to attempt this examined how osteochondral defects influence the
740 ongoing degeneration and stress concentrations of cartilage in the knee joint during compression
741 based on the geometry and anatomical location of the defect as seen in Figure 8 [Pena et al.,
742 2007]. Healthy material properties were identical to Pena et al., [2006] described in detail above
743 and therefore included human and canine tissue. However, when modelling cartilage with defects
744 the elastic modulus of the cartilage was adjusted to 1.5 MPa with data originally sourced from
745 Athanasiou et al., [1995] who explored the elastic modulus of rabbit cartilage with artificially
746 induced OA. A similar study by Dong et al., [2011] also explored the cartilage defects but kept
747 the elastic modulus consistent for both healthy and OA simulations.
748
749 Although not modelling a whole knee, consecutive studies by Mononen et al., [2011; 2012]
750 segmented the femoral and tibial cartilage from 29 and 61 year old healthy males for FE analysis
751 modelling the cartilage with fibril-reinforced poroviscoelastic properties. Mononen et al., [2011]
752 compared normal, OA and repaired cartilage giving a strain dependent fibril network modulus of
753 673 MPa, 168 MPa and 7 - 505 MPa respectively; an initial fibril network modulus of 0.47 MPa,
754 0.47 MPa and 0.005 - 0.35 MPa respectively; an elastic modulus of 0.31 MPa, 0.08 MPa and
755 0.31 MPa respectively; and finally a Poisson's ratio of 0.42 for all samples. Mononen et al.,

[2012] compared only normal and OA samples with the same material properties. When following the referencing chain and tracing cartilage material properties back to their original research they used input data from bovine articular cartilage [DiSilvestro & Suh, 2001; Korhonen et al., 2003] where OA was artificially induced [Korhonen et al., 2003].

Discussion

Material Properties

There is considerable variation in the elastic modulus of articular cartilage obtained from the human knee joint within the literature. This can be at least attributed to differences in testing parameters and structure and quality of the tissue sample, in addition to known and ambiguous variation in donor characteristics. To summarise, samples within the literature include hydrated [Wilusz et al., 2013; Kleemann et al., 2005; Silver et al., 2002; Hori & Mockros, 1976; Franz et al., 2001; Wang et al., 2013; Shepherd & Seedhom, 1997; Shepherd & Seedhom, 1999a] and dehydrated [Wen et al., 2012] femoral and tibial localities and ages between 32 and 89 years. Furthermore OA samples have been graded using the Collins [Collins, 1939 and Collins, 1949 cited in Wilusz et al., 2013], Bollet [Bollet et al., 1963 cited in Hori & Mockros, 1976] and Outerbridge [Outerbridge, 1961] scoring systems, creating inconsistencies in categorisation. Both confined and unconfined compression testing has been employed [Kleemann et al., 2005; Silver et al., 2002; Hori & Mockros, 1976; Thambyah et al., 2006] alongside indentation techniques [Franz et al., 2001; Shepherd & Seedhom, 1997; Shepherd & Seedhom, 1999a] and AFM [Wen et al., 2012; Wilusz et al., 2013; Wang et al., 2013]. Research also incorporates

779 extensive ranges in testing specifications including indentation tip radius (10 nm – 1 mm) [Wen
780 et al., 2012; Franz et al., 2001; Shepherd & Seedhom, 1997; Shepherd & Seedhom, 1999a;
781 Thambyah et al., 2006], loading force (0.019 - 11.8 N) [Kleemann et al., 2005; Hori & Mockros,
782 1976] and recovery phases (5 – 120 mins) [Silver et al., 2002; Thambyah et al., 2006].
783
784 With these variations in mind elastic modulus for hydrated healthy cartilage samples varies
785 between 0.1 – 7000 MPa [Wilusz et al., 2013; Silver et al., 2002; Thambyah et al., 2006;
786 Brittberg & Peterson, 1998; Bae et al., 2003; Shepherd & Seedhom, 1997; Shepherd & Seedhom,
787 1999a], hydrated OA grade 1 samples range between 0.5 - 10.2 MPa [Kleemann et al., 2005;
788 Hori & Mockros, 1976; Franz et al., 2001; Wang et al., 2013] and hydrated OA grade 2 and 3
789 between 0.1 - 0.5 MPa [Wilusz et al., 2013; Kleemann et al., 2005; Wang et al., 2013], noting
790 that different OA grading systems are used across these studies. Furthermore, age ranges stated
791 within the literature have a wide variation, the broadest being 33 - 80 years within one study
792 [Shepherd & Seedhoom, 1999a]. Some values cannot be explicitly linked to age ranges. Future
793 work is required to more definitely define changes in cartilage material properties associated to
794 explicitly with age and therefore help understand how alterations through disease can be
795 separated from alterations during healthy ageing.
796
797 In comparison to the available data on human knee joint cartilage, there is significantly less data
798 for femoral or tibial bone samples. Indeed, we were able to find only one study that
799 quantitatively measured material properties of cortical bone from the human knee joint [Rho et
800 al., 1997]. Data on trabecular properties is present but it is difficult to reconcile data from
801 different anatomical locations collected with different techniques, specifically traditional

802 compression approaches [e.g. Lindahl, 1976; Goldstein et al., 1983; Burgers et al., 2008] and
803 more recent nanoindentation methods [Rho et al., 1997], which is yet to be applied to the human
804 femoral condyle. Similar ambiguity in the relationship between age and material properties also
805 exists. Age ranges vary between 14 - 92 years across studies with the smallest age cohort (with
806 the exception of individual donors) spanning 20 years in one study [Goldstein et al., 1983]. Some
807 studies also used donors under the age of 30 where donors may not have reached skeletal
808 maturity and material properties may not reflect peak bone mass [Matkovic et al., 1994]. Overall,
809 trabecular bone elastic modulus ranges from 1.9 - 664.0 MPa across reviewed studies [Behrens et
810 al., 1974; Ducheyne et al., 1977; Carter & Hayes, 1977; Lindahl, 1976; Goldstein et al., 1983;
811 Hvid & Hansen, 1985; Burgers et al., 2008; Zysset et al., 1994] and cortical bone from 22,500 -
812 25,800 MPa [Rho et al., 1997].
813
814 Studies reviewed in *Section A* mostly involve experimental work on trabecular bone which is less
815 commonly used within FE models. Compression techniques utilised to obtain macro-scale
816 measurements of trabecular bone as a whole structure as opposed to measuring individual
817 trabeculae, will inevitably produce lower elastic modulus values due to the nature of testing;
818 however more sophisticated techniques incorporating tissue level material properties can more
819 accurately represent a structure such as trabecular bone at the level in which it is typically
820 modelled in FE research [Nigg & Herzog, 2006]. This variability in techniques inevitably makes
821 a comparison between studies challenging as well as the lack of distinct age cohorts to ultimately
822 define young and old parameters in order to definitively link this to a change in properties due to
823 injury or disease, such as OA. Despite some research incorporating material properties of
824 varying OA grades there are no healthy controls included to explicitly link significant findings to

825 OA status [Zysset et al., 1994]. Evidently there is also no material property data for human
826 trabecular bone obtained from the distal femur or proximal tibia at the tissue level, comparing
827 healthy and OA samples.
828
829 Likewise, there is also significant variation in ligament tensile properties reported in the
830 literature and this could be attributed to a number of factors including the variation in cadaver
831 cohorts, equipment and testing protocol and technique. Experimental procedures for ligament
832 material properties vary between cross-sectional samples [Momersteeg et al., 1995] or bone-
833 ligament-bone samples spanning a variety of age ranges with current data in the literature
834 ranging from 16 - 97 years old [Harner et al., 1995; Quapp & Weiss, 1998; Butler et al., 1992;
835 Robinson et al., 2005; Trent et al., 1976; Noyes & Grood, 1976; Butler et al., 1986; Race &
836 Amis, 1994; Woo et al., 1991; Chandrashekar et al., 2006]. Preconditioning, which is often
837 included as a 'warm up' for the ligament to achieve load-displacement parameters that are
838 repeatable [Momersteeg et al., 1995] is absent from some research studies [Momersteeg et al.,
839 1995; Noyes & Grood, 1976]. Furthermore data varies across individual studies where elastic
840 modulus of the knee ligaments ranges between 1.7 - 447.0 MPa [Quapp & Weiss, 1998; Butler et
841 al., 1992; Noyes & Grood, 1976; Butler et al., 1986; Race & Amis, 1994; Chandrashekar et al.,
842 2006] and failure load between 194.0 - 2160.0 N [Harner et al., 1995; Robinson et al., 2005;
843 Trent et al., 1976; Noyes & Grood, 1976; Race & Amis, 1994; Woo et al., 1991; Chandrashekar
844 et al., 2006]. Comparisons between young and old have been correlated for the ACL in two
845 studies [Noyes & Grood, 1976; Woo et al., 1991] both concluding that young donors have a
846 higher stiffness and failure load. However, this is yet to be explored in the PCL, MCL and LCL

