THE PHYSIOPATHOLOGY OF OSTEOARTHRITIS: APPLYING BIOARCHAEOLOGICAL MEASURES TO A MODERN SURGICAL POPULATION

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ABSTRACT

Osteoarthritis (OA) is a set of overlapping conditions involving the loss of articular cartilage and changes to the underlying subchondral bone; ultimately, the structure and function of an affected synovial joint can be compromised. Pain is a hallmark of the condition, but the source of pain is poorly understood. OA is an ancient disease, with evidence of its presence in human populations dating to more than 7000 years ago. Paleopathological criteria for OA diagnosis include eburnation, marginal and surface osteophyte presence, porosity, and alteration in joint contour. This research combined the knowledge and techniques of clinical medicine and bioarchaeology to observe and analyse OA lesions on dry bone to identify potential pain sources. Sixty-two tibial plateaus removed from patients (male=31; female=31) undergoing total knee replacement surgery due to OA were reduced to dry bone and observed and scored using the Buikstra and Ubelaker (1994) standards for archaeological dry bone. The study sought to answer four main questions: 1) Are there macroscopically visible OA-related lesions present on the study plateaus? 2) Are there significant male and female differences in the patterning of lesions observed? 3) Are there specific lesions or lesion patterns that may be associated with a source of pain? 4) Are there consistently observed lesions that are not included on bioarchaeological measures of OA lesions? Results indicated that articular surface OA lesions were present in all study specimens, and there were few significant differences in lesion severity between male and female plateaus. There were several lesions, not included on bioarcheological measures of OA, consistently observed in the non-articular portions of the plateau: proliferative bone in the intercondylar region, and areas of dense appearing trabecular bone and lytic defects, both on the inferior (cut) side of the plateaus. It is suggested that the inferior lytic defects may be physical evidence of bone marrow lesions (BML), an OA symptom visible only via MRI. Previous research has linked BML to pain, as well as inflammation and ligament pathology. The latter conditions have also been linked to both intercondylar enthesophytes and third intercondylar tubercle of Parsons (TITP), as observed in the intercondylar regions of these samples. The results suggest numerous avenues for future research in both bioarchaeology and clinical medicine.

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Introduction

Osteoarthritis (OA), a progressive synovial joint disease, currently affects over 4 million Canadians (Arthritis Alliance of Canada, 2011). Already the most common cause of workplace disability, estimates indicate that the disease's prevalence will only increase over the foreseeable future (Silverwood et al., 2015; Weinans et al., 2012). By 2040, it is expected that one in four Canadians will be affected by the condition (Arthritis Alliance of Canada, 2011). At present, data from other countries indicate similar projected growth rates (Andersen, Thygesen, Davidsen, & Helweg-Larsen, 2012; Garstang & Stitik, 2006; Palazzo, Nguyen, Lefevre-Colau, Rannou, & Poiraudeau, 2016; Wallace et al., 2017). While not life-threatening, OA can be characterized as a life-limiting condition. Individuals with suspected OA present clinically with pain, swelling, crepitus, and impaired movement in the affected joint(s) (Hunter & Felson, 2006). Symptoms may initially be intermittent; with the disease's progression, symptoms tend to become chronic, affecting an individual's work and leisure activities, as well as the ease with which s/he is able to perform daily tasks of living (Hunter & Felson, 2006).

OA is not merely a condition of modern, industrialized life. Archaeological evidence from Eurasia, for example, suggests that OA has existed for more than 7000 years (Crubézy et al., 2002; Lieverse, Weber, Bazaliiskii, Goriunova, & Savel'ev, 2007). Dequeker and Luyten (2008) describe osseous lesions associated with OA found in a 100 million year old dinosaur fossil, as well as in the first identified examples of *H. neanderthalensis* (450,000-35,000 years BP). The disease seems to have affected hunter-fisher-gatherer and agrarian populations alike (Crubézy et al., 2002; Eng, 2016; Lieverse et al., 2007). In examining dry bone, archaeologists are able to clearly see the osteological signs of OA: osteophyte development, porosity, sclerotic bone formation, eburnation, and joint contour modification due to reactive bone growth and resorption (Buikstra & Ubelaker, 1994; Ortner, 2003; Waldron, 2008).

In spite of its long history of causing pain and incapacity in humans and other animals, and its being the focus of intensive research, OA remains surprisingly elusive. Pain is a hallmark of the disease, yet its sources are not clear (Felson, 2005; Yusuf, Kortekaas, Watt, Huizinga, & Kloppenburg, 2011). The condition's etiology is complex and multifactorial; research now indicates that, rather than constituting a single disease, OA is a set of related and overlapping conditions involving articular, or hyaline, cartilage deterioration and destruction, and concomitant subchondral bone modification (Garstang & Stitik, 2006). Current OA research is

equally complex and multifactorial, focusing on a myriad of risk factors, structural and chemical dynamics, effective imaging technologies, and analgesic and treatment options (e.g., Botter et al., 2011; Cox, Van Donkelaar, van Rietbergen, Emans, & Ito, 2013; Muratovic et al., 2016; Raynauld et al., 2008).

The purpose of this research is to bring together the knowledge and techniques of clinical medicine and bioarchaeology in order to enhance both disciplines' understanding of OA and the potential association of OA-related bone lesions with pain. This purpose will be accomplished by applying bioarchaeological measures of OA bone lesions to tibial plateaus surgically removed from an extant population of OA sufferers (n=62). The study mainly addresses the following questions: 1) Are there macroscopically visible OA-related lesions present on the study plateaus? 2) Are there significant male and female differences in the patterning of lesions observed? 3) Are there specific lesions or lesion patterns that may be associated with a source of pain? 4) Are there consistently observed lesions that are not included on bioarchaeological measures of OA lesions?

The following chapter provides background information on OA. Beginning with a description of normal synovial joint function, it then reviews current research on the disease's pathogenesis and risk factors. The chapter closes with a discussion of bioarchaeological research on OA. Subsequent chapters provide a more detailed description of the research questions, the study sample, and the research methodology employed.

Chapter 1
Background and Research Problem

1.1 Normal Synovial Joint Components and Function

Osteoarthritis affects the synovial, or diarthrodial, joints; these provide the body with movement and flexibility (Martini, Timmons & Tallitsch, 2015). Synovial joints are complex structures, consisting of a number of interrelated parts which, under normal conditions, operate in concert to maintain joint homeostasis, structural integrity, and function. Every synovial joint consists of subchondral bone, articular cartilage, a synovial membrane, and synovial fluid, all encased in a joint capsule (Martini et al., 2015). Depending upon its location and function, a synovial joint may also contain labral tissue, interosseous ligaments, menisci, and fat pads (Garstang & Stitik, 2006; Martini et al., 2015; McGonagle, Tan, Carey, & Benjamin, 2010).

Like bone in other parts of the skeleton, subchondral bone is comprised of a layer of dense cortical bone (the subchondral bone plate) covering trabecular bone, which contains bone marrow, blood vessels, and sensory nerves (Li et al., 2013; Suri & Walsh, 2012). The subchondral cortical bone is substantially thinner than the cortical bone found in a typical long bone diaphysis; the shock absorbing properties of the underlying trabecular bone protect the articular cartilage from damage (Imhof et al., 2000; McGonagle et al., 2010). Garstang and Stitik (2006) report that subchondral bone absorbs approximately 10 times as much load force as hyaline cartilage. In addition to structural support, normal subchondral bone provides nutritional support to the deepest layers of calcified cartilage via vascular channels that penetrate the subchondral bone surface from the deeper trabecular bone (Imhof et al., 2000; Suri & Walsh, 2012).

Hyaline, or articular, cartilage is an avascular, aneural tissue that functions to reduce friction, absorb shock, and bear and distribute loads (Pearle, Warren, & Rodeo, 2005). Its avascular nature means that it regenerates slowly, if at all. Cartilage is made up of chondrocytes (cartilage maintenance cells) and a dense extracellular matrix that consists mainly of water, type II collagen, and proteoglycans (Garstang & Stitik, 2006; Huber, Trattnig, & Lintner, 2000). Type II collagen, along with smaller amounts of other collagens, forms the fibrous 'scaffolding' of the tissue (Huber et al., 2000). In cartilage, proteoglycans (molecules consisting of protein cores

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surrounded by chains of glycosaminoglycan) aggregate to form aggrecans; these have elastic properties that both expand in solution and provide cartilage with its durability and compression tolerance (Huber et al., 2000; McGonagle et al., 2010).

There are four structurally and functionally distinct layers of cartilage, which may be easily seen in histological assessments (Imhof et al., 2000). The superficial zone is outermost, providing a smooth, friction-free, gliding surface. Also known as the tangential layer, this zone contains the most collagen; collagen fibres are oriented parallel to the joint surface (Garstang & Stitik, 2006; Pearle et al., 2005). The thick middle zone has fewer, obliquely oriented collagen fibres, and a much higher compressive capacity compared to the superficial zone (Pearle et al., 2005).

The third deep zone consists of thick collagen fibres oriented perpendicular to the articular surface. These fibres attach to the underlying subchondral bone plate through the fourth layer consisting of calcified cartilage. The junction between the deep uncalcified cartilage and calcified cartilage layers is called the tidemark, a single line of basophilic cells, approximately 10 µm thick (Lyons, McClure, Stoddart, & McClure, 2006; Suri & Walsh, 2012).

As will be discussed in some detail below, it is this osteochondral junction—the subchondral bone plate, calcified cartilage layer, tidemark, and deepest layer of uncalcified cartilage—that is of significant interest to researchers examining the mechanism of OA initiation and progression (Findlay & Kuliwaba, 2016; Li et al., 2013; Suri & Walsh, 2012). Research indicates that in a normal joint, the tidemark clearly delineates the calcified and uncalcified cartilage layers, but is not a flat plane across the joint (Huber et al., 2000; Lyons et al., 2006). Rather, the tidemark is a three-dimensional structure that separates the two layers, even as the uncalcified layer dips into calcified territory, and occasionally into subchondral bone (Lyons et al., 2006). The calcified cartilage layer or zone, often referred to in literature as the CCZ, contains calcium salts at an even higher level than the underlying subchondral bone plate (Wang et al., 2009). Three-dimensional modelling work on the CCZ and subchondral bone interface demonstrates that the two are held firmly together by a "comb-anchor" structure (Wang et al., 2009, p. 359). Imhof and colleagues (2000) describe this concept as a "jigsaw puzzle", wherein calcified cartilage plugs into the uneven surface of the subchondral bone (p. 582).

Bone and cartilage are surrounded by the joint capsule, which is lined by the synovial membrane. Cells of this membrane produce synovial fluid, the main function of which is to

lubricate and provide nutrients to articular cartilage (McGonagle et al., 2010). In addition, synovial fluid prevents protein deposition on the articular surface and provides a barrier to prevent inflammation and debris movement within the capsule (Garstang & Stitik, 2006; Scanzello & Goldring, 2012; Smith 2011).

As mentioned previously, all synovial joints contain the structures detailed above. Menisci and ligaments may also be components of a synovial joint. Both are found in the knee, which figures prominently in a great deal of current OA clinical research (e.g. Katsuragi et al., 2015; Muratovic et al., 2018; Palazzo, Nguyen, Lefevre-Colau, Rannou, & Poiraudeau, 2016; Zhang et al., 2011). Ligaments, consisting of fibrous connective tissue, primarily guide and limit joint movement, and may have some involvement in proprioception, or the ability to sense stimuli regarding body position, motion, or balance (McGonagle et al., 2010). They may be thickened areas of the joint capsule, or independent structures. Menisci are fibrocartilaginous discs, thought to be modified ligaments, whose functions include joint cushioning and load distribution, as well as channelling the flow of synovial fluid and compensating for variations in the shape of articular surfaces (Martini et al., 2015; McGonagle et al., 2010).

1.2 Soft Tissue Effects of OA

OA can affect all of the components of a normal synovial joint. Each OA case may have different or multiple structures of origin (McGonagle et al., 2010). As this thesis is mainly concerned with the bone and cartilage effects of OA (i.e., osteophytes, bone marrow lesions, cartilage degradation, and subchondral bone alteration), these will be dealt with in detail in subsequent sections. However, just as a healthy joint is the sum of its normally-functioning structures, a joint affected by OA usually consists of both hard (bone and cartilage) and soft tissue involvement (Loeser, Goldring, Scanzello, & Goldring, 2012). While not observable as bone lesions, OA-affected soft tissue is visible on various imaging modalities, appears to be an important component in the patient experience of OA, and may be part of a whole-joint biochemical cycle (Felson, 2005; Hunter & Felson, 2006; Loeser et al., 2012).

Ligament and meniscus damage have long been recognized as contributing factors in the development of secondary OA (i.e., comorbid with an existing injury or pathological condition) (Garstang & Stitik 2006). In animal studies, inducing ligament injury or meniscal displacement is the typical method by which OA is produced in the experimental subjects (Botter et al., 2011;

Dedrick, Goulet, O'Connor, & Brandt, 1997; Sniekers et al., 2008). McGonagle and colleagues (2010) suggest that radiologically observable joint space narrowing in human knees, usually attributed to the thinning and degradation of articular cartilage, may be due to meniscal displacement; the researchers then present a likely cascade of effects, including localized synovitis (i.e., synovial membrane inflammation) and cartilage damage, and ligament strain. The latter is associated with joint malalignment, which in turn adversely influences joint stability, loading capacity, and other biomechanical factors (Garstang & Stitik, 2006).

OA has traditionally been categorized as a non-inflammatory condition, in contrast with rheumatoid arthritis (RA), for which inflammation is a primary diagnostic criterion (Scanzello & Goldring, 2012). However, since the 1980s, clinicians have observed similar patterns of synovial membrane inflammation in OA patients as in RA sufferers; this was initially attributed to irritation caused by the presence of bone or cartilage detritus in the synovial fluid (Revell, Mayston, Lalor, & Mapp, 1988; Scanzello & Goldring, 2012). Now, researchers recognize that synovitis has a number of manifestations, including synovial membrane inflammation or vascularization, effusion, and changes in synovial membrane permeability (Scanzello & Goldring, 2012). Much of the additional knowledge of synovial symptoms in OA is due to the availability and use of imaging technologies that allow for the viewing of soft tissue and fluid in a living individual. Both magnetic resonance imaging (MRI) and ultrasound are capable of this; instances of synovial membrane vascularization are easily detected by ultrasound in Doppler mode (Iagnocco, 2014; Keen & Conaghan, 2009).

Scanzello and Goldring (2012) suggest that changes to the synovial membrane may have more deleterious effects on the whole joint than may be initially apparent. As mentioned previously, the cells of the synovial membrane produce synovial fluid, which provides lubrication and nutrients to the articular cartilage. The membrane itself has the additional role of selective permeability; low molecular weight particles pass through the membrane, but high weight particles, including those involved in lubrication, do not. Membrane inflammation changes the permeability, and eventually, the composition of the synovial fluid, adversely affecting its lubricating qualities (Scanzello & Goldring, 2012; Smith, 2011). Other research links synovial inflammation in OA to an immune response that results in the synovial cells releasing cartilage-degrading enzymes into the synovial fluid (Guilak et al., 2004; Long, Blake, Song, Lark, & Loeser, 2008; Scanzello et al., 2009). Further inflammatory mediators are also

released into the joint, which have the effect of increasing cartilage degradation and maintaining inflammation (Garstang & Stitik, 2006). Research by Ayral and colleagues (2005) and Birn and colleagues (2014) appears to provide support for these findings; both studies found a correlation between synovitis and effusion (excess synovial fluid) and the progression of OA, as measured by cartilage degradation and bone destruction.

The experience of pain due to OA is the main impetus for people to seek medical attention for the condition, as well as a primary factor in disability and eventual joint replacement (Arthritis Alliance of Canada, 2011; Hall et al., 2014; Sofat, Ejindu, & Kiely, 2011). However, the source and cause of the pain is poorly understood. As Felson (2005) notes, cartilage is aneural; therefore, the cartilage damage inherent in OA is normally thought to be an unlikely source of pain. Radiographic imaging is typically used to confirm an OA diagnosis when an individual presents clinically with symptoms resembling OA (Felson, 2006). Only osteophyte presence, joint space narrowing attributed to cartilage loss or meniscal damage, and sclerosis of the subchondral bone surface are visible using this technology (Laxafoss, Jacobsen, Gosvig, & Sonne-Holm, 2010). Studies attempting to link patient-reported pain with radiographically visible OA are inconclusive; some show a strong relationship between the two (Laxafoss et al., 2010; Neogi et al., 2009), while others report virtually no relationship (Bedson & Croft, 2008; Chan, Sit, Wu, & Ngai, 2014). Given the lack of decisive results, one could conclude that there must be other factors, undetectable by current clinical imaging technologies, at least contributing to the pain, if not exclusively causing it (Sofat et al., 2011).

As mentioned above, most studies attempting to correlate patient pain with known OA symptoms have been inconclusive. Only research examining synovitis/effusion and bone marrow lesions showed a moderately positive relationship (Yusuf et al., 2011). Bone marrow lesions (BML), sometimes referred to as bone marrow edema, are areas of intense marrow signal in fluid-sensitive, fat supressed MRI sequences (Alliston, Hernandez, Findlay, Felson, & Kennedy, 2017). Simply put, they are areas within the trabecular bone underlying the subchondral bone plate that appear as fluid-filled spaces. Zhang and colleagues (2011) demonstrated a positive relationship between synovial inflammation and increased knee pain, as well as a link between pain amelioration and diminishing BML size. Other studies, however, found no relationship between reported changes in knee pain and MRI-measured changes in synovial hypertrophy or

effusion (Hall et al., 2014). It is evident that OA-related pain may be as multifactorial as the condition itself.

1.3 Bone and Cartilage Effects of OA

Much of the current research on the processes and structures associated with OA has benefitted from advances in imaging technology. Researchers and clinicians are now able to view internal bone arrangement and changes, even in living individuals. This has allowed for the correlation of structural changes with both disease progression and patient experience. However, by necessity, considerable work is still being performed *ex vivo* and/or with animal models. The next section of the paper will describe the current understanding of the effects and mechanisms of OA on bone and cartilage. For organizational purposes, the various components will be discussed in order of their ease of access and observation, from those visible on radiographs, to those which require histological analysis.

1.3.1 Osteophytes

In work with both living patients and archaeological remains, osteophyte presence is one of the most accepted and visible components of OA. Along with joint space narrowing, osteophytes are also part of the accepted radiographic diagnosis of OA (Felson et al., 2005; Kellgren & Lawrence, 1957). van der Kraan and van den Berg (2007) define osteophytes as synovial joint-specific bony outgrowths, covered with fibrocartilage, that arise from the periosteum at the junction of cartilage and bone. They distinguish these, true osteophytes, from enthesophytes and syndesmophytes, both of which are associated with the insertion points of ligaments and tendons (van der Kraan & van den Berg, 2007).

Past research has painted an unclear picture of the possible effect(s) of osteophytes. Their presence, especially on synovial vertebral elements, may cause pain and neurological issues, yet in appendicular joints, there may be no association with pain (van der Kraan & van den Berg, 2007). Some suggest that osteophytes act to reclaim diminished joint space or stabilize a pathologically unstable joint (Felson et al., 2005). Therefore, much of the osteophyte centred research is concerned with the question of whether osteophytic growth is a pathological reaction or a functional response to joint alteration. Felson and colleagues (2005) argue that, if the latter were the case and osteophytes served a joint stabilizing purpose, then their presence should have

no significant relationship to OA progression. However, a number of studies have concluded that the presence of large osteophytes is, in fact, associated with disease progression, as well as correlates of disease progression such as joint malalignment and adjacent cartilage loss (Boegård, Rudling, Petersson, & Jonsson, 1998; D. T. Felson et al., 2005; Katsuragi et al., 2015).

As noted above, osteophyte presence is one of the diagnostic criteria for radiographic OA; in this case, only marginal osteophytes (around the perimeter of the joint surface) are considered, due to the constraints of radiographic imaging (Kellgren & Lawrence, 1957; van der Kraan & van den Berg, 2007). Advances in imaging technology have allowed researchers to investigate radiographically undetectable osteophytes, especially in the femoral intercondylar notch. This area is not easily visible in standard radiograph views, but researchers are able to detect osteophytes via three-dimensional reconstructions of MRI views (Katsuragi et al., 2015; Sasho et al., 2017). Early data indicate that osteophyte presence in the femoral intercondylar notch is correlated with the subsequent development of radiographically visible OA within two years (Katsuragi et al., 2015).

Much of the research on osteophyte genesis relies heavily on evidence from murine models. The formation process appears to be similar to that of endochondral ossification, one of the two processes of bone formation and repair (van der Kraan & van den Berg, 2007). Here, the chondrocytes of a cartilaginous model expand, mineralize the surrounding matrix and die, creating a cavity for the invasion of osteoblasts, osteoclasts, and other cells (Martini et al., 2015). In the case of an osteophyte, once fully developed, it remains covered with a fibrous layer and is integrated with the subchondral bone (van der Kraan & van den Berg, 2007). Mesenchymal stem cells in the periosteum and synovium may serve as initiating cells, and growth factors produced by synovial macrophages may contribute to osteophyte formation (van der Kraan & van den Berg, 2007). Interestingly, many of the same biochemicals involved in enzymatic reactions that may contribute to osteophyte formation are included in discussions on the effects of synovial inflammation. While biomechanical factors may be involved in osteophyte formation, the process involves many of the same signal pathways as callus formation in a healing fracture, as well as enzymes from an inflamed synovium which stimulate chondrogenesis, eventually initiating the process of endochondral ossification and osteophyte development (van der Kraan and van den Berg, 2007). Studies of osteophyte presence only on joint regions still retaining some articular cartilage appear to suggest that the processes of chondrogenesis and endochondral

ossification are involved in osteophyte development (Hayeri, Shiehmorteza, Trudell, Hefflin, & Resnick, 2010).

Other research suggests that there may be individual metabolic processes involved in osteophytic growth. A number of studies have documented significant positive correlations between osteophyte development and other features associated with 'bone formers' (Rogers, Shepstone, & Dieppe, 1997), such as increased enthesophyte (ossification of tendon or ligament insertion sites) size and number and higher bone mineral density (Hardcastle et al., 2014; Mays, 2016; Rogers et al., 1997). An altered bone responsiveness, the tendency to form bone in response to stress, may unite these various conditions, possibly related to underlying genetic factors (Hardcastle et al., 2014; Rogers et al., 1997).

1.3.2 Bone Marrow Lesions

As Eriksen and Ringe (2012) note, the availability of MRI for clinical research has resulted in increased interest in and knowledge of bone marrow lesions (BML) or bone marrow edemas, as they were referred to in earlier literature. The latter name emerged in response to the lesions' appearance on MRI as increased water signal in the marrow space. With the MRI technology available early on, the lesions initially appeared to have a relatively homogeneous appearance, without clearly delineated borders (Eriksen & Ringe, 2012). However, histological analysis indicates that the lesions are not edema in the strictest sense; rather, they contain a mixture of bone marrow, sclerotic and necrotic bone, fibrous marrow tissue, and lymphocytic elements (Eriksen & Ringe, 2012; Hunter et al., 2009; Muratovic et al., 2016). The known etiology of BML suggests that they are a common response to bone injury from a variety of causes, including trauma, infection, neoplasms, and both inflammatory and degenerative versions of arthritis (Eriksen & Ringe, 2012). Microfractures or other cortical or trabecular bone defects appear to be a common factor in BML development and presence; histological and biochemical analyses have determined that BML occur in areas of rapid bone remodelling, with increased levels of angiogenic and inflammatory factors (Alliston et al., 2017; Eriksen & Ringe, 2012; Muratovic et al., 2018). Research suggests that some BML may be reversible, including those associated with non-chronic conditions and asymptomatic OA (Antony et al., 2016; Eriksen & Ringe, 2012; Zhang et al., 2011).

Research on OA-related BML has mainly centred on the lesions' relationship to disease progression and patient experiences of pain. In terms of the latter, while the OA-specific etiology

of BML remains unclear, their correlation to patient-reported pain and pain fluctuations is evident (Antony et al., 2016; Ip et al., 2011; Wluka et al., 2015; Zhang et al., 2011). As mentioned previously, some BML appear to be reversible, decreasing in size or even disappearing altogether, accompanied by a pain decrease (Zhang et al. 2011). BML presence is also linked to pain progression; in longitudinal studies, patients with BML have increased odds of reporting worsening pain and physical limitations (Mattap et al., 2018).

Beyond reported pain, BML appear to be positively correlated with the progression of other manifestations of OA. BML presence is highly correlated with and predictive of subchondral bone attrition (flattening or depression of the bony articular surface) in the same region (Roemer et al., 2010). A number of studies detail the positive relationship between BML incidence and cartilage degradation and loss over time (Mattap et al., 2018; Raynauld et al., 2008; Tanamas et al., 2010b; Wluka et al., 2015). Perhaps not surprisingly, BML presence and severity is also positively associated with total knee replacement surgery (Mattap et al., 2018; Tanamas et al., 2010b).

Many researchers interpret BML presence as indicative of regions of mechanical stress and subchondral bone remodelling (Crema et al., 2010b; Hunter et al., 2009; Muratovic et al., 2018; Roemer et al., 2010; Tanamas et al., 2010b). As previously mentioned, BML appear to be a common, perhaps temporary response to bone injury, the repair of which involves bone remodelling (Eriksen & Ringe, 2012). Studies of OA-related BML indicate that they are associated with areas of increased bone matrix microdamage (Muratovic et al., 2018), as well as changes in bone mineralization and remodelling (Hunter et al., 2009). Hunter and colleagues (2009) found that, compared to samples taken from the same joint but beyond the BML region, BML samples appeared to be sclerotic, with increased bone volume and trabecular thickness. However, the trabecular arrangement was more plate-like, and significantly reduced in mineral density, potentially leading to mechanical weakness and instability, thereby leaving the area vulnerable to further damage and bone attrition (Hunter et al., 2009). This idea is supported by the work of Muratovic and colleagues (2018), who found similar changes in trabecular microstructure, but also microdamage in both cortical and trabecular bone of BML samples taken largely from the anterior medial tibial plateau. The nature of the damage was consistent with the involvement of both compressive and tensile loading pressures (Muratovic et al., 2018).