847 along with research into how ligament tensile properties are correlated to pathological existence
848 in the form of OA.
849
850 *FE Modelling*
851
852 FE Models have been used for various applications involving the whole knee joint including
853 healthy representation [e.g. Pena et al., 2006; Wang et al., 2014], joint replacement mechanics
854 [e.g. Baldwin et al., 2012; Tuncer et al., 2013], meniscectomy research [Tanska et al., 2015],
855 cartilage contact stresses [e.g. Li et al., 2001; Guo et al., 2009] and ligament-bone interaction
856 [e.g. Blankevoort et al., 1991] to name a few. Material properties used within the reviewed FE
857 models are often sourced from the literature including previous modelling studies or primary
858 experimental research. This typically results in highly variable data sets based on multiple
859 structures and species. The material properties of human tissue vary according to its mineral and
860 protein composition and the orientation of its micro-architecture [Wilusz et al., 2013; Marticke et
861 al., 2010; Temple-Wong et al., 2009]. These factors in turn vary with anatomical location (e.g.
862 femur vs humerus; knee vs ankle), age and health of the tissue. Therefore, donor characteristics
863 will significantly impact results. It is clear that current whole joint FE models use material
864 properties with highly variable, or non-specific material properties, with variation in the age,
865 species, location and disease state of the tissue from which material properties were obtained
866
867 When the values used for material properties within published FE models are traced to their
868 original research citation it becomes clear that there is considerable variation in terms of age
869 range. FE models produced by Beillas et al., [2004] and Donlagic et al., [2008] have a total age

range across all structures of 16 - 97 years. The smallest age range used for material properties within a single study is 43 - 74 years [Li et al., 2001; Blankevoort & Huiskes, 1991; Blankevoort et al., 1991; Li et al., 1999; Yang et al., 2010], with other ages ranging between 37 - 74 years [Pena et al., 2005], 33 - 80 years [Mootanah et al., 2014], 29 - 93 years [Kazemi et al., 2014], 29 - 98 years [Kazemi & Li, 2014; Bendjaballah et al., 1995; Jilani et al., 1997; Shirazi et al., 2008; Bendjaballah et al., 1997; Bendjaballah et al., 1998, Moglo & Shirazi-Adl, 2003] and 25 - 98 years [Wang et al., 2014]. In many FE modelling studies, some information including age of donors from the original sources of material properties could not be traced [Pena et al., 2005; Pena et al., 2006; Wang et al., 2014; Li et al., 2001; Guo et al., 2009; Mootanah et al., 2014; Kazemi & Li, 2014; Blankevoort & Huiskes, 1991; Blankevoort et al., 1991; Li et al., 1999; Donlagic et al., 2008; Bendjaballah et al., 1995; Jilani et al., 1997; Shirazi et al., 2008; Yang et al., 2010; Bendjaballah et al., 1997; Bendjaballah et al., 1998, Moglo & Shirazi-Adl, 2003; Beillas et al., 2004]. Where material properties are categorised by age there are considerable differences between cohorts, most noticeably in ligament data [Noyes & Grood, 1976; Woo et al., 1991]. In particular Woo et al., [1991] recorded the site of failure in ligaments when loaded in the anatomical location and concluded that in younger donors the ACL will predominantly fail by avulsion and in older donors the ACL will predominantly fail at the mid-substance, due to a change in material properties. This is especially important to factor into FE models if safety factors in the joint are being researched. The effect of using material properties from broad, and in some cases unknown age ranges, impacts on the conclusions of FE modelling is currently unclear because at present no study has compared these models to one constructed using anatomical geometry and material properties for all tissues from the same individual, or a

892 homogeneous age and gender cohort of individuals. Such a model would clearly represent the
893 'gold-standard' with respect to geometry and material property definition in a FE knee model.
894
895 As well as wide variation in age, some FE models use material property data based just on tibial
896 plateau cartilage [Kazemi & Li, 2014; Donlagic et al., 2008; Bendjaballah et al., 1995; Jilani et
897 al., 1997; Shirazi et al., 2008; Bendjaballah et al., 1997; Bedenjaballah et al., 1998; Moglo &
898 Shirazi-Adl, 2003; Beillas et al., 2004] or bone samples lacking any femoral condyle
899 measurements [Wang et al., 2014]. Furthermore, they may be based on non-knee joint
900 anatomical locations including femoral neck and mid femur bone material properties [Donlagic
901 et al., 2008; Beillas et al., 2004] and humeral head for cartilage material properties [Kazemi et
902 al., 2011; Kazemi & Li, 2014]. As an example of the magnitude of disparity in material
903 properties between different anatomical locations, Shepherd & Seedhom, [1999a] tested the
904 elastic modulus of ankle, knee and hip joint cartilage finding differences of up to 6.8 MPa (36.6
905 %) between ankle and knee cartilage samples from the same donor and 3.6 MPa (30.54 %)
906 between knee and hip cartilage samples from the same donor. Indeed, it has been shown that
907 variations in material properties from the same tissue exists within and across the knee joint
908 suggesting that a location dependent modulus for various tissues would be most appropriate for
909 FE models [Behrens et al., 1974; Deneweth et al., 2015; Akizuki et al., 1986]. Thus, while better
910 than using values from outside the knee joint itself, representing structures with homogeneous
911 (i.e. only one value) properties, or for example, assuming tibial and femoral material properties
912 are identical, may be sub-optimal and functionally important. Ligament material properties are
913 also often replicated where original data is only based on selective ligaments of the knee joint
914 [Wang et al., 2014; Li et al., 2001; Kazemi & Li, 2014; Blankevoort & Huiskes, 1991;

915 Blankevoort et al., 1991; Li et al., 1999; Bendjaballah et al., 1995; Jilani et al., 1997; Shirazi et
916 al., 2008; Yang et al., 2010; Bendjaballah et al., 1997; Bedenjaballah et al., 1998; Moglo &
917 Shirazi-Adl, 2003]. In some instances tendon data is used for the representation of ligament
918 material properties including the quadriceps tendon [Wang et al., 2014], patella tendon [Wang et
919 al., 2014; Kazemi et al., 2011; Kazemi & Li, 2014], Achilles tendon [Kazemi et al., 2011;
920 Kazemi & Li, 2014] and rodent tail tendon [Kazemi et al., 2011; Kazemi & Li, 2014].
921
922 Animal material property data is also commonly used in the representation of human knee FE
923 models including bovine [Wang et al., 2014; Mootanah et al., 2014; Shepherd & Seedhom,
924 1999b; Kazemi & Li, 2014; Donlagic et al., 2008; Beillas et al., 2004; Mononen et al., 2011;
925 Mononen et al., 2012], canine [Pena et al., 2005; Pena et al., 2006; Guo et al., 2009], porcine
926 [Donlagic et al., 2008], rat [Kazemi et al., 2011; Kazemi & Li, 2014] and rabbit [Pena et al.,
927 2007] data. A number of recent studies have highlighted the structural, mechanical and
928 physiological differences between bovine and human soft tissue and questioned the suitability of
929 bovine material property data for functional studies of humans [Demarteau et al., 2006; Jeffrey &
930 Aspden, 2006; Nissi et al., 2007; Pedersen et al., 2013; Plumb & Aspden, 2005]. Athanasiou et
931 al., [1991] explored the differences between material properties of cartilage from the femoral
932 condyle of different species and found variation between the Poisson's ratio of human (0.074 -
933 0.098), canine (0.3 - 0.372), bovine (0.383 - 0.396), and rabbit (0.197 - 0.337) along with
934 aggregate modulus of human (0.588 - 0.701 MPa), canine (0.603 - 0.904 MPa), bovine (0.894 -
935 0.899 MPa) and rabbit (0.537 - 0.741 MPa). Although differences were not statistically
936 significant, potentially due to low samples numbers (n = 4 – 10) there was evidently a difference
937 between species all of which have been used in some of the reviewed FE models.

As discussed earlier, it is very common for FE modeling studies to source and reference their material property data from previous modelling studies rather than the original experimental studies in which practical measurements were obtained. However, when the referencing chain is followed through sequentially cited modeling papers it is often the case that the primary experimental source of material property data is untraceable [e.g. Yang et al., 2010; Pena et al., 2006]. In other instances it eventually becomes clear that material property values are not source for direct experimental measures, but have been derived directly or indirectly from theoretical research in which mathematical solutions for modelling a specific structure have been derived [e.g. Mak et al., 1987 cited in Pena et al., 2005; Pena et al., 2006; Li et al., 2001; Guo et al., 2009].

Use of varying ages, species and anatomical locations for material property information undoubtedly represent important limitations in current FE models, but the magnitude of error is presently difficult to quantify and probably varies widely across studies due to the highly 'mixed' nature of input data used. At present, the best indication of error comes from studies that have conducted sensitivity analyses on material properties. Li et al., [2001] conducted a sensitivity analysis varying cartilage elastic modulus from 3.5 – 10 MPa and showed that peak contact stresses linearly increased by up to 10%, whilst an increase in Poisson's ratio significantly varied peak von Mises stress by 100% in the knee joint cartilage. Additionally, a more sophisticated sensitivity analysis was carried out by Dhaher et al., [2010] who adjusted the intrinsic material properties of knee joint ligaments to aid understanding of the functional consequences of different activity levels, age, gender and even species. The research measured

simulation outcomes by incorporating a multi-factorial global assessment, which indicated a change in tibial-femoral internal and external rotation, patella tilt and patella peak contact stresses, associated with modified ligament material properties [Dhaher et al., 2010].

Our review of published material property (*Section A*) and FE modelling (*Section B*, above) studies of the human knee raises the question of how well specific cohorts or even human demographics can currently be accurately represented in a FE model. For example, does sufficient material property data exist to construct a whole-knee joint FE model representative of a young, healthy human or to represent a knee of any age with a specific category of OA? Attempting to build an FE model of a healthy knee joint from the literature data tabulated in *Section A* (Tables 1-3) yields data for healthy femoral and tibial cartilage, although without the breakdown of age specific material properties; healthy tibial cortical bone from older donors; healthy ACL, PCL, MCL and LCL from young donors, and ACL, PCL and MCL from healthy older donors. Thus, 'healthy' material properties can be pieced together from different studies for most tissues but mixing gender and a considerable age range (16 - 97 years) is necessary. In terms of a model for studying OA, data exists for cartilage material properties based on OA grades 1 - 3 although this is not broken down into age categories, whilst trabecular bone material properties do exist for OA grades 1 - 3 for older donors although challenges occur as no healthy control was used within this particular study as a baseline measurement. Further no study has yet explored the effect of OA on cortical bone material properties in the human knee. There is currently no data incorporating the effect of OA on ligament material properties despite it being well known that there is a relationship between OA and ligament injury [Mullaji et al., 2008; Cushner et al., 2003]. However, there are currently no research papers to the authors' knowledge

that have collected primary data on bone and cartilage material properties and used these measurements to build a subject specific FE model. Hence, material properties are still collated from various sources within the literature. A key goal for future research should be adoption of a more subject specific approach in which material properties from all tissues are derived from homogenous donor cohorts to improve accuracy and precision of knee FE models.

Conclusions and Future Directions

Integrating tissues-specific material property data into FE models has the potential to provide considerable insight into both healthy and diseased knee joint mechanics, circumventing the difficulty of direct invasive measures of human functionality. Herein, we have provided a comprehensive summation and evaluation of existing material property data for human knee joint tissues with all numerical values tabulated as a reference resource for future studies. A renaissance in material testing and engineering approaches in the last decade has yielded an abundance of data on the mechanical properties of both hard and soft tissues from the human knee joint. However, comparison of material properties between studies can be challenging due to the differences in cadaver age, data collection techniques, including orientation of the tissue and loading specifics [Chandrashekar et al., 2006]. It is well documented that material properties alter during ageing [Hansen et al., 2006a], therefore the demographics of cadavers will highly influence material property data. Our review highlights that material properties from multiple (>1) tissue types have rarely been collected from cadavers with homogeneous age, gender and health status characteristics. More consistent data collection with particular emphasis on extracting data on multiple tissues from the same donors will enable a much more robust examination of the structural and mechanical changes occurring during ageing, injury and

disease, notably during OA progression which currently represents a significant socio-economic burden that is likely to increase further within ageing populations.

The benefits of a more exhaustive subject- or cohort-specific approach to materials testing will inherently feed directly into improved FE models of whole-knee function. Efforts have been made to produce an openly available finite element model for clinical and scientific explorations to be made [Erdemir, 2016]. With more accurate material property data from cohort specific sources data could be applied into this freely available model without the need to obtain medical imagery to create a new FE model which is costly in time and resources. More demographically homogenous material property data sets will eliminate the current widespread use of material properties sourced from distinctively diverse human cadavers and/or animal specimens. Embracing this more systematic subject- or cohort-specific approach to FE modelling can only improve comparisons between injured and diseased tissue within the knee joint, and enhance understanding of behavioural response to mechanical loads observed during ageing or disease progression. It is notable at present that no FE modelling study has compared healthy and OA whole-knee joints. Increasing ageing populations within western societies provide particular incentive for this research with a clear need to direct research efforts into better integration of mechanical engineering approaches and biomechanical simulation, particularly in the presence of disease status.

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Table 1(on next page)

Summary of cartilage material properties

Table 1. Summary of current literature for human knee cartilage material property compression or indentation testing including age, gender, health status of specimens, number and location of samples tested and technique used to obtain elastic modulus values. Abbreviations: NS (not specified); F (female); M (male); OA (osteoarthritis); AFM (atomic force microscopy); ECM (extra cellular matrix); PCM (peri-cellular matrix). *Samples were dehydrated prior to testing.

Author	Quantity & Locality	Age, Gender & Health Status	Testing Technique	Results: Elastic Modulus (MPa)	
Hori & Mockros, 1976	20 x Donors Proximal Tibia	Age: NS; Gender: NS; Health: Healthy & OA Grade 1	Uniaxial Confined Compression	*Healthy & OA Grade 1*	1.3-10.2
Shepherd & Seedhom, 1997	5 x Donors Femoral Condyle & Tibial Plateau	Age: NS; Gender: NS; Health: Healthy	Spring Loaded Indentation	*Healthy*	2.6-18.6
Shepherd & Seedhom, 1999a	11 x Donors Femoral Condyle & Tibial Plateau	Age: 33-80 ; Gender: 8F/3M; Health: Healthy	Spring Loaded Indentation	*Healthy*	6.0-11.8
Franz et al., 2001	24 x Femoral Condyle	Age: 32-89; Gender: NS; Health: Healthy & OA Grade 1	Handheld Indentation	*Healthy & OA Grade 1*	4.3-4.9
Silver et al., 2002	39 x Donors Femoral Condyle	Age: 65 (Average); Gender: 21F/18M; Health: Healthy & OA (Ungraded)	Uniaxial Unconfined Compression	*Healthy Perpendicular* *Healthy Parallel* *OA Perpendicular*	2210.0 7000.0 131.0
Kleemann et al., 2005	21 x Donors Tibial Plateau	Age: 70±13; Gender: 15F/6M; Health: OA Grades 1-3	Uniaxial Unconfined Compression	*OA Grade 1* *OA Grade 2* *OA Grade 3*	0.5 0.4 0.3
Thambyah et al., 2006	7 x Donors Tibia	Age: 62-70; Gender: M; Health: Healthy	Uniaxial Unconfined Compression	*Healthy*	2.1-5.1
Wen et al., 2012	3 x Donors Knee Samples	Age: 35-59; Gender: F; Health: Healthy & OA Grade 1	AFM	*Healthy* *OA Grade 1*	2650.0-3700.0* 2370.0-5640.0*
Wilusz et al., 2013	8 X Donors	Age: 53-83;	AFM	*Healthy PCM & ECM*	0.1 & 0.3

	Femoral Condyle	Gender: NS; Health: Healthy & OA Grades 2-3		*OA Grade 2-3 PCM & ECM*	0.1 & 0.5
Wang et al., 2013	5 x Donors Femoral Condyle	Age: NS; Gender: NS; Health: Healthy & OA Grade 1-3	AFM	*Healthy* *OA Grade 1* *OA Grade 2-3*	0.2 0.6 0.2

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Table 2 (on next page)

Summary of bone material properties

Table 2. Summary of current literature for human knee bone material property compression or indentation testing including age, gender, health status of specimens, number and location of samples tested and technique used to obtain elastic modulus values. Abbreviations: GNS (gender not specified); F (female); M (male); OA (osteoarthritis). *Elastic modulus value for individual OA grade not specified – value taken as approximation from graph.