Research involving the use of different MRI sequences indicates that BML are not homogenous entities; subtypes of potentially different origin and composition appear to exist (Muratovic et al., 2016, 2018; Wluka et al., 2015). The various MRI sequences (T1, T2, PDFS-weighted, fat-supressed or saturated, etc.) provide visualization of different tissue composition, and therefore potentially different BML etiology and stage of progression. Overall, researchers agree that using multiple imaging sequences is most useful for the early and accurate detection of BML (Wluka et al., 2015). However, at this point, research is inconclusive on the relationship between BML detected by specific or multiple MRI sequences and OA severity and progression (Mattap et al., 2018; Muratovic et al., 2018).

The relationship between BML and subchondral bone cysts (SBC) has received some attention over the last number of years. The latter lesion refers to apparent cavities in the subchondral bone; Li and colleagues (2013) note that SBC were first identified as appearing adjacent to osteoarthritic joint surfaces more than seventy years ago. 'Cyst' is a misnomer, as the lesions are not uniformly fluid-filled (Bancroft, Peterson, & Kransdorf, 2004), but instead contain fibrous tissue that may ossify over time (McErlain et al., 2012). While the exact etiology of the lesions is still unclear, like BML, SBC occur in areas of micro-trauma and rapid bone remodelling, and appear to be associated with regions of cartilage damage (Crema et al., 2010b; McErlain et al., 2012). Various MRI studies suggest that SBC develop most commonly in existing BML regions (Carrino, Blum, Parellada, Schweitzer & Morrison, 2006; Crema et al., 2010a; Crema et al., 2010b; Crema et al., 2008; Tanamas et al., 2010a). Thus, Tanamas and colleagues (2010a) suggest that SBC presence may indicate more serious and advanced BML. In light of these results and their own research indicating that SBC do not appear as typical cysts on MRI, Crema and colleagues (2010a) propose the term "subchondral cyst-like bone marrow lesion" (p. 5) as a more accurate description of the lesion. It is likely that further research on BML detected by different MRI sequences will be able to clarify the apparent relationship between BML and SBC. In this thesis, the term BML will be used as an all-encompassing term referring to subchondral cavitory lesions.

1.3.3 Cartilage and Subchondral Bone

As might be expected, significant research attention has focused on the cartilage and subchondral bone effects and processes associated with OA, especially those of the osteochondral junction (e.g. Findlay & Kuliwaba, 2016; Li et al., 2013; Sharma, Jagga, Lee, &

Nam, 2013). Through it is widely known that OA involves cartilage damage, thinning, and eventual loss, and subchondral bone remodelling (Suri & Walsh, 2012), a remaining subject of debate is why and how these things occur, and in what order. This section will discuss some of the recent research around these topics, and then move to the review of studies dealing with subchondral bone plate attrition and porosity.

Histologically, the differences between normal articular cartilage and cartilage in the early stages of OA are striking; deep clefts in the cartilage and areas of chondrocyte necrosis are clearly observed in the latter case (Pearle et al., 2006). The process of cartilage loss begins at the superficial level with the loss of proteoglycan integrity, which in turn leads to a more permeable extracellular matrix (Pearle et al., 2006). This diminishes the compressive resistance of the cartilage; macroscopically, it is thus much softer than it should be. Initially, normal collagen levels in the cartilage are maintained, but the fibers misalign (Pearle et al., 2006). Furthermore, in OA, chondrocytes that are usually stable may become active, proliferate, and produce both matrix-building and destructive enzymes (Loeser et al., 2012). The matrix degrading enzymes then set off a chain of events that results in collagen degradation, eventually reaching a level at which repair is impossible (Loeser et al., 2012).

Normal chondrocytes secrete anti-angiogenic factors that prevent the invasion of the cartilage by vascular tissue; proteoglycans also repel angiogenesis (Suri & Walsh, 2012). However, in an OA-affected joint, proteoglycan loss diminishes the defence against angiogenesis, and chondrocytes actually begin to produce pro-angiogenic factors (Suri & Walsh 2012). With these features at play, cartilage is vulnerable to invasion by vascular tissue arising from the subchondral bone. Suri and Walsh (2012) characterize OA as the loss of integrity of the osteochondral junction. As deep fissures form in the articular surface of the cartilage, osteoclastic activity in the subchondral bone cuts channels through the bone and calcified cartilage layer, thereby creating a path for angiogenesis, sensory nerve infiltration, and contact between bone and synovial fluid.

As the calcified cartilage layer is infiltrated by vascular elements, a process begins that is similar to endochondral osteogenesis during growth and development (Loeser et al., 2012; Suri & Walsh, 2012). During the original process, hypertrophic chondrocytes release angiogenic factors that encourage the growth of blood vessels from the subchondral bone space. Hypertrophic chondrocytes are typically found in the calcified cartilage layer, and even in the

healthy middle zone (Mahjoub, Berenbaum, & Houard, 2012). Researchers suggest that some aspect of OA causes the hypertrophic chondrocytes to 'reawaken' and begin the endochondral growth process again (Suri and Walsh, 2012; Aho et al., 2017). This has the effect of advancing the calcified cartilage zone, and thus the tidemark, into the uncalcified zone of cartilage (Goldring, 2012).

Increased subchondral bone remodelling is also a hallmark of OA. In normal bone tissue, resorption and formation is an ongoing process, influenced by hormonal and biomechanical factors, that typically results in no change in joint shape. In OA, in addition to the osteoclastic actions mentioned above, there is progressive thickening (sclerosis) of the subchondral bone plate, as well as changes in subchondral trabecular architecture (Goldring & Goldring, 2010). Earlier research suggests that OA-induced subchondral bone tissue is stiff and has less energy absorbing capacity than normal bone (Radin & Rose, 1986). This has the effect of placing more pressure and shear force on the cartilage, leading to its gradual degradation. Other researchers have also suggested mechanical forces as the reason behind the bone changes. For example, an increase in the volume of horizontal trabeculae throughout the course of OA progression is thought to be a load distribution mechanism (Goldring, 2012). Burr and Gallant (2012) provide a detailed review of research on the process of subchondral bone changes in OA. They note that, in the early stages of the disease, increased remodelling leads to both subchondral plate thinning and the loss of trabecular bone, leaving the trabeculae thinner and more separated (Li et al., 2013). In the later stages, trabecular bone remains diminished, while the plate thickens, aided by the advancement of the calcified cartilage layer described above (Burr & Gallant 2012). Despite the thickening of the subchondral plate, its hardness is substantially reduced from that of normal bone, due to decreased mineralization in the bone matrix (Findlay & Kuliwaba, 2016; Grynpas, Alpert, Katz, Lieberman, & Pritzker, 1991; Li et al., 2013).

The degree of subchondral bone remodelling appears to be directly related to the amount of overlying cartilage degeneration (Bobinac, Spanjol, Zoricic, & Maric, 2003). Microscopic damage observed on macroscopically normal cartilage suggests that cartilage damage may be the instigator for subchondral bone changes (Bobinac et al., 2003). In fact, more than one mechanism may be involved in OA-related bone and cartilage changes (Cox et al., 2013). High joint loading and a reactivation of endochondral ossification each appear to produce distinct patterns of trabecular number, thickness, and bone volume fraction (Cox et al., 2013). In some

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cases, there is evidence for both patterns in the same bone sample, suggesting that both mechanisms may be at work simultaneously (Cox et al., 2013).

1.3.4 Subchondral Plate Porosity

Studies of the OA-affected osteochondral junction indicate that osteoclastic actions in the subchondral bone lead to the vascular invasion of the calcified cartilage layer, up to and perhaps past the tidemark (Suri & Walsh, 2012). This, and the apparently cyclic nature of cartilage degeneration and ossification, has led to the idea of 'cross talk' between the subchondral bone and synovial capsules, i.e., biochemical 'conversations' that influence the progression and manifestation of OA (Burr & Gallant, 2012). While biochemistry is beyond both the scope of this thesis and the expertise of this writer, the vascular channels themselves are of interest. Several researchers have noted the presence of structures variously referred to as vascular cones, vascular channels, pits, and pores in the osteoarthritic subchondral bone plate (e.g., Lyons et al., 2006; Shibakawa et al., 2005; Sniekers et al., 2008). Unfortunately, much of the research on these structures has been limited to animal models, but there are interesting possibilities for human application.

One of the early animal model studies involved comparing induced knee OA in dogs also undergoing neurological surgery (which meant that they experienced no pain and therefore did not preferentially load the undamaged knee) with that of neurologically normal dogs with induced OA (Dedrick et al., 1997). While trabecular bone showed no difference, cortical bone in the neurologically intact dogs thickened, and the neurologically altered samples showed cortical thinning and porosity (Dedrick et al., 1997). Later canine model studies of induced OA also showed a decrease in subchondral plate thickness, and markedly more porosity, especially within a month of induction surgery (Sniekers et al., 2008). In these cases, the researchers were struck by how quickly subchondral bone changes started and suggested that the increased porosity of the bone may induce vascular invasion of cartilage, and increase biomolecular exchange between bone and cartilage (Sniekers et al., 2008).

Murine model studies show similar results. Soon after OA induction, the subchondral plate shows obvious thinning and porosity (Botter et al., 2011; Iijima et al., 2016). Micro-CT scans of the subchondral plate show significantly more perforations into the trabecular bone and bone marrow in OA plates as compared to control samples (Botter et al., 2011). The correspondence of porosity to local cartilage damage varies depending on the study. In general,

researchers suggest that osteoclasts are active early in the OA process, likely in response to mechanical stress. The perforations they create allow increased fluid to flow to the subchondral bone, thereby leading to fluid loss in the cartilage and subsequent damage (Botter et al., 2011; Iijima et al., 2016). By four weeks into the process, osteoblasts become active, reduce the perforations to the normal number, and repair the thinned subchondral bone (Botter et al., 2011). However, while osteoblast and osteoclast activity normalizes, bone remodelling homeostasis does not return to a pre-damage state, and by fourteen weeks after OA induction, the subchondral bone of OA plates remains thinner than that of control samples (Botter et al., 2011).

Ex vivo studies of osteoarthritic and normal human knee joints delineated two types of 'reabsorption pits' (i.e., porosity), one extending from the subchondral bone to within the calcified cartilage, and another extending into the tidemark (Shibakawa et al., 2005). The former type was found in equal numbers in both OA and control samples, whereas the latter was significantly more common in OA samples. Histological examination showed that the second pit type was associated with cartilage degradation and nearby depleted proteoglycan. Some pits contained active bone marrow cells, while others were surrounded by mature lamellar bone, resulting in indents in the subchondral bone plate (Shibakawa et al., 2005). Mechanical loading may influence the second type of pit, given its predominance on knees that were mainly medial-type OA (Shibakawa et al., 2005).

1.4. Risk Factors of OA

As the previous discussion suggests, the etiology of OA is complex, multifocal, and even after years of intensive research, unclear. Much the same may be said for the various risk factors of OA. While both anecdotal data and systematic clinical research have produced substantial evidence to support the nature of some factors' involvement in OA, other supposed risk factors have a less well-defined relationship with the condition (Blagojevic, Jinks, Jeffery, & Jordan, 2010; Kerkhof et al., 2014). In some cases, the link between risk factor and OA is well-established, but the mechanism of the relationship is unclear (Berenbaum, Eymard, & Houard, 2013; Srikanth et al., 2005). This section will examine the most common risk factors of OA and discuss and synthesize current research on their mechanisms of involvement in the condition.

1.4.1 Aging

Age is considered one of the strongest risk factors for OA (Anderson & Loeser, 2010). As with other risk factors, age does not directly cause OA, but rather creates a physical environment that is conducive to the development of the condition. Traditionally, the relationship between age and OA was attributed to the cumulative effect of a lifetime of 'wear and tear' on the joints (Hügle, Geurts, Nüesch, Müller-Gerbl, & Valderrabano, 2012). However, research now indicates that the effects of aging on joints, including sarcopenia (loss of muscle mass), loss of proprioception and balance, increased ligament laxity, and age-related changes to bone structure and cartilage homeostasis, combine with other risk factors (sex, obesity, genetics, etc.) to increase a person's susceptibility to OA development (Anderson & Loeser, 2010).

There is no doubt that an individual's age is highly correlated with his/her risk of developing OA. The incidence of both knee and hip OA increases with age, as does spine and hand OA, seemingly independently of any environmental risk factors (Cho, Morey, Kang, Kim, & Kim, 2015; Prieto-Alhambra et al., 2014; Skousgaard et al., 2015; Skousgaard, Skytthe, Möller, Overgaard, & Brandt, 2016).

As mentioned above, research now focuses on the components of aging that may predispose an individual to the development of OA. While the 'wear and tear' explanation is now considered overly simplistic, work still revolves around the biomechanical effects of aging on a joint, and the subsequent propensity for OA development. For example, walking speed is generally consistent throughout adulthood, but declines after age 70; this may be a compensatory mechanism due to muscle weakness in the lower legs, or a fear of falling (Hügle et al., 2012). In comparisons of gait differences in samples of young (20s), middle-aged (early 50s) and older (mid 60s) adults without OA, the middle-aged and older group tends to have a more internally rotated and posteriorly translated tibia during the stance phase of walking (Boyer & Andriacchi, 2016). Interestingly, this gait characteristic is also common in ACL-impaired knees (Chaudhari, Briant, Bevill, Koo, & Andriacchi, 2008). In examining the relationship between extension/flexion and adduction/abduction of the knee, Boyer and Andriacchi (2016) noted that the middle-aged and older groups showed the opposite motion pattern of the younger group: greater knee flexion accompanied by abduction in early stance and adduction in late stance. The authors suggest that age-related changes in muscle function could account for these differences (Boyer & Andriacchi, 2016).

According to Perry and colleagues (2013), age adversely affects the function of the Na^+-K^+-ATPase (NKA) pump. Simply put, this pump plays a vital role in the excitation of skeletal muscle by transporting sodium and potassium ions across cellular membranes. Muscle NKA content is increased through physical exercise and decreased through inactivity. Significantly lower muscle NKA content in older (over 68) individuals, both with and without OA, suggests a deficiency in NKA pump function, thereby leading to insufficient skeletal muscle excitation (Perry et al., 2013).

Alignment changes and muscle weakness are closely related elements; as discussed more fully below, muscle weakness may change joint alignment, which alters both the biomechanical loading pattern of the joint as well as the contact points of the joint's articular surfaces. Eventually, cartilage damage and concomitant subchondral bone changes lead to a diagnosis of OA (Hügle et al., 2012).

The normal aging process involves alterations in cartilage homeostasis. Chondrocytes appear particularly vulnerable to age-related changes. Under normal circumstances, these cells are long-lived, and undergo little or no death or division. However, as they age, chondrocytes show less anabolic activity, tipping the homeostatic balance towards catabolic, or destructive activity (Anderson & Loeser, 2012). The number of chondrocytes near the superficial zone of articular cartilage decreases by over 50% between the ages of 20 and 90, leading to softening of the cartilage (Lotz & Caramés, 2011). Age-related damage of a specific chromatin protein expressed in the superficial zone leads to chondrocyte death, and the loss of extra-cellular matrix. This, in turn, leaves the superficial zone vulnerable to surface damage, beginning the OA pathological process (Lotz & Caramés, 2011). In addition, cartilage is adversely affected by oxidative damage from free radicals, which accumulate over time and can cause DNA damage; free radical damaged DNA has been found in OA-affected cartilage (Davies, Guilak, Weinberg, & Fermor, 2008).

1.4.2 Sex

Researchers have been aware of male and female differences in OA incidence, severity, and experience for over 50 years, since the first heritability study firmly linked increased incidence of hand OA with females (Williams, 2007). In spite of this, a good deal of the research on OA etiology and pathogenesis since that time has focused on risk factors and causes without considering the interaction of sex on any of these (Boyan et al., 2012; O'Connor, 2007).

However, as the incidence of OA has increased worldwide, researchers and clinicians have recognized the importance of examining all aspects of the condition, including male and female differences.

Women show a higher incidence of knee, hip, and hand OA compared to males at all age levels; this disparity is expected to be maintained throughout the projected increase in OA incidence over the next 30 years (Boyan et al., 2012; Srikanth et al., 2005). In addition, females tend to have more severe OA symptoms (e.g., pain, stiffness, ability to function normally) and greater symptom progression when compared to males of a similar grade of radiographic OA severity (i.e., osteophyte presence and joint space narrowing) (Cho, Chang, Yoo, Kim, & Kim, 2010; Glass et al., 2014; Srikanth et al., 2005).

There is some evidence that the pain aspect of the female OA experience is due to central sensitization; females are also more prone to such chronic pain conditions as fibromyalgia, headaches, and temporomandibular pain, all of which are associated with altered central pain processing (Glass et al., 2014). Central sensitization refers to an alteration in the central nervous system resulting in a stronger, more temporally persistent, and/or more generalized pain response than the pain-inducing stimulus should actually warrant (Bartley et al., 2016). Females tend to report more widespread pain and greater sensitivity to pain both related and unrelated to the OA-affected joint, lending credence to the influence of central sensitization (Bartley et al., 2016; Glass et al., 2014).

Issues of pain perception aside, the differences in OA incidence and severity between males and females fall into two main categories: biomechanical and biochemical/hormonal (Boyan et al., 2013; O'Connor, 2007). The former category encompasses such factors as joint alignment, bone, muscle, and ligament size and shape, baseline cartilage thickness, and gait differences, while the latter involves the effects of cellular communication on joint components.

Lower extremity alignment differences between males and females have been examined in terms of their relationship to knee, specifically anterior cruciate ligament (ACL), injuries (Mitani, 2017; Tillman, Bauer, Cauraugh & Trimble, 2005). As will be seen in a subsequent section, injury is an independent risk factor for OA. Research generally focuses on male and female differences in the Q-angle (i.e., the angle between the force vector of the quadriceps muscle group and the patellar tendon), and internal and external hip rotation. Females have a larger Q-angle, and a greater degree of internal hip rotation than males (Mitani, 2017; Nguyen &

Shultz, 2007; Tillman et al., 2005). A greater Q-angle predisposes females to ACL injury, as it increases the horizontal forces of the quadriceps group, thereby pulling the patella further laterally and exposing the ligaments and menisci of the knee to greater loads and torsion (Tillman et al., 2005). Additionally, females have a greater degree of knee hyperextension and knee valgus (tibia at a lateral angle compared to femur, also known as 'knock-knees'), which is affected by both Q-angle and tibiofemoral angle (Nguyen & Schultz, 2007). Knee hyperextension is thought to be tied to ligament laxity, since the knee should be restricted in its anterior-posterior variation if the ACL is adequately taut (Nguyen & Schultz, 2007).

Alignment translates directly into movement and gait; females walk, run and squat with greater hip adduction and knee abduction angles than their male counterparts (Phinyomark, Osis, Hettinga, Kobsar, & Ferber, 2016; Willy, Manal, Witvrouw, & Davis, 2012). These differences appear to hold true in comparisons between healthy individuals and those with OA; OA status does not manifest itself in differences in specific gait elements in either males or females (Phinyomark et al., 2016). Both valgus and varus (tibia at a medial angle compared to femur, or 'bow-legs') knee alignments are more predictive of OA development and progression than neutral alignment, regardless of sex (Nicolella et al., 2012). Varus alignment, again regardless of sex, is associated with diminished hip extension and increased foot eversion, both of which are seen in cases of medial compartment knee OA (Barrios & Strotman, 2014). Taken together, these studies suggest that male and female alignment differences resulting in gait changes do not themselves seem to be significantly related to OA development. However, higher Q angles appear to predispose females to a greater risk of ACL injury which, as discussed in Section 1.4.5, is itself a risk factor for OA.

Another biomechanical aspect of OA development is cartilage volume and loss. Individuals with a lower baseline cartilage volume experience more rapid cartilage loss due to physical activity than their high cartilage volume counterparts (Teichtahl et al., 2016). Research indicates that males have significantly more cartilage than females, both as children and adults, independent of body and bone size (Ding, Cicuttini, Scott, Glisson, & Jones, 2003; Jones, Glisson, Hynes, & Cicuttini, 2000). Notably, the volume differences are more marked in subjects over 50, suggesting that women lose cartilage more rapidly in middle age (Ding et al., 2003). If females, on average, have a lower baseline cartilage volume, they are at greater risk for cartilage loss and resultant subchondral bone damage and joint inflammation.

Obesity is a known OA risk factor for both males and females, especially with regard to lower limb OA (Franklin, Ingvarsson, Englund, & Lohmander, 2009). Recent research on the role played by cytokines, cell signalling molecules, produced by adipose (i.e., fat) tissue has shed new light on the mechanism of the relationship between obesity and OA. This is discussed in some detail in the next section, but it is important to note that females may be more affected by this relationship, as they have a larger proportion of body fat than males (Teichtahl, Wluka, Proietto, & Cicuttini, 2005).

As mentioned previously, cartilage loss in females progresses rapidly after age 50, as does the incidence of OA in all joints except the hands (de Klerk et al., 2009; Ding et al., 2003; Prieto-Alhambra et al., 2014; Wluka, Davis, Bailey, Stuckey, & Cicuttini, 2001). Therefore, some relationship between post-menopausal changes in circulating hormones or tissue sensitivity to hormones, and aspects of OA appears likely (Ding et al., 2003; Hussain et al., 2014). Research conducted by Richmond and colleagues (2000) confirmed the presence of estrogen receptors on adult articular cartilage. In fact, cartilage contains receptors for estrogen, androgens, and progesterone. Females have more estrogen receptors than males, and female growth plate chondrocytes convert testosterone to estrogen (Boyan et al., 2013). Estrogen, especially 17β estrodial, promotes the proliferation of chondrocytes and growth of collagen, as well as reduces the production of biochemicals associated with extracellular matrix degradation (Boyan et al., 2013; Koelling & Miosge, 2010). Estrogen appears to play an important role in skeletal mineralization and epiphyseal maturation, as well as in the amelioration of the effects of inflammatory conditions such as rheumatoid arthritis and some heart diseases, both of which increase in severity after menopause (Martín-Millàn & Casteñada, 2013). The protective effect that estrogen appears to have on cartilage diminishes with decreasing post-menopausal estrogen levels, leaving cartilage more vulnerable to damage and loss. Additionally, OA involves cartilage angiogenesis and, some suggest, a reawakening of the endochondral ossification process that had ended with epiphyseal maturity (Suri & Walsh, 2012). As estrogen protects against angiogenesis and contributes to epiphyseal maturity, a lack of estrogen would logically perform the antagonist action (Martín-Millàn & Casteñada, 2013).

Post-menopausal hormone replacement therapy (HRT) has been suggested as a possible treatment for OA, as well as other conditions. Wluka and colleagues (2001) and Bay-Jensen and colleagues (2012) suggested that women receiving estrogen therapy had more knee cartilage and

a lower incidence of knee and hip OA. However, not all post-menopausal women develop OA, indicating that other risk factors are at play, or that some individuals have additional protective factors to their advantage.

1.4.3 Obesity

Obesity, as defined by the World Health Organization, is constituted by a body mass index (BMI) of over 30 kg/m^2; a BMI between 25 and 30 kg/m^2 is considered overweight (Salih & Sutton, 2009). While the cause of obesity remains controversial and continues to be debated among health professionals and researchers, what is undeniable is obesity's dramatic increase in incidence over the past 30 years. Since 1980, the prevalence of obesity has doubled worldwide; in developed countries, one third to one half of the adult population is overweight or obese (Salih & Sutton, 2013; Sartori-Cintra, Aikawa, & Cintra, 2014). The rise of obesity has generally paralleled the rise of OA incidence, and is considered one of the major risk factors in OA's expected prevalence in the future (Arthritis Association of Canada, 2011).

The link between obesity and OA has been well-established in the literature, which shows a high correlation between increased body weight, and both radiographic and symptomatic evidence of OA (Koonce & Bravman, 2013; Mork, Holtermann, & Nilsen, 2012; Salih & Sutton, 2013). The explanation for this relationship has typically focused on the biomechanical effects of obesity on joints. Logically, increased weight places high biomechanical load and stress on joints, potentially high enough to overcome the joint's ability to adapt to the heighted strain. Gait and joint alignment differences between obese individuals and those of normal weight have also been implicated in biomechanical changes. However, in the past 15-20 years, research has begun to focus on the biochemical components of obesity, and their relationship to inflammation and OA. This section will discuss research on both the biomechanical and biochemical effects of obesity, and the resulting implications for OA development and progression.

Literature focusing on joint and gait biomechanics accompanying obesity indicates that overall, obese individuals walk more slowly than normal weight comparison populations, and take shorter and wider steps (Runhaar, Koes, Clockaerts, & Bierma-Zeinstra, 2011). The obese study populations are more likely to walk with a greater toe-out angle, and to spend more time in the stance portion of the walking process. These differences serve to reduce the joint load experience while walking, but also introduce rotational malalignment in the knee, which may have implications for excess cartilage loading and eventual damage (Runhaar et al., 2011).

Higher BMI is associated with increased thigh and leg muscle forces, which is attributed to a neuromuscular response to an increased need for both joint stability and propulsion, depending upon the stage of the gait process (Harding, Dunbar, Hubley-Kozey, Stanish, & Astephen Wilson, 2016). BMI also has a one to one positive relationship with tibiofemoral compression; as the BMI increases, so does the compressive force. This may accelerate the process of joint damage, especially over the long term (Harding et al., 2016).