Author	Quantity & Locality	Age, Gender & Health Status	Testing Technique	Results: Elastic Modulus (MPa)	
Behrens et al., 1974	10 x Donors Femoral Condyle & Tibial Plateau Trabecular Bone	Age: 40-92; Gender: 6F/4M; Health: Healthy	Uniaxial compression	*Femoral Condyle* *Tibial Plateau*	158.9-277.5 139.3-231.4
Lindahl, 1976	8 x Donors Tibial Plateau Trabecular Bone	Age: 14-89; Gender: 4F/4M ; Health: Healthy	Uniaxial compression	*Males* *Females*	34.6 23.1
Carter & Hayes, 1977	100 x Samples Tibial Plateau Trabecular Bone	Age: NS; Gender: NS; Health: Healthy	Uniaxial compression		56.6-83.7
Ducheyne et al., 1977	6 x Donors Femoral Condyle Trabecular Bone	Age: 43-77; Gender: 2F/2M; Health: Healthy	Uniaxial compression		1.9-166.1
Goldstein et al., 1983	5 x Donors Tibial Plateau Trabecular Bone	Age: 50-70; Gender: 2F/3M; Health: Healthy	Uniaxial compression		4.2-430
Hvid & Hansen, 1985	12 x Donors Tibial Plateau Trabecular Bone	Age: 26-83; Gender: 3F/9M; Health: Healthy	Uniaxial compression	*Medial* *Lateral*	13.8-116.4 9.1-47.5
Zysset et al., 1994	6 x Donors Tibial Trabecular Bone	Age: 61-91; Gender: NS; Health: OA Grades 1-3	Uniaxial Compression	*Subchondral* *Epiphyseal/ Metaphyseal*	31.0-1116.0* 8.0-1726.0*
Rho et al., 1997	2 x Donors Tibial Cortical Bone	Age: 57 & 61; Gender: M; Health: Healthy	Nanoindentation		22500.0-25800.0
Burgers et al., 2008	10 X Donors	Age: 45-92;	Uniaxial		131.0-664.0

	Femoral Trabecular	Condyle Bone	Gender: NS; Health: Healthy	Compression

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Table 3(on next page)

Summary of ligament material properties

Table 3. Summary of current literature for human knee ligament material properties including location and number of samples, age, gender, health status of donors, testing technique and resultant data. N.B. for comparison purposes only those papers testing ligaments to failure will be included in this table. Abbreviations: GNS (gender not specified); F (female); M (male); ACL (anterior cruciate ligament); PCL (posterior cruciate ligament); MCL (medial collateral ligament); LCL (lateral collateral ligament). *Values are approximated from graph data.

Author	Quantity & Locality	Age, Gender & Health Status	Testing Technique	Results					
					Stiffness N/mm	Failure Load N	Elastic Modulus MPa	Max Stress MPa	Max Strain %
Trent et al., 1976	7 x ACL, PLC, MCL & LCL	Age: 29-55; Gender: NS; Health: Healthy	Bone-Ligament-Bone	*ACL* *PCL* *MCL* *LCL*	138.3 179.5 70.6 59.8	620.8 658.0 515.8 376.6			
Noyes & Grood, 1976	26 x ACL	Age: 16-86; Gender: NS; Health: Healthy	Bone-Ligament-Bone	*Young* *Old*	182.0 129.0	1730.0 734.0	*111.0* *65.3*	*37.8* *13.3*	*44.3* *30.0*
Butler et al., 1986	3 x ACL, PLC & LCL	Age: 21-30; Gender: 2F/1M; Health: Healthy	Bone-Ligament-Bone	*ACL* *PCL* *LCL*			*278.0-310.0** *280.0-447.0** *375.0-25.0**	*30.0-40.0** *34.0-44.0** *31.0-43.0**	*14.0-16.0** *14.0-19.0** *11.0-17.0**
Woo et al., 1991	27 x ACL Bilateral	Age: 22-97; Gender: NS; Health: Healthy	Bone-Ligament-Bone	*Young 22-35* *Middle 40-50* *Old 60-97*	218.0-242.0 192.0-220.0 124.0-180.0	1602.0-2160.0 1160.0-1503.0 495.0-658.0			
Butler et al., 1992	7 x ACL	Age: 26±4; Gender: NS; Health: Healthy	Bone-Ligament-Bone	*Anteromedial Fibres* *Anterolateral Fibres* *Posterior Fibres*			238.1 285.9 154.9	54.7 30.6 15.4	19.1 16.1 15.2

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Race & Amis, 1994	10 x PCL	Age: 53-98; Gender: NS; Health: Healthy	Bone-Ligament-Bone	*Anterolateral Fibres* *Posteromedial Fibres*	*347.0* *77.0*	1620.0 258.0	248.0 145.0	35.9 24.4	18.0 19.5
Harner et al., 1995	5 x PCL	Age: 48-77; Gender: NS; Health: Healthy	Bone-Ligament-Bone	*Anterolateral Fibres* *Posteromedial Fibres*	120.0 57.0	1120.0 419.0			
Quapp & Weiss, 1998	10 X MCL	Age: 62±18; Gender: NS; Health: Healthy	Ligament Sample Only	*Longitudinal* *Transverse*			38.6 1.7		17.1 1.7
Robinson et al., 2005	8 x MCL	Age: 77±5.3; Gender: NS; Health: Healthy	Bone-Ligament-Bone	*Superficial MCL* *Deep MCL* *Posteromedial capsule*		534.0 194.0 425.0			
Chandrasekhar et al., 2006	17 x ACL	Age: 17-50; Gender: 9F/8M; Health: Healthy	Bone-Ligament-Bone	*ACL Total* *Male* *Female*	250.0 308.0 199.0	1526.0 1818.0 1266.0	113.0 128.0 99.0	24.4 26.4 22.8	

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Table 4(on next page)

Summary of human knee finite element models

Table 4. Summary of recent FE models of whole human knee joints and the type of sample each original primary data collection was based on including location of sample, and age if human samples were used. *Age not specified in original research article. **Multiple references are available in cited reference – unclear as to which study the FE model is using. ***Material properties are not represented – papers are referenced with use of geometry and orientation of structure. Abbreviations: ACL (anterior cruciate ligament); PCL (posterior cruciate ligament); MCL (medial collateral ligament); LCL (lateral collateral ligament).

	Bone	Cartilage	Menisci	Ligaments
Blankevoort et al., 1991	N/a	Information untraceable**	N/a	Human (ACL, PCL, LCL) 43-74 years; Some information untraceable [Butler et al., 1986; Blankevoort et al., 1988***]
Blankevoort & Huiskes, 1991	N/a	Information untraceable**	N/a	Human (ACL, PCL, LCL) 43-74 years; Some information untraceable [Butler et al., 1986; Blankevoort et al., 1988***
Bendjabellah et al., 1995	N/a	Human (tibial plateau) 48-70 years [Hayes & Mockros, 1971]	Human (menisci) 29-45 years; Some information untraceable [Tissakht & Ahmed, 1995]	Human (ACL, PCL, LCL) 53-98 year* [Butler et al., 1988; Race & Amis, 1994]
Bendjabellah et al., 1997	N/a	Human (tibial plateau) 48-70 years [Hayes & Mockros, 1971]	Human (menisci) 29-45 years; Some information untraceable [Tissakht & Ahmed, 1995]	Human (ACL, PCL, LCL) 53-98 year* [Butler et al., 1988; Race & Amis, 1994]
Jilani et al., 1997	N/a	Human (tibial plateau) 48-70 years [Hayes & Mockros, 1971]	Human (menisci) 29-45 years; Some information untraceable [Tissakht & Ahmed, 1995]	Human (ACL, PCL, LCL) 53-98 year* [Butler et al., 1988; Race & Amis, 1994]
Bendjabellah et al., 1998	N/a	Human (tibial plateau) 48-70 years	Human (menisci) 29-45 years; Some information untraceable	Human (ACL, PCL, LCL) 53-98 year*