Weight loss in individuals with symptomatic OA is associated with reductions in knee compressive forces, pain, and the presence of inflammatory biomarkers in the blood, suggesting that a reduction in biomechanical stress reduces the severity of OA symptoms (Messier et al., 2013). As well as decreased OA symptoms, obese individuals undergoing weight loss also show a decelerated rate of cartilage loss, which holds true even if the individuals increase their peak knee compression force after weight loss (Henriksen et al., 2013). This result suggests that biomechanical loading might not be the sole explanation for the relationship between OA and obesity.

Cartilage damage and subchondral bone remodeling are integral components of OA pathology and progress. BMI has a significant effect upon the architecture of subchondral trabecular bone of the tibial plateau (Reina et al., 2017). Research demonstrates that thickening of subchondral cortical bone and increases in trabecular thickness and bone volume fraction (i.e., trabeculae becoming thicker but reducing in number) precedes cartilage degeneration in OA; these subchondral bone changes are exacerbated by increased weight, which could lead to accelerated cartilage damage (Reina et al., 2017). Across studies, there is a consistent positive relationship between BMI and MRI evidence of cartilage degeneration (Mezhov et al., 2014). When body composition is taken into consideration, the results are slightly different; fat mass is significantly positively related to cartilage damage, whereas non-fat, mainly skeletal muscle mass tends to have a positive correlation with cartilage volume (Mezhov et al., 2014). Again, this suggests that biomechanical loading may not be the sole factor linking BMI and OA.

Recent research on the interactions of mechanical loads on joints has revealed that the relationship may be more complex than originally supposed. Chondrocytes are equipped with mechanoreceptors that detect physical signals, including strain, changes in fluid pressure, alterations to the tissue charge, and change in chondrocyte shape and volume (Guilak, 2011). When under excessive stress, some of these mechanoreceptors produce cytokines, biochemicals

that have been linked to inflammatory responses and eventual cartilage degradation (Koonce & Bravman, 2013). While normal levels of mechanical loading are beneficial to cartilage homeostasis and metabolism, abnormal loading, whether due to joint misalignment, repetitive overload, or excessive torsion, has a deleterious effect on cartilage. Inflammatory responses, collagen damage, and chondrocyte death have all been associated with excessive mechanical stress and the stress responses of the chondral mechanoreceptors (Guilak, 2011). Knowledge of this additional property of cartilage adds both complexity and understanding to the effects of abnormal biomechanical loading, whether due to physical or occupational activity, injury, or obesity.

Even with the recognition of a biochemical component of biomechanical loading, various studies indicate that joint stress is not the sole arbiter of the relationship between obesity and OA. As mentioned previously, when body composition was examined separately from weight, researchers saw different results (Mezhov et al., 2014; Teichtahl, Wang, Wluka, & Cicuttini, 2008). BMI is used as the measure of obesity in the vast majority of studies; this, however, does not take into account the muscle to fat ratio of the individual. When fat mass is used as the measure, studies report a high correlation between fat and the loss of cartilage volume, both radiographic and symptomatic progression of OA, and the need for joint replacement surgery (Teichtahl et al., 2008). Fat-free mass, however, showed no such correlation (Mezhov et al., 2014). In addition, there is a high correlation between obesity and the incidence of OA in the hand, even though this cannot be demonstrably linked to biomechanical stress (Thijssen, Van Caam, & Van Der Kraan, 2014). All of this evidence suggests that there is more to the relationship of obesity and OA than just weight-induced mechanical stress.

Considerable research has focused on the nature of adipose tissue and its relationship to OA. Adipose tissue, in addition to its energy storage function, secrets cytokines, generally referred to as adipokines, to the degree that it is now considered an endocrine organ (Sandell, 2009). Adipose hypertrophy increases adipokine secretion; in excess, some of these adipokines have an inflammatory effect, while others affect the hypothalamus, resulting in insulin resistance and the increased likelihood of further weight gain (Sartori-Cintra et al., 2014). Berenbaum and colleagues (2013) detailed the function of a number of adipokines linked to OA in *in vitro* experiments. Chemerin, an adipokine usually involved in glucose metabolism, can be detected in the synovial fluid of an OA-affected joint; it is specifically linked to the stimulation of other pro-

inflammatory cytokines (Berenbaum et al., 2013). Visfatin, another inflammatory adipokine, appears to inhibit extracellular matrix synthesis in cartilage (Berenbaum et al., 2013). Although OA is considered a non-inflammatory condition, unlike rheumatoid arthritis, it is characterised by synovial membrane inflammation, which causes the release of inflammatory enzymes into the synovial fluid. There is evidence, as discussed above (Section 2) that these contribute to the first signs of cartilage damage (Scanzello & Goldring, 2012).

Leptin is an adipokine that has received a great deal of research attention in terms of its relationship to both obesity and OA. Known for its function as a regulator of food intake and energy expenditure, its role in OA pathogenesis is still unclear (Thijssen et al., 2015). Leptin receptors have been found in articular cartilage, as well as in osteophytes, synovium, and the infrapatellar fat pad (Lee & Kean, 2012). Research has indicated that leptin's level in synovial fluid is positively correlated with cartilage destruction and pain in hip and knee OA, suggesting a catabolic relationship with cartilage metabolism (Lee & Kean, 2012; Thijssen et al., 2014; Vuolteenaho, Koskinen, Moilanen, & Moilanen, 2012). However, in *in vitro* experiments on human chondrocytes, leptin increased both chondrocyte proliferation and extracellular matrix synthesis, suggesting an anabolic relationship (Lee & Kean, 2012).

Other adipokines are also known to be proinflammatory. Resistin, for instance, is produced by both adipose tissue and cartilage, and is known to increase the production of various enzymes related to OA. At times of joint trauma, resistin levels are elevated, causing extracellular matrix degradation and the release of inflammatory cytokines from the articular cartilage (Sandell, 2009).

While there remains a great deal that is unknown about the relationship of adipokines, obesity, and OA, the link between obesity as a state of chronic inflammation and the inflammatory aspects of OA is becoming increasingly obvious. Undoubtedly, future research will further clarify the relationship between the mutual rise of obesity and OA incidence.

1.4.4 Physical and Occupational Activity

Physical activity and OA continue to be contested topics among OA researchers. While there is considerable evidence that moderate physical activity may have a protective effect on joints prior to an OA diagnosis, some controversy remains over the efficacy and wisdom of encouraging those already experiencing the pain and other symptoms of OA to engage in

physical activity. In addition, there is evidence that certain types of physical activity, either recreational or occupational, may lead to a higher probability of an OA diagnosis later in life.

In the past, the notion of OA as exclusively a disease of excessive joint use and resultant degeneration over time led to the logical conclusion that too much physical activity, especially in older adulthood, was irrevocably tied to OA development (Esser & Bailey, 2011). It is now known that OA's etiology and risk factors are not such a simple equation, especially with regards to physical activity. Overall, moderate recreational activity of a wide variety of types (e.g., running, dance, team sports, tennis, etc.) does not appear to be related to the development of knee OA; in examining various activities individually, participants and non-participants do not differ significantly in their incidence of OA (Lefèvre-Colau et al., 2016). What does appear to be related to a higher incidence of OA is participation in activities that place high levels of impact or torsional force on joints, knees in particular, especially when practiced at an elite or at a more frequent than moderate level (Lefèvre-Colau et al., 2016; Roemer et al., 2015; Verweij, Van Schoor, Deeg, Dekker, & Visser, 2009). Radiographic OA (measured as osteophyte presence and degree of joint space narrowing) is far more commonly associated with team or power sports (soccer, rugby, racket sports) than endurance activities (running, cycling); this fits with the finding that OA is correlated with high impact or torsional forces on a joint (Lefèvre-Colau et al., 2016; Verweij et al., 2009). Researchers note that activities most associated with the development of OA are also associated with a high risk of joint injury which, as discussed below (Section 1.4.5), is an OA risk factor in itself (Roemer et al., 2015; Lefèvre-Colou et al., 2016).

Physical activity, especially among the elderly, may even be an important preventative measure against OA. Elderly individuals who are physically active show lower incidences of both radiographic and symptomatic OA (Felson et al., 2013), whereas sedentary behaviour is strongly related to increased physical frailty, which in turn is linked to an increased risk of OA progress and/or injury (Song et al., 2015). In fact, physical exercise performed in middle age (i.e., 25-50) appears to have a protective effect against sarcopenia and gait changes in later years; as discussed previously (Section 1.4.1), both of these elements of aging promote conditions conducive to the development of OA (Akune et al., 2014). Among obese individuals, high levels of physical activity have no detrimental effect on OA development despite the presence of a known risk factor, and may, in fact, have a protective role to play in the development and progression of OA (Mork et al., 2012).

Although there appears to be a beneficial role for moderate physical activity, concerns still exist over the potential for activity-induced cartilage damage, especially in the presence of existing defects. However, MRI-based studies indicate that there is no correlation between moderate activity and further cartilage degeneration, although changes in cartilage composition, a prelude to degeneration, appear to be more severe in individuals at the lowest and highest levels of physical activity (Kwee et al., 2016; Lin et al., 2013).

The general conclusion of physical activity studies that repetitive, high stress, or torsional activities increase an individual's risk of developing OA is also supported by work examining specifically occupation-related activities and OA. Overall, occupations with higher levels of repetitive physical activities, heavy lifting and standing, and squatting or kneeling were associated with higher levels of OA and an increased likelihood of requiring joint replacement surgery (Franklin, Ingvarsson, Englund, & Lohmander, 2010; Muraki et al., 2011; Rossignol et al., 2003; Sulsky et al., 2012). As with recreation-related physical activities, these occupational activities place repeated mechanical stress on a joint and are tied to a higher incidence of joint injury, thereby increasing the likelihood of OA development.

Research on the effect of physical activity appears to support information reported by Esser and Bailey (2011): mature, healthy cartilage receives nourishment via the movement of synovial fluid, which is enhanced by physical activity, as is the production of extracellular matrix components related to lubrication and shock absorption. Previously-injured cartilage, altered loading patterns, or excessive joint force, especially over a long period of time, disrupts the equilibrium, resulting in chondrocyte death, changes in extracellular matrix content, and biochemical alterations to both the extracellular matrix and synovial fluid (Guilak, 2011). Eventually, cartilage degradation is inevitable, leading to the cycle of OA changes in the affected joint.

1.4.5 Injury

In most research, primary OA and its risk factors are considered separately from those of secondary OA, mainly because the latter often involves OA as a comorbid condition of a pre-existing disease (McGonagle et al., 2010). However, post-traumatic OA, that associated with previous joint injury, is an exception to this. Joint injury has long been acknowledged as an independent risk factor for the development of OA. Considerable research has centred on the relationship of knee OA and knee injury (Driban et al., 2014; Muthuri, McWilliams, Doherty, &

Zhang, 2011), particularly ACL and meniscal damage. Indeed, deliberate damage to these components is a common method of OA induction in animal studies (Dedrick et al., 1997; Iijima et al., 2016; Sniekers et al., 2008).

The ACL, as with other knee ligaments, functions as a stabilizer, absorbing and counterbalancing force and rotation being applied across the knee (Simon et al., 2015). Both cruciate ligaments (anterior and posterior) act as primary stabilizers of anterior-posterior motion of the tibia and femur when the knee is flexed, and as the 'locking mechanisms' of tibiofemoral positioning when the knee is at full extension (Simon et al., 2015). Chaudhari and colleagues (2008) report that ACL impairment produces significant tibiofemoral positioning differences in both gait and stance which, in turn, change the tibiofemoral contact points from what is typically seen in a knee with no ACL injury (Chaudhari et al., 2008).

Generally, individuals with an ACL injury are almost four times as likely to develop OA than uninjured control groups, whether the injured ACL was surgically treated or not (Ajuied et al., 2014). While ACL reconstruction appears to lessen the overall likelihood of OA development, if individuals who have undergone ACL reconstruction are diagnosed with OA, they are twice as likely to have moderate to severe radiographic evidence compared to individuals who have not had reconstructive surgery (Ajuied et al., 2014). While reconstructive surgery improves the knee's biomechanical stability, it does not restore it to a pre-injury state (Friel & Chu, 2013); the alignment and loading patterns of the knee remain abnormal (Wen & Lohmander, 2014).

Much of the research linking ACL injury to the likelihood of OA development later in life centres on these alignment changes, which alter the biomechanical loading of the joint and increase forces on cartilage and joint components (Friel & Chu, 2013). MRI studies of normal articular cartilage show that the thickest areas are those corresponding with the areas of greatest tibiofemoral contact and therefore load bearing. Abnormal loading and motion damages the cartilage, leading to an ongoing cycle of progressively abnormal loading, further cartilage degeneration, and eventual OA (Chaudhari et al., 2008). The process of cartilage and collagen degeneration that occurs in the year after an ACL injury is similar to that of early OA (Friel & Chu, 2013). As discussed above (Section 1.4.3), research indicates that abnormal or increased mechanical stress changes the biochemical makeup of the cartilaginous extra-cellular matrix, leading to chondrocyte death and the production of inflammatory biochemical markers (Guilak,

2011). As an ACL injury permanently alters the tibiofemoral alignment, this combination of biomechanical and biochemical affects appears to be a significant factor in the later development of OA.