		[Hayes & Mockros, 1971]	[Tissakht & Ahmed, 1995]	[Butler et al., 1988; Race & Amis, 1994]
Li et al., 1999	N/a	Information untraceable**	N/a	Human (ACL, PCL, LCL) 43-74 years; Some information untraceable [Butler et al., 1986; Blankevoort et al., 1988***
Li et al., 2001	N/a	Information untraceable	N/a	Human (ACL, PCL, LCL) 43-74 years; Some information untraceable [Butler et al., 1986; Blankevoort et al., 1988***]
Moglo & Shirazi-Adl, 2003	N/a	Human (tibial plateau) 48-70 years [Hayes & Mockros, 1971]	Human (menisci) 29-45 years; Some information untraceable [Tissakht & Ahmed, 1995]	Human (ACL, PCL, LCL) 53-98 year* [Butler et al., 1988; Race & Amis, 1994]
Beillas et al., 2004	Human (proximal femur and mid femur) 28-91 years* Bovine (distal femur and patella) Some information untraceable [Lotz et al., 1991; Reilly & Burstein, 1975; Mente & Lewis, 1994]	Human (tibial plateau) age not specified* Some information untraceable [Repo & Finlay, 1977]	Human (menisci) age not specified* [Fithian et al., 1990]	Human (ACL, PCL, MCL, LCL) 16-97 years*; Some information untraceable [Trent et al., 1976; Noyes & Grood, 1976; Woo et al., 1991]
Pena et al.,	N/a	Information untraceable	Canine (menisci)	Theoretical Data

2005			[LeRoux & Setton, 2002]	[Weiss & Gardiner, 2001]
Pena et al., 2006	N/a	Information untraceable	Canine (menisci) [LeRoux & Setton, 2002]	Human (ACL, PCL, MCL, LCL) 37-74 years* [Butler et al., 1986; Gardiner & Weiss, 2003; Blankevoort et al., 1988***; Brantigan & Voshell, 1941***; Butler et al., 1990]
Donlagic et al., 2008	Human (proximal femur and mid femur) years* Bovine (distal femur and patella) Some information untraceable [Lotz et al., 1991; Reilly & Burstein, 1975; Mente & Lewis, 1994]	Human (tibial plateau) age not specified*; Bovine (femoral condyle and tibial plateau); Porcine (femoral condyle and tibial plateau); Some information untraceable [Repo & Finlay, 1977; Laasanen, 2003]	Human (menisci) age not specified* [Fithian et al., 1990]	Human (ACL, PCL, MCL, LCL) 16-97 years*; Some information untraceable [Trent et al., 1976; Noyes & Grood, 1976; Woo et al., 1991]
Shirazi et al., 2008	N/a	Human (tibial plateau) 48-70 years [Hayes & Mockros, 1971]	Human (menisci) 29-45 years; Some information untraceable [Tissakht & Ahmed, 1995]	Human (ACL, PCL, LCL) 53-98 year* [Butler et al., 1988; Race & Amis, 1994]
Guo et al., 2009	Information untraceable	Information untraceable	Canine (menisci) [LeRoux & Settton, 2002]	Information untraceable
Yang et al., 2010	N/a	Information untraceable**	Information untraceable	Human (ACL, PCL, LCL) 43-74 years; Some information untraceable [Butler et al., 1986; Blankevoort et al., 1988***]

Kazemi et al., 2011	N/a	Bovine (humeral head) [Langelier & Buschmann, 1999; Woo et al., 1976]	Human (menisci) 29-45 years [Tissakht & Ahmed, 1995]	Human (Patella Tendon, Achilles Tendon) 29-93 years; Rat (Tail Tendon) [Hansen et al., 2006b; Johnson et al., 1994; Louis-Ugbo et al., 2004; Ault & Hoffman, 1992a]
Wang et al., 2014	Human (tibial plateau and femoral neck) 53-93 years* [Rho et al., 1993; Zysset et al., 1999]	Human (femoral condyle and tibial plateau) 33-80 years [Shepherd & Seedhom, 1999a]	Human (menisci) 29-45 years*; Bovine (menisci); Some information untraceable [Tissakht & Ahmed, 1995; Skaggs et al., 1994]	Human (ACL, PCL, LCL, Quadriceps Tendon, Patella Ligament) 24-98 years*; Some information untraceable [Butler et al., 1986; Race & Amis, 1994; Staubli et al., 1999; Blankevoort et al., 1988***; Brantigan & Voshell, 1941***]
Mootanah et al., 2014	Human (femoral condyle and tibial plateau) 45-68 years [Hobatho et al., 1991]	Human (femoral condyle and tibial plateau) 33-80 years [Shepherd & Seedhom, 1997; Blankevoort et al., 1988***]	Information untraceable	Human (ACL, PCL, MCL, LCL) 50 years Primary Data
Kazemi et al., 2014	N/a	Human (tibial plateau) 48-70 years; Bovine (humeral head) [Langelier & Buschmann, 1999; Woo et al., 1976; Hayes & Mockros, 1971]	Human (menisci) 29-45 years [Tissakht & Ahmed, 1995]	Human (ACL, PCL, LCL, Patella Tendon, Achilles Tendon) 29-98 years*; Rat (Tail Tendon) [Butler et al., 1986; Race & Amis, 1994; Blankevoort et al., 1988***; Brantigan & Voshell, 1941***; Hansen et al., 2006b;

	Johnson et al., 1994; Louis-Ugbo et al., 2004; Ault & Hoffman, 1992a]

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Table 5(on next page)

Summary of material properties included in finite element models

Table 5. Material property values included in each of the finite element modelling studies. Abbreviations: *E* (elastic modulus), *v* (Poisson's ratio), NM (not modelled), NS (not specified); ACL (anterior cruciate ligament); PCL (posterior cruciate ligament); MCL (medial collateral ligament); LCL (lateral collateral ligament).

	Bone		Cartilage		Menisci		ACL		PCL		MCL		LCL	
	E (MPa)	ν	E (MPa)	ν	E (MPa)	ν	E (MPa) OR Stiffness (N)	Initial Strain (%/mm)	E (MPa) OR Stiffness (N)	Initial Strain (%/mm)	E (MPa) OR Stiffness (N)	Initial Strain (%/mm)	E (MPa) OR Stiffness (N)	Initial Strain (%/mm)
Wang et al., 2014	20,000	0.3	10	0.05-0.45	20-140	0.2	NS	0.0-0.1%	NS	0.0-0.1%	NS	0.0-0.1%	NS	0.0-0.1%
Pena et al., 2006	Rigid	Rigid	5	0.46	59	0.49	1.95 MPa	0.0-0.1%	3.25 MPa	0.0-0.1%	1.44 MPa	0.0-0.1%	1.44 MPa	0.0-0.1%
Pena et al., 2005	Rigid	Rigid	5	0.46	59	0.49	5.83 MPa	NS	6.06 MPa	NS	6.43 MPa	NS	6.06 MPa	NS
Guo et al., 2009	11,000	0.3	5	0.45	59	0.46	NS	NS	NS	NS	NS	NS	NS	NS
Mootanah et al., 2014	1,000	0.3	25	0.45	20-120	0.2-0.3	154 MPa	NS	40 MPa	NS	43 MPa	NS	56 MPa	NS
Kazemi et al., 2011	Rigid	Rigid	0.26-1600	0.36	0.5-28	0.36	10-14,000 MPa	NS	10-14,000 MPa	NS	10-14,000 MPa	NS	10-14,000 MPa	NS
Kazemi & Li, 2014	Rigid	Rigid	0.413-367.14	NS	0.0-12.84	NS	46.47 - 1118.6 MPa	2.5%	46.47-1118.6 MPa	0%	46.47-1118.6 MPa	2%	46.5-1118.6 MPa	2%
Potocnik et al., 2008	1,000	0.3	67.6	0.3	130	0.3	200-260 MPa	NS	200-260 MPa	NS	114-134 MPa	NS	114-134 MPa	NS
Li et al.,	Rigid	Rigid	3.5-10	0.45	NM	NM	5000N	0.3-	9000N	2.3-	2750N	0.2-	2000N	-