An ACL injury does not occur in isolation; other research focuses on concomitant conditions. At the time of the initial injury, inflammatory biomarkers are released into the synovial fluid; many of these are also present in the synovial fluid of an osteoarthritic joint (Friel & Chu, 2013; Dare & Rodeo, 2014). These biomarkers resolve over time. However, if the injured individual undergoes surgery, this produces another inflammatory response. At the time of injury, bone and chondral trauma are inevitable (Dare & Rodeo 2014). MRI-visible cartilage damage and 'bone bruises' are present in the majority of individuals with an ACL injury; in follow-up imaging, one third of the bone bruises appear as bone marrow lesions. As various researchers have suggested (see Section 1.3.2), bone marrow lesions are associated with a number of OA symptoms, including pain, cartilage loss, bone attrition, and cartilage angiogenesis (Eriksen & Ringe, 2012; Raynauld et al., 2008; Roemer et al., 2010; Tanamas et al., 2010b).

Meniscal injury at the time of an ACL injury is extremely common; estimates indicate that at least half of ACL injuries are accompanied by meniscal tears (Simon et al., 2015). Overall, there is a moderately significant relationship between a medial meniscal injury accompanying an ACL injury and the later development of OA, whereas no similar relationship exists for lateral meniscal injury (Van Meer et al., 2015). ACL repair surgery is often accompanied by a full or partial meniscectomy (Simon et al., 2015). Research suggests that retaining as much of the meniscus as possible is beneficial; Dare and Rodeo (2014) suggest that a loss of only 10% of the meniscal volume increases cartilage load by almost two-thirds. Meniscal damage is thought to increase the alteration of loading patterns already inherent in ACL injury, with the additional factor of a further loss of compressive material (Dare & Rodeo, 2014).

Complex, wide, or long tears of the medial meniscus are, by themselves, significantly related to OA development, as is meniscal extrusion (Badlani, Borrero, Golla, Harner, & Irrgang, 2013). The latter is thought to show up radiographically as joint space narrowing and can lead to the meniscal volume loss effects discussed above. Large tears may alter joint loading, thereby disrupting normal knee biomechanics and commencing the destructive cycle of OA (Badlani et al. 2013).

As indicated previously, a great deal of injury-centred OA research focuses on knees. However, injury resulting in joint instability is also a leading risk factor for OA development in the ankle and shoulder, as well as knee (Brooks, Andrade, Middleton, & Wallen, 2015). While the aftermath of ankle fractures of various types are thought to account for more than a third of post-traumatic ankle OA cases (Thomas, Hubbard-Turner, Wikstrom, & Palmieri-Smith, 2017), Valderrabano and colleagues (2006) indicate that ligamentous weakness and damage related to severe or recurrent ankle sprains constitute a major risk factor in the development of ankle OA. As is the case with injured knees, muscle and ligament weakness as well as other damage, alters the loading pattern and motion of a joint, thereby eventually damaging articular cartilage (Chaudhari et al., 2008). Depending upon the type of injury, cartilage damage may be well underway; in the case of articular surface fractures, chondrocyte death begins along fracture lines and progresses rapidly in the first 48 hours after injury (Tochigi et al., 2011).

The structure of the normal shoulder joint capsule, with relatively large spaces between the bony components, allows the arm to move freely; however, with the freedom of movement comes the added risk of dislocation or muscle injury (Brooks et al., 2015). Dislocation can lead to further injury (labrum tears, depressed fractures of the humeral head or glenoid cavity), especially in recurrent cases (Owens et al., 2007). One of the more common traumatic shoulder injuries is the rotator cuff tear, wherein one or more of the rotator cuff tendons (*Infraspinatus, Supraspinatus, Subscapularis, Teres minor*) is partially or completely torn from the humerus (Martini et al, 2015). A specific category of OA, Cuff Tear Arthropathy (CTA), develops in around 4% of individuals suffering a severe rotator cuff tear (Zingman et al., 2017). At this point, the etiology of this condition is unclear, but the attrition and destruction of muscles stabilizing the shoulder joint, thereby leading to altered biomechanical loading and motion, is thought to be a significant contributing factor (Visotsky, Basamania, Seebauer, Rockwood, & Jensen, 2004).

Abnormal hip joint morphology, especially femoroacetabular impingement (FAI), is recognized as a major factor in the etiology of hip OA (Bardakos & Villar, 2009; Ganz, Leunig, Leunig-Ganz, & Harris, 2008; Murphy, Eyles, & Hunter, 2016). Here, the morphology of either the acetabulum or the femoral head/neck means that the hip labrum and acetabular cartilage are abnormally compressed during movement, leading to eventual damage of both structures (Murphy et al., 2016). While some individuals are congenitally predisposed to the hip morphology involved in FAI, repetitive rotational maneuvers and flexion may contribute to the

development of FAI (Ellis, Briggs, & Philippon, 2011). Hip and groin pain, especially in elite hockey, football, and rugby players, is often related to labral damage and may require surgical relief of FAI (Ellis et al., 2011).

1.4.6 Genetics

As Williams (2007) noted, anecdotal evidence of OA's heritability has been discussed for decades. Prior to the 2000s, research on OA's genetic component was limited to sibling, especially twin, studies that indicated a genetic component to OA. The strength of the apparent relationship varied, depending upon which joint was involved and the potentially confounding factors characterizing the study participants. The sequencing of the human genome opened new avenues for researchers explore the particular genes involved in OA, and to investigate the mechanisms of OA inheritance and phenotypic expression.

In 1944, Stecher and Hersh first suggested that OA had a genetic component, finding a familial link for Heberden's nodes associated with hand OA, particularly for females (Stecher & Hersh, 1944). MacGregor and Spector (1999) detailed a number of earlier familial clustering studies that provided further support for the apparent heritability of hand and hip OA, as well as generalized OA involving multiple joints. Later studies investigated the incidence of radiologic evidence of hand and knee OA in mono- and dizygotic female twins, concluding that 39-65% of the variation in OA symptoms among the study subjects was due to genetic factors, with the higher percentage associated with monozygotic twins, who share an identical genetic inheritance (Spector et al., 1996).

Various familial studies indicate that within a general diagnosis of OA, individual joints may show different etiological mechanisms and differing levels of heritability. Osteophyte presence at the interphalangeal and carpo-metacarpal joints appears to be the most heritable characteristic of hand OA (Ishimori et al., 2010). While there is strong evidence for a familial relationship for hand OA, evidence for the heritability of hip and knee OA is more variable (MacGregor, Li, Spector, & Williams, 2009; Riyazi et al., 2005). Siblings of individuals with hip OA appear to be more prone to developing hip OA themselves (Lanyon et al., 2000; Riyazi et al., 2005), with over 40% of the variability in hip OA ascribed to genetic factors (Skousgaard et al., 2015). Other studies suggest no correlation between familial relationship and the development of hip OA, or attribute any correlation found to the confounding influence of shared familial environmental factors (Lanyon et al., 2000; MacGregor et al., 2009).

In contrast, the heritability of knee OA is much less clear. In studies of the offspring of patients undergoing OA-related knee replacement surgery, these individuals showed increased evidence of radiographic OA and worsening of knee structural changes when compared to those of a control group (Khan et al., 2015; Pan et al., 2015). Other research suggests that genetic heritability accounts for only 18% of the variation in knee OA; environmental factors, both shared familial and unique (BMI, physical activity or occupation, etc.) account for the majority of the variability (Skousgaard et al., 2016).

Overall, family-based heritability studies confirmed the long-standing anecdotal evidence of OA's genetic component. However, these studies also reinforced OA's multi-factorial nature; a genetic predisposition for OA is not the only explanation for an individual's development of the condition. The influence of genetic inheritance seemed to vary depending on the joint(s) affected, with hand and hip involvement showing a stronger genetic basis. In the research, knee OA appeared to be far more influenced by non-genetic risk factors. All of this indicated the strong probability that OA was a polygenic condition, with different phenotypes of the disease reflecting the actions of different sets of genes (MacGregor et al., 2009).

The combination of twin based studies and the sequencing of the human genome have allowed researchers to begin to associate genes and gene combinations with aspects of OA. Williams (2007) detailed a number of earlier studies that attempted to link OA phenotypes with related genetic loci. Evidence for genes related to OA susceptibility has been found throughout the genome: 18 of 22 autosomes, plus the X chromosome have at least one locus of susceptibility (Williams 2007).

Minafra and colleagues (2014) combined a study of radiographic and clinical OA assessments with analyses of some of the loci and single nucleotide polymorphisms (SNP) associated with OA in a group of elderly Sicilian individuals. Some of the genes and SNP examined have, in previous studies, been shown to be involved in bone and joint maintenance, growth hormone regulation, and cartilage breakdown. In addition to correlations between radiographic levels and clinical assessments of OA, the researchers found a correlation between the severity of radiographic OA and an SNP (OS5 r143383) that had been consistently linked to OA in previous studies. This polymorphism causes a decrease in the function of a gene that encodes a protein involved in the growth, homeostasis, and repair of cartilage, bone, and other tissue (Minafra et al., 2014).

As well as identifying the specific genes and SNP associated with OA, recent research has centred on the epigenetic aspects of OA. Epigenetic (literally "above" genetic) research centres on the modification of the function of DNA, RNA, or proteins, without the alteration of their primary sequence (van Meurs, 2017). Epigenetic factors can depend upon environmental stimuli, may be tissue specific, and may be passed on for several generations (van Meurs, 2017). For example, Aref-Eshghi and colleagues (2015) studied DNA methylation, one of the more common epigenetic modification types, in cartilage samples from individuals with and without OA, finding a number of sites and genes across the genome were differentially methylated in the OA cartilage. Most of these had not previously been known to play a role in OA etiology, but were related to skeletal development (Aref-Eshghi et al., 2015).

1.5 OA Indicators in Paleopathology and Archaeology

OA is an ancient disease, well documented in the fossil and archaeological record (Dequeker & Luyten, 2008; Jurmain & Kilgore, 1995; Ortner, 2003; Rogers & Waldron, 1995). As with the diagnosis of any disease from archaeological skeletal remains, the diagnosis of OA is limited by the absence of soft tissue, a lack of knowledge of the individual's medical history and pain experience, and often damaged and fragmentary or incomplete skeletal remains. Only the condition's direct effect on bone is visible. Rogers and colleagues (1987) denote four OA diagnostic conditions for any synovial joint: the presence of marginal osteophytes; subchondral bone reactions, including sclerosis and eburnation (see below); the alteration of normal joint contours; and pitting (porosity) of the joint surfaces.

The first, osteophyte growth, or abnormal proliferation of bone on a joint margin or surface, is a known radiographically-visible symptom of OA (Kellgren & Lawrence, 1957; Laxafoss et al., 2010; Rogers & Waldron, 1995). Sclerosis may also be visible on radiographs as bright white cortical bone, depending upon its location and the angle of the beam and detector. In general, sclerotic bone is dense cortical bone, formed in response to a concomitant stressor; in the case of OA, it forms in subchondral bone as a reaction to damage of the overlying cartilage (Ortner, 2003). Eburnation refers to sclerotic bone that has a polished, shiny appearance; this is taken as evidence of complete focal cartilage destruction resulting in bone-on-bone contact, especially if grooves are observed in the lesion (Ortner, 2003). Waldron (2008) suggests that the presence of eburnation on a joint is diagnostic of OA in itself. In its absence, at least two of the

other conditions must be present (Waldron 2008). Joint contour change is related to reactive bone growth in response to severe cartilage damage and joint displacement (Rogers, Waldron, Dieppe, & Watt, 1987). In dry bone, this is seen as bone proliferation or resorption that changes the overall shape of a joint and/or the articulation of individual bones within a joint (Rogers and Waldron, 1995).

Porosity, or pitting, is a somewhat enigmatic item. Ortner (2003) interprets it as evidence of bone destruction, even suggesting that the pits may lead deeper into the subchondral bone. Buikstra and Ubelaker (1994) include porosity on their diagnostic and scoring criteria for OA, with more and connected porosity receiving a higher score. However, Rothschild (1997) argues that the presence of porosity on normal joints precludes it as a diagnostic criterion for OA, while Woods (1995) suggests that porosity is a secondary effect of OA, rather than a primary indicator. Currently, porosity alone is not considered diagnostic for OA in dry bone (Waldron, 2008). Little research has been performed since to discover the significance of porosity in normal or osteoarthritic skeletal remains, beyond taphonomy-specific studies of bone porosity (Bosch et al., 2014; Mansilla et al., 2014).

1.5.1 Implications for Archaeological Work

Some of the clinical work discussed previously has implications for the interpretation of OA in archaeological skeletal remains. One interesting question arising from studies of cartilage structure and histology is whether or not joint surfaces on archaeological remains are subchondral cortical bone *in sensu stricto*. Traditionally, it has been assumed that one is examining cortical bone. However, it is possible that the calcified cartilage layer has remained on the bone and that the tidemark, or the junction between the deep uncalcified cartilage and the calcified cartilage zone (CCZ), is being observed instead. This layer is more saturated with calcium salts than the underlying cortical bone (Wang et al., 2009). During the course of their research, Wang and colleagues (2009) were unable to separate the CCZ from the bone. After decalcification, the researchers were able to manually remove the uncalcified cartilage, but the CCZ remained intact. Furthermore, Benjamin and colleagues (2002) suggest that, at least on entheses (muscle and ligament attachment sites), the tidemark remains on dry bone. There is no reason to assume that this is not also the case for joint surfaces.

The nature of bone porosity is a subject of interest for both clinicians and paleopathologists. Clinical research suggests that subchondral bone plate porosity plays a role in

OA; the precise nature of that role has not yet been clarified. Porosity appears to increase markedly in the early stages of the OA, and then decrease (Botter et al., 2011; Sniekers et al., 2008). Therefore, porosity may indicate an earlier stage of the disease, or an incident of re-activation after a period of stasis. Other research indicates that at least some porosity is present in healthy bone (Botter et al., 2011; Lyons et al., 2006; Shibakawa et al., 2005). As such, OA represents a significant increase in porosity, or an increase in some types of porosity (Shibakawa et al., 2005). This may help to partially explain Rothschild's (1997) results on archaeological bone, wherein porosity was observed on joint surfaces both with and without OA.

As mentioned previously, OA is an ancient condition in both hominins and other animals (Dequeker and Luyton, 2008). Among anatomically modern humans, the condition has been part of the human experience for more than 7000 years (e.g., Crubézy et al., 2002; Lieverse et al., 2007). While retrospective analysis of ancient risk factors is problematic, if not impossible, some things can be postulated from what is known of ancient conditions and lifestyles. Among hunter-fisher-gatherer populations, a high level of physical activity and workload was a fact of life (Eng, 2016; Lieverse, Mack, Bazaliiskii, & Weber, 2016; Lieverse et al., 2007). Therefore, it is highly plausible that physical activity and injury played a major role in the development of OA among these populations. In addition, there is no reason to assume that estrogen deficiency in post-menopausal women would have any different an effect on cartilage homeostasis than it does today. What is quite different is the prevalence of obesity; due to diet and unavoidable physical activity, hunter-fisher-gatherers were unlikely to be overweight (Faccia et al., 2016). Given the strong tie between obesity and OA prevalence today, it is possible that some aspect of OA or human physiology has changed over the past several thousand years. However, in an examination of long-term knee OA incidence, Wallace and colleagues (2017) found that age, BMI, and sex were insufficient explanations for the almost two-fold increase in knee OA seen in their post-industrial (1800s-1900s) sample, compared to pre-industrial and hunter-gatherer samples. The researchers suggest that OA is a "mismatch disease", a term used to describe conditions that are more severe or common because human bodies are not well-adapted to modern environmental or lifestyle conditions (Wallace et al., 2017). Increased attention to the genetic aspects of OA may eventually unravel this puzzle; it may be that an OA-associated gene has undergone modification or methylation in the intervening time period, changing its sensitivity or reaction to adipokines or other biochemical factors.

1.6 Problem Statement

As previously mentioned, the purpose of this research is to bring together the knowledge and techniques of clinical medicine and bioarchaeology, in order to provide both fields with further insight into the causes and physical manifestations of OA pain. In dealing with living patients, clinical medicine's focus tends to be on pain amelioration and other treatment options. Observation of OA-related bone lesions and other internal indicators of the condition is, by necessity, limited to medical imaging technology, most often radiographs. As noted in the previous chapter, the correlation between radiographically observed OA symptoms and patient-reported symptoms and severity is inconclusive at best. In contrast, bioarchaeology's study of OA is limited to observation of lesions on dry bone, with no access to patient-reported levels of pain or symptom severity. This study will attempt to forge a link between patient-reported pain and observed bone lesions.

For modern OA sufferers, total joint replacement surgery is available as a final treatment option for those suffering from chronic pain and impaired movement due to OA. In 2016-17, just over 67,000 total knee replacements were performed in Canada on patients with severe OA symptoms (Canadian Institute for Health Information, 2018). In this operation, the joint capsule is exposed, ligaments cut or moved aside, and the tibial plateau (including the proximal articular surface) is removed via a thin cut with a surgical saw. The bone of the articular portions of the distal femur is removed, and both proximal tibia and distal femur are capped with prostheses, usually made of metal alloys (Scuderi, 2006; W. Dust, personal communication, March 22, 2018). The patella may or may not be replaced as well. Typically, the removed tibial plateau is destroyed as biological waste.

For this study, the removed plateaus were retained and reduced to dry bone, thereby allowing for the observation of OA-related lesions on both the articular and inferior (i.e., internal trabecular) portions. This will allow for the direct association between a sample population with known clinical information (age, sex, pain/debilitation, and *intra vitam* radiographs) and OA-related bony lesions. Thus, observations of lesion type, prevalence, severity, and extent can be directly correlated with known patient information and experience in order to provide insight into the cause(s) of OA pain.

Chapter 2
Materials and Methodology

2.1 Study Sample

The study design was approved by the University of Saskatchewan Biomedical Research Ethics Board (Bio 17-108, Appendix A). Study sample plateaus were obtained from patients undergoing knee replacement surgery due to the effects of OA; the majority of these individuals were patients of Dr. W. Dust, while some were patients of other orthopedic surgeons. Informed consent (Appendix B) for the use and study of the removed plateaus was obtained by Dr. Dust either at the patient's pre-surgery appointment or, in the case of patients scheduled for surgery before the research project began, immediately before surgery. After the plateau's removal (in the manner described in the previous section), it was immediately placed in a specimen jar labelled with a patient number and containing a 10% formalin solution. The jar was then transported to Dr. Dust's office at the Royal University Hospital (RUH) for storage. Once a sufficient number of plateaus had accumulated, they were collected by the researcher. All the patients participating in the research also gave consent for their pre-operative X-rays to be provided to the researcher; these were identified only by the patient number assigned to the associated plateau. Electronic versions of the X-rays were copied to the researcher's flash drive when the associated plateaus were being collected. The master list connecting patient information and patient number was held by Dr. Dust's office; the researcher was only given each individual's sex and age, and in rare instances, limited pertinent health information (e.g., one patient had previous ACL surgery). No permission to share radiographic images in the thesis or any subsequent publications was sought or granted.

2.2 Cadaver Sample

Initially, it was hoped that control (no diagnosed OA) plateaus could be obtained from Saskatoon Health Region Organ/Tissue Donation protocols, but this proved to be impossible, due to changes in the types of tissue being harvested. After consultation with the U of S Department of Anatomy and Cell Biology (ACB), permission was granted to obtain bone samples from three cadaver specimens who were part of the Body Bequeathal Program. These specimens were transported from the ACB anatomy lab to an operating room at RUH, where the tibial plateaus

were removed using the same techniques, instruments, and personnel employed on living patients. These plateaus were placed in formalin-containing specimen jars and labelled with their identification numbers. The remainders of the specimens were returned to the Anatomy Lab. As with the study samples, only sex and age were known.

2.3 Bone Processing

Study and cadaver plateaus were processed in the same manner. After collection, the samples were transported to either the ACB anatomy laboratory or the Western College of Veterinary Medicine (WCVM) anatomy laboratory. There, the superior and inferior sides of each specimen were photographed using a Panasonic Lumix digital camera. The condition of the articular cartilage for the whole plateau was rated according to the Outerbridge classification system (Outerbridge, 1961), a macroscopic ordinal grading system for scoring cartilage degradation (Table 2.1). Other observations of the plateaus were also recorded, including such items as location of areas of total cartilage loss, presence of marginal osteophytes, and areas of 'spongy'-appearing trabeculae on the inferior. For statistical comparison purposes, the Outerbridge rating for each specimen was converted into a present/absent score for areas of total cartilage loss, where 1=areas of total cartilage loss present and 0=some or all cartilage remaining. Thus, Outerbridge ratings of 0-3 became scores of 0 (total cartilage loss absent) and Outerbridge ratings of 4 became scores of 1 (total cartilage loss present). The location(s) of areas of total cartilage loss was also recorded.

Table 2.1
Outerbridge Cartilage Classification (Outerbridge, 1961)

Grade of Cartilage Degradation	Description	Converted Score for Presence/Absence of Total Cartilage Loss (0=absent; 1=present)
0	Normal	0
1	Softening and swelling of cartilage	0
2	Fragmentation and fissuring in an area half an inch (1.5 cm) or less in diameter; fissures do not reach subchondral bone	0
3	Fragmentation and fissuring in an area more than half an inch (1.5 cm) in diameter; fissures reach the level of subchondral bone	0
4	Erosion of cartilage down to the bone; areas of subchondral bone exposed	1

Soft tissue removal was performed at the Western College of Veterinary Medicine (WVCM) anatomy lab. The plateaus were wrapped in cheesecloth and simmered in a large kettle for 4-6 hours. The first batch of plateaus obtained were initially simmered in plain water; this left both the remaining articular cartilage and ligament attachments mainly intact, and difficult to remove without damaging the bone surface. Following the research of Thompson (2015), the specimens were re-simmered in a 2% solution of sodium bicarbonate. This proved effective in breaking down the remaining soft tissues enough to remove without bone damage, and the rest of the specimens were processed in this manner. After simmering, the remaining soft tissue was removed via a combination of rubbing with a cloth and scraping with a gloved fingernail or plastic modelling tool.

The plateaus were then degreased in a bath of 35% hydrogen peroxide for approximately 12 hours, then dried for at least 24 hours. A thick coat of clear nail polish was applied to an appropriately smooth and flat area of the plateau margin. This provided a base for marker labelling of each plateau with the associated patient number. After a top coat of clear nail polish had dried, the specimens were taken to the Archaeology laboratory for the remaining photography, scoring, and observations. Each dry bone plateau was photographed, using the same Panasonic Lumix camera, from a number of angles: superior and inferior, as well as anterior/posterior and medial/lateral.

2.4 Scoring and Observations

Scoring of the OA lesions on the articular surfaces of each plateau was based largely on the standards outlined by Buikstra and Ubelaker (1994). These standards allow for the scoring of both the degree of lesions (again, on an ordinal scale), as well as the extent of the bone surface affected by these lesions. As it became obvious through observation that there were medial and lateral condylar differences in the majority of the plateaus, each condyle was scored separately. For each condyle, degree (severity) and extent (proportion of the surface affected) scores were recorded for three lesion categories: lipping (marginal osteophytes), porosity (pitting), and eburnation. Degree only was recorded for surface osteophytes. Each of these was recorded on a 4-point ordinal scale (0-3, with 0 representing 'not present') with the exception of surface osteophytes, which used a 3-point scale (0-2) (Table 2.2).

Table 2.2
Articular Surface Lesion Scoring (after Buikstra & Ubelaker, 1994, p. 115, 8.0.0-8.7.2)

Lesion Type	Degree	Extent of Surface Affected
Lipping	0 - not present 1 - barely discernable 2 – sharp ridge, sometime curled with spicules 3 – extensive spicule formation	0 – not present 1 - <1/3 2 – 1/3-2/3 3 - > 2/3
Porosity	0 – not present 1 - pinpoint 2 - coalesced 3 – both pinpoint and coalesced	0 -not present 1 - <1/3 2 – 1/3-2/3 3 - >2/3
Eburnation	0 - not present 1 - barely discernable 2 – polish only 3 – polish with groove(s)	0 - not present 1 - <1/3 2 - 1/3-2/3 3 - > 2/3
Surface Osteophytes	0 – not present 1 – barely discernable 2 – clearly present	

To facilitate quantitative comparisons among lesion types and severity, severity indices similar to those employed by Mack (2016) and Lieverse and colleagues (2016) were created for the lesions for which both degree and extent were recorded. Degree scores remained as a 4-point ordinal scale, while extent scores were converted to decimal equivalents of ordinal scale descriptions; scores of 0 remained as 0, but scores of 1, 2, or 3 were converted to .33, .67., and 1.00 respectively. Thus, a severity score for each lesion type on each condyle could be calculated for each plateau by multiplying the degree and extent scores (maximum score of 3 in all cases). Adding the resulting severity scores for each lesion type produced an overall severity score for each condyle (maximum score of 9); adding these scores in turn yielded an overall severity score for each plateau (maximum score of 18). These severity scores (now continuous variables) were the data used for the statistical analyses described in Section 2.6. Surface osteophyte scores remained as ordinal variables, since extent was not recorded for these lesion types.

The Buikstra and Ubelaker (1994) standards concentrate on OA lesions found on articular surfaces of joints; observations of the study plateaus revealed that there were OA-type and other lesions consistently appearing in non-articular portions of the specimens, specifically the intercondylar area and the inferior (trabecular) side of the plateau. Proliferative bone growth, porosity, and eburnation were observed in the intercondylar area, while lytic areas and patches of denser-appearing trabeculae were seen on the inferior side of the plateaus. The latter were

defined as areas of trabecular bone appearing noticeably denser than trabecular bone on the rest of the plateau. No microscopic examination was performed, so it not known whether these areas constituted zones of thicker trabecular rods, more trabecular rods, or some combination thereof. These intercondylar and inferior side lesions were common enough in the sample population that some consistent scoring method was deemed necessary. The lesion type and scoring method is detailed in Table 2.3. The majority of the scoring is on a 2-point, present/absent or yes/no scale. For these measures, locations of the lesions were also recorded.

Table 2.3
Intercondylar Eminence and Inferior Scoring

Lesion Type	Scoring
Intercondylar Area Proliferative Lesions	0 – not present 1 - present
Osteophytes on Tuberosities	0 - not present 1 - present
Enthesophytes in Other Intercondylar Areas	0 - not present 1 - present
Intercondylar Enthesophyte Location	Actual location(s) recorded
Intercondylar Area Eburnation	0 - not present 1 - present
Intercondylar Eburnation Location	Actual location(s) recorded
Intercondylar Area Porosity	0 - not present 1 - present
Intercondylar Porosity Extends to Inferior (at least one instance)	0 – no 1 – yes
Inferior Areas of Dense Trabeculae	0 - not present 1 - present
Location of Areas of Dense Trabeculae	Actual location(s) recorded
Inferior Areas of Dense Trabeculae Associated with Eburnation on Superior	0 - no 1 - yes
Size of Area of Dense Trabeculae Compared to Associated Eburnation	0 - not present 1 - dense area smaller than that of eburnation 2 - dense area approximately the same size as eburnation 3 - dense area larger than that of eburnation
Inferior Lytic Areas	0 - not present 1 - present
Number of Inferior Lytic Areas	Number recorded
Lytic Areas Extend to Superior (at least one instance)	0 - no 1 - yes
Superior Features/Lesions Above Lytic Areas (at least one instance)	0 - no 1 - yes
Lytic Areas with Sclerotic Border/Interior (at least instance)	0 - not present 1 - present
Number of Lytic Areas with Sclerotic Border/Interior	Number recorded

Diameter of Largest Lytic Area	0 – not present
	1 - < 2mm
	2 - 2-4mm
	3 - > 4mm
Location of Lytic Areas	Actual location(s) recorded

X-ray images were also examined and clinical OA diagnostic criteria scored from them, again using a 2-point scale to denote the presence/absence of each lesion type: osteophytes, joint space narrowing, and sclerosis. A Kellgren/Lawrence (K/L) severity score was also assigned, based on the presence and severity of these criteria (Kellgren and Lawrence, 1957). Locations for each of the features were recorded as well.

Table 2.4
X-ray Data Scoring

Lesion Type	Scoring
Marginal Osteophytes	0 - not present
	1 - present
Joint Space Narrowing (JSN)	0 – not present
	1 - present
Joint Space Narrowing Location	Actual location(s) recorded
Sclerotic Bone Areas	0 – not present
	1 - present
Sclerotic Bone Location	Actual location(s) recorded
K/L Score	0 – no radiographic features of OA present
	1 – doubtful JSN and possible osteophytic lipping
	2 – definite osteophytes and possible JSN
	3 – multiple osteophytes, definite JSN, sclerosis, possible bony deformity
	4 – large osteophytes, marked JSN, severe sclerosis, and definite bony deformity
	(Kellgren & Lawrence, 1957)

2.5 Study Specimens Used in Analyses

At the conclusion of the specimen collection period, the study (OA-affected) sample consisted of 70 plateaus (right=40; left=30), representing 62 individuals (male=31; female=31). Eight individuals had undergone bilateral knee replacements. While all specimens were photographed, observed, and scored, it was decided that only one plateau per individual would be included in statistical analyses. The decision of which plateau to include was based first on which plateau was least damaged by surgery; if the plateaus were of equal quality, one was randomly selected. Weight-bearing activity in the lower limbs is typically symmetrical; thus, no

differences between left and right were anticipated. Therefore, for statistical analyses, the study sample consisted of 62 plateaus (right=36; left=26), again representing equal numbers of male and female patients (31 each).

The cadaver sample consisted of 3 plateaus (male=1, female=2; right=1, left=2).

2.6 Analyses

The cadaver specimens were scored and observed in the same manner as the study specimens, with the exception of X-ray data, which were not available. However, due to the small size of the sample (n=3), no statistical analyses comparing OA lesions between the cadaver and study groups were performed. Comparisons between the two groups will be discussed in the next chapter. It is also important to note that, along with its small size, the average age of the cadaver group was much higher than that of the study group (92 years vs. 65.8 years). In addition, all cadaver specimens had some evidence of OA lesions.

All statistical analyses were done using IBM SPSS Version 25. The analyses performed on study sample specimens included paired sample t-tests to ascertain mean differences between medial and lateral condyle lipping, porosity, eburnation, and overall severity scores. Male and female differences in these severity scores were analysed via independent sample t-tests, as were sex differences in overall joint severity scores, number of inferior lytic areas, and number of inferior lytic areas with sclerotic border/interior. For medial and lateral surface osteophyte presence, differences in distribution were tested using the Wilcoxon Signed-rank test, the non-parametric version of a paired-sample t-test, as the t-test is inappropriate for use with ordinal data. Sex differences for medial and lateral osteophyte presence were tested using the Mann-Whitney U test, the non-parametric version of the independent samples t-test. The Mann-Whitney U test was also used to test sex differences in distribution for two ordinal variables listed in Table 2.3: size of patches of inferior dense trabeculae compared to associated eburnation; and diameter of the largest inferior lytic area. For the dichotomous variables (i.e., yes/no; present/absent) listed in Tables 2.3 and 2.4, frequencies and percentages of each were calculated. The extent to which sex was associated with each of these variables was tested using Fisher's Exact test, the non-parametric version of Pearson's chi-square test. The latter is not recommended in cases of small sample sizes, or if there are few observations in individual cells of the 2x2 contingency table. For many of the variables, there were cells with no observations.

Correlations and associations between various variables were measured by a variety of tests. Spearman's rank-order correlation is appropriate for ascertaining the relationship between continuous and ordinal variables; thus, this test was used to measure the correlation between overall joint severity and both size of patches of inferior dense trabeculae compared to associated eburnation and diameter of the largest inferior lytic area, as well as between medial and lateral total eburnation severity and distribution of opposite-condyle surface osteophytes. Pearson's product-moment correlation is used to test the correlation strength of continuous variables. This was used to test the association between overall joint severity and the number of inferior lytic areas, both with sclerotic border/interior and overall. Point-biserial correlation, a special case of Pearson's correlation, tests the relationship between continuous and dichotomous variables. This was used to measure the relationship between overall joint severity and several of the dichotomous variables listed in Table 2.3, as well as the relationship between overall joint eburnation severity and presence of areas of total cartilage loss. Finally, Pearson's chi-square test was employed to test the association between the dichotomous variables of X-ray-visible JSN and areas of total cartilage loss, as well as X-ray-visible sclerosis and areas of inferior dense trabeculae. For all analyses, significance levels were set at 0.05.

As with comparisons of cadaver and study specimens, a number of comparisons were deemed to be inappropriate for statistical analyses, because the data were not normally distributed. These data are explored descriptively and discussed in the next chapter. Frequency and percentage data for locations of intercondylar and inferior lesions as well as X-ray-visible features were calculated, as was the distribution and combinations of sclerotic and non-sclerotic bordered inferior lytic areas. Study sample mean severity scores (lipping, porosity, eburnation, overall condyle, and overall joint severity) were compared with those of the cadaver sample.

Chapter 3

Results

3.1 Medial and Lateral Comparisons

Tests of intra-joint symmetry for scores of total lipping severity, total porosity severity, and total eburnation severity, and overall condyle severity revealed significant differences between medial and lateral condyles for scores of total porosity, eburnation, and overall severity (see Table 3.01). Medial scores on these variables were significantly higher (i.e., more severe) than corresponding lateral scores. The summarized data are presented in Table 3.01, while the paired t-test results are in Table 3.02.

A Wilcoxon Signed-Ranks test indicated that the median severity scores for lateral surface osteophyte presence (*Mdn*=.74) were significantly higher than those of medial surface osteophytes (*Mdn*=.16), *Z*= -3.962, *p*<.001.

Table 3.01
Summary of intra-joint severity symmetry data

Measure	Mean	N	Std. Deviation	Std. Error Mean
Medial Total Lipping	2.5410	61	.50245	.06433
Lateral Total Lipping	2.4918	61	.50408	.0454
Medial Total Porosity	.4316	62	.45905	.05830
Lateral Total Porosity	.1437	62	.29649	.03765
Medial Total Eburnation	.9052	62	.74896	.09512
Lateral Total Eburnation	.2574	62	.70992	.09016
Medial Overall Severity	3.8368	62	1.45886	.18527
Lateral Overall Severity	2.9011	62	1.21866	.15477

N=number of individuals

Table 3.02

Results of intra-joint analyses for total severity scores of medial vs. lateral condyles

Measures	Mean	Std. Deviation	Std. Error Mean	95% Confidence Level of the Difference (lower, upper)	t	df	p
Medial and Lateral Total Lipping	.4918	.61715	.07902	(-.10888, .20724)	.622	60	.536
Medial and Lateral Total Porosity	.28790	.56357	.07157	(.14478, .43102)	4.022	61	**<.001**
Medial and Lateral Total Eburnation	.64774	1.17006	.14869	(.35060, .94488)	4.359	61	**<.001**
Medial and Lateral Overall Severity	.93565	1.94983	.24763	(.44048, 1.43081)	3.778	61	**<.001**

p=p-value of paired sample t-tests (bold if statistically significant)

3.2 Dichotomous Variables

A summary of results for dichotomous (0=no/absent; 1=yes/present) scoring items (see Tables 2.3 and 2.4) is presented in Table 3.03. Intercondylar and inferior side lesions, as well as radiographic evidence of OA are present in at least 90% of specimens. Inferior dense trabeculae are associated with eburnation immediately superior to the dense area in 82.3% of the study specimens.

Table 3.03
Frequency and percent data for dichotomous variables

Variable		Frequency (/62)	Percent
X-ray Osteophytes	Present	62	100
X-ray JSN	Present	61	98.4
X-ray Sclerotic Areas	Present	61	98.4
Porosity On/Adjacent to Eburnation	Present	37	59.7
Intercondylar Proliferative Lesions	Present	62	100
Osteophytes on Tubercles	Present	59	95.2
Enthesophytes in Other IC Areas	Present	59	95.2
Intercondylar Eburnation	Present	19	30.6
Intercondylar Porosity	Present	57	91.9
IC Porosity Extends to Inferior	Yes	16	25.8
Inferior Dense Trabecular Areas	Present	61	98.4
Inferior Dense Trabeculae with Eburnation on Superior	Present	51	82.3
Presence of Inferior Lytic Areas	Present	52	83.9
Lytic Areas Extend to Superior	Yes	19	30.6
Superior Features/Lesions Above Lytic Areas	Present	33	53.2
Lytic Areas with Sclerotic Border/Interior	Present	39	62.9

3.3 Sex Comparisons

Summary data and results comparing male and female scores are presented in Tables 3.04–3.10 below. Table 3.04 is a summary of male and female comparison data on scores of total lipping severity, total porosity severity, and total eburnation severity, overall condyle severity, and number of inferior lytic areas overall and with sclerotic borders. Table 3.05 presents the independent samples t-test results. Males and females did not differ significantly on any of these scores.

Independent Samples Mann-Whitney U tests indicated that while the distribution of Lateral Surface Osteophytes did not differ significantly between the sexes (*U*=430.5, *p*=.433), the distribution of Medial Surface Osteophytes did (*U*=356.6, *p*=.003). All plateaus showing the presence of medial condyle surface osteophytes were those of males (n=8).

The association of dichotomous (0=no/absent; 1=yes/present) scoring items with sex is summarized in Table 3.06. The results of Fisher's Exact Test indicate that the dichotomous variables did not differ significantly between male and female sample specimens.

Table 3.04
Summary of Male and Female Comparison Data

Variable	Sex	N	Mean	Std. Deviation	Std. Error Mean
Medial Total Lipping	female	30	2.4667	.50742	.09264
	male	31	2.6129	.49514	.08893
Lateral Total Lipping	female	31	2.4839	.50800	.09124
	male	31	2.4839	.50800	.09124
Joint Lipping Total Severity	female	31	4.8710	.88476	.15891
	male	31	5.0968	.87005	.15627
Medial Total Porosity	female	31	.3939	.42105	.07562
	male	31	.4694	.49825	.08949
Lateral Total Porosity	female	31	.1916	.33841	.06078
	male	31	.0958	.24390	.04280
Joint Porosity Total Severity	female	31	.5748	.48175	.08653
	male	31	.5652	.58778	.10557
Medial Total Eburnation	female	31	.9126	.85050	.15275
	male	31	.8977	.64585	.11600
Lateral Total Eburnation