2001								0.8mm		3mm		0.4mm		0.4mm
Li et al., 1999	Rigid	Rigid	5	0.45	NM	NM	5000N	0.3-0.8mm	9000N	2.3-3mm	2750N	0.2-0.4mm	2000N	-0.4mm
Blankevoort et al., 1991;	Rigid	Rigid	5	0.45	NM	NM	5000N	0.06-0.1%	9000N	-0.03--0.24%	2750N	0.03-0.04%	2000N	-0.05 – -0.25%
Blankevoort & Huiskes, 1991;	Rigid	Rigid	5	0.45	NM	NM	5000N	0.06-0.1%	9000N	-0.03--0.24%	2750N	0.03-0.04%	2000N	-0.05 – -0.25%
Bendjabellah et al., 1995;	Rigid	Rigid	12	0.45	8-15	0.45	NS	1.2-4%	NS	-1 – -16.9%	NS	1.8-3.4%	NS	2.6-5%
Bendjabellah et al., 1997;	Rigid	Rigid	12	0.45	8-15	0.45	NS	1.2-4%	NS	-1 – -16.9%	NS	1.8-3.4%	NS	2.6-5%
Bendjabellah et al., 1998;	Rigid	Rigid	12	0.45	8-15	0.45	NS	1.2-4%	NS	-1 – -16.9%	NS	1.8-3.4%	NS	2.6-5%
Jilani et al., 1997;	Rigid	Rigid	12	0.45	8-15	0.45	NS	1.2-4%	NS	-1 – -16.9%	NS	1.8-3.4%	NS	2.6-5%
Moglo & Shirazi-Adl, 2003;	Rigid	Rigid	12	0.45	8-15	0.45	NS	1.2-4%	NS	-1 – -16.9%	NS	1.8-3.4%	NS	2.6-5%
Shirazi et al., 2008	Rigid	Rigid	12	0.45	8-15	0.45	NS	1.2-4%	NS	-1 – -	NS	1.8-3.4%	NS	2.6-5%

										16.9%				
Yang et al., 2010	Rigid	Rigid	15	0.45	20-140	0.2-0.3	5000N	0.06-0.1%	9000N	-0.03--0.24%	2750N	0.03-0.04%	2000N	-0.05 – -0.25%
Bellias et al., 2004	75-17500	0.3	20	0.45	250	0.45	150 MPa	NS	150 MPa	NS	60 MPa	NS	60 MPa	NS

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Figure 1(on next page)

Cartilage stiffness during degeneration

Figure 1. Stiffness reduction of degenerated cartilage with increasing International Cartilage Repair Society (ICRS) Grade related to boxplots displaying median values and interquartile range. (Adopted from Kleemann et al., [2005]: Elsevier License Permission: 4095850046133).

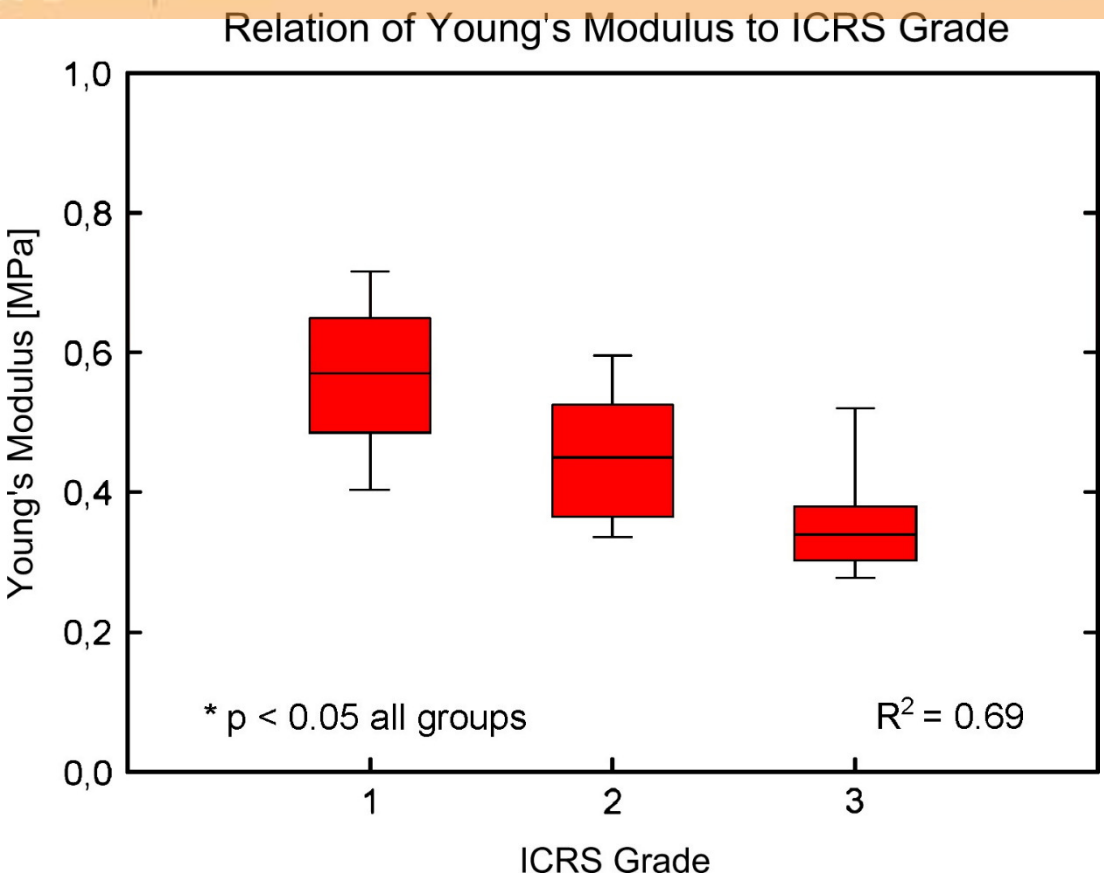
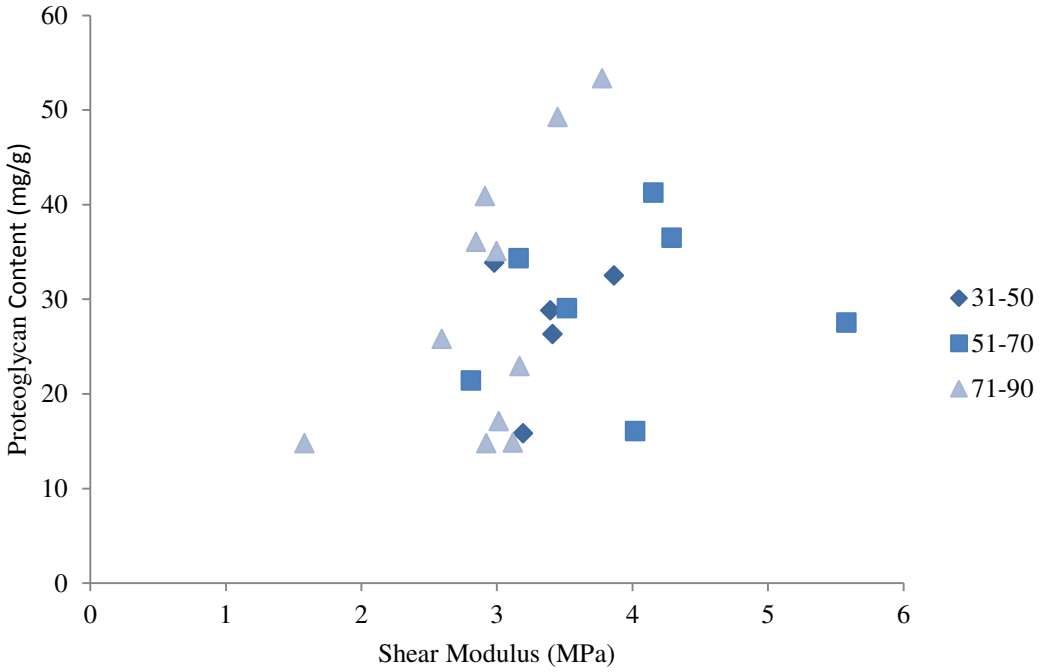


Figure 2(on next page)

Cartilage shear modulus to proteoglycan and collagen content in young and old

Figure 2. Total proteoglycan content (mg/g tissue wet weight) versus cartilage compressive stiffness (shear modulus in MPa) for the lateral femoral condyle, and total collagen content (mg/g tissue wet weight) versus cartilage compressive stiffness (shear modulus in MPa) for the lateral femoral condyle. All subjects are divided into three age groups (31 – 50 years, 51 – 70 years, 71 – 90 years) to demonstrate that the variation of total proteoglycan and collagen content is not due to the large age range. (Recreated from Franz et al., [2001]: Elsevier License Permission: 4095850249345).



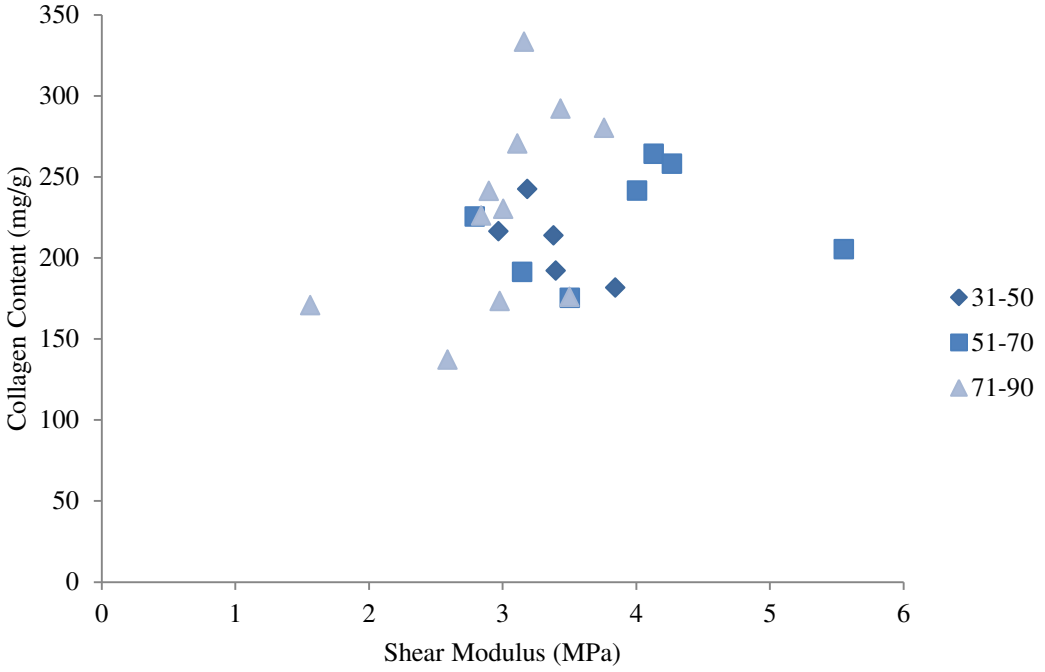


Figure 3(on next page)

Compressive elastic modulus of subchondral bone in osteoarthritis

Figure 3. Compressive axial elastic modulus of subchondral bone for a range of osteoarthritis (OA) grades (1-3). Average elastic modulus decreases with degenerative grade in the medial (MED) and especially lateral (LAT) compartments. (Recreated from Zysset et al., [1994]: Elsevier License Permission: 4095850483612).

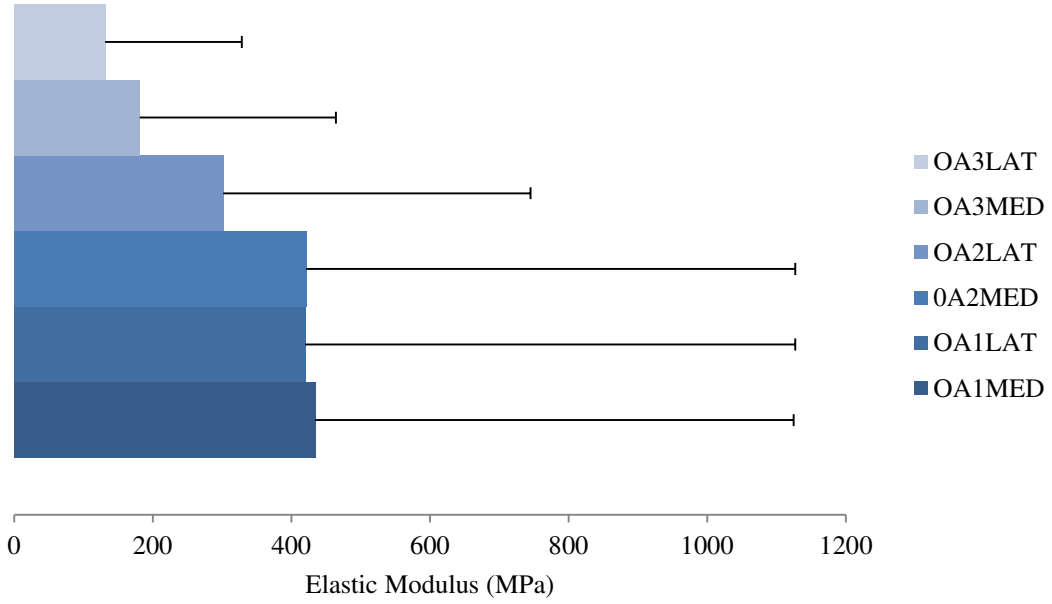


Figure 4(on next page)

Example bone-ligament-bone sample

Figure 4. MCL bone–ligament–bone tensile testing specimen which is divided into the 1) sMCL (superficial medial collateral ligament) (image is post-failure of this fibre attachment at the medial epicondyle of femur), 2) PMC (posteromedial capsule) fibres and bone block, 3) dMCL (deep medial collateral ligament) fibres and bone block. (Adopted from Robinson et al., [2005]: Elsevier License Permission: 4095850605057).

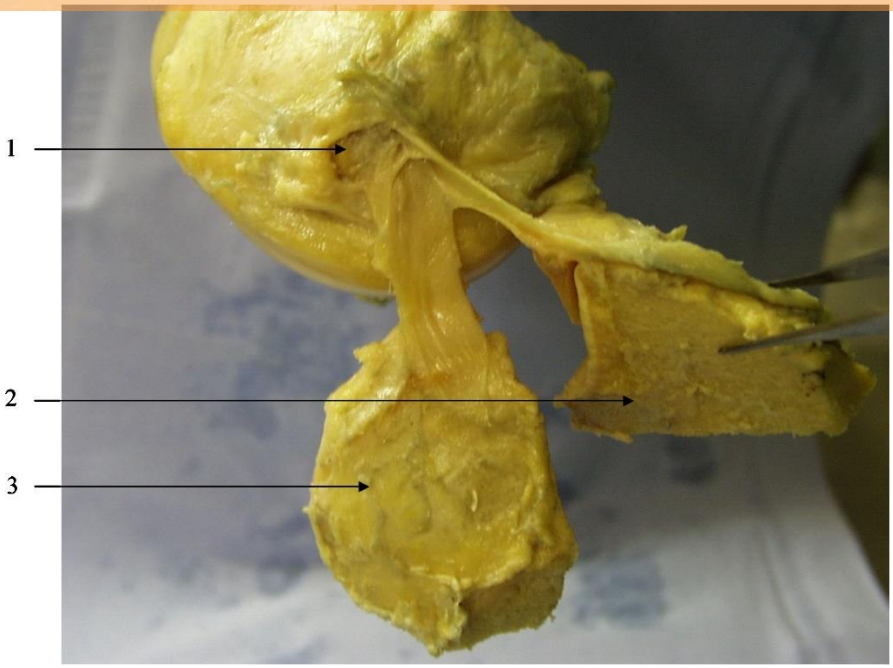


Figure 5(on next page)

Effect of specimen age on anterior cruciate ligament ultimate load

Figure 5. Effect of specimen age on anterior cruciate ligament (ACL) ultimate load. Data on ultimate load as a function of specimen age and orientation demonstrated that the strength of the ACL decreases in an exponential manner. (Recreated from Woo et al., [1991]: Sage Publishing Gratis Reuse Granted).

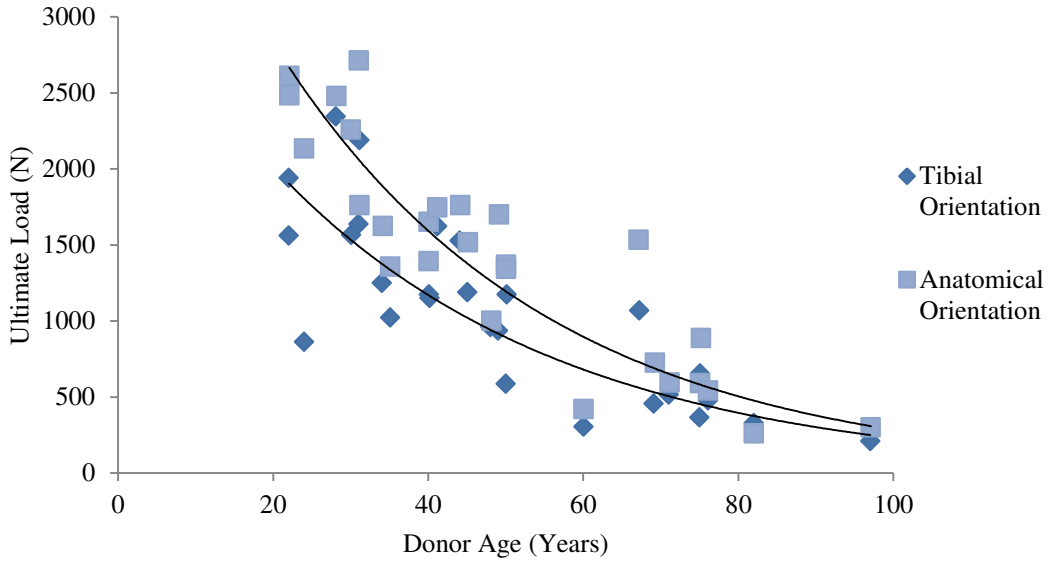


Figure 6(on next page)

A finite element model of the knee joint

Figure 6. A FE model of the knee joint in (a) Kneeling position and (b) standing position. All structures are modelled in three dimension including the distal femur, proximal tibia and patella bones, femoral and tibial cartilage, medial and lateral menisci, ACL (anterior cruciate ligament), PCL (posterior cruciate ligament), MCL (medial collateral ligament), LCL (lateral collateral ligament) and patella tendon (Reproduced from Wang et al., [2014]: Elsevier License Permission: 4095850783229).

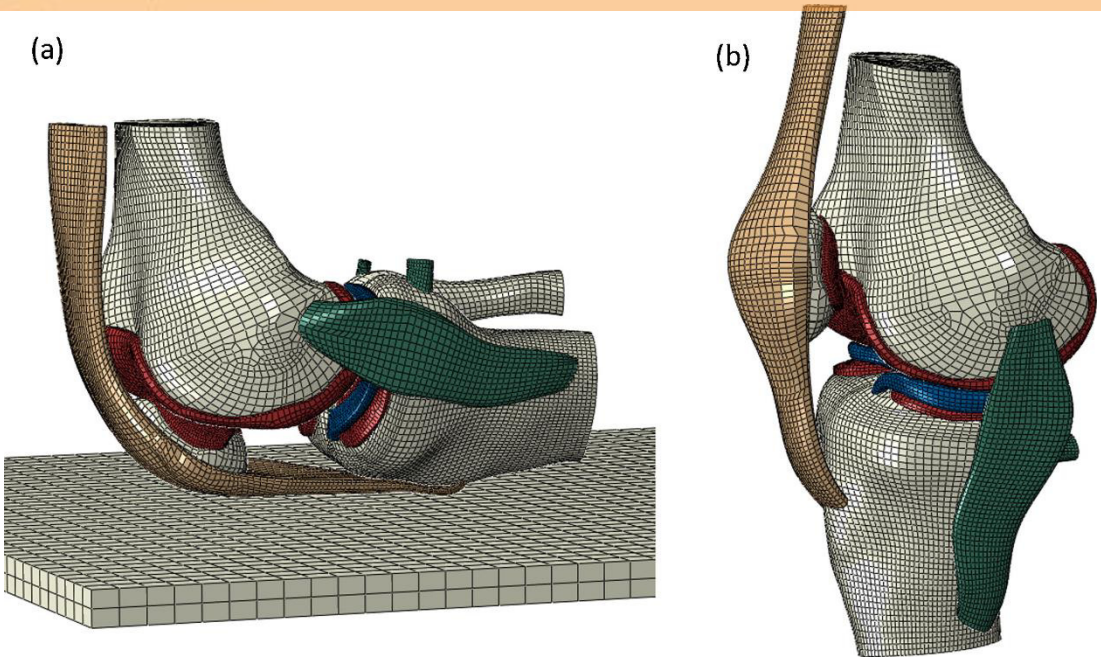


Figure 7 (on next page)

Human knee finite element mesh

Figure 7. Posterior view of a finite element mesh showing soft tissues (menisci and articular cartilage layers). Ligaments are modelled as one dimensional line elements. Rigid bodies representing the femur and the tibia are not shown. (Reproduced from Shirazi et al., [2008]: Elsevier License Number: 4095851087452).

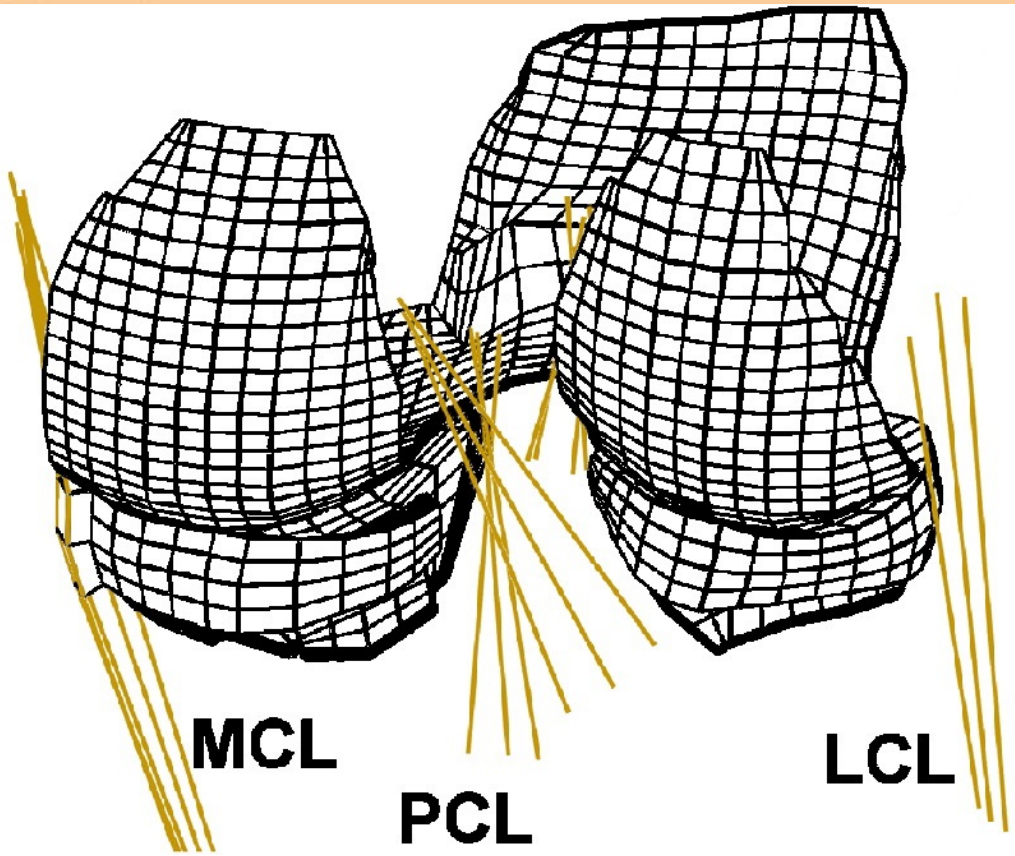


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Figure 8(on next page)

Human knee finite element model of cartilage defects

Figure 8. A FE model of cartilage defects in a high-weight-bearing area in the medial condyle: (a)0.19 cm^2 area defect; (b)0.78 cm^2area defect; (c)1.76 cm^2area defect; and (d)3.14 cm^2area defect and a low-weight-bearing area in the medial condyle: (e)0.19 cm^2area defect; (f)0.78 cm^2area defect; (g)1.76 cm^2area defect; and (h)3.14 cm^2area defect. (Adopted from Pena et al., [2007]: Elsevier License Number: 4095850931678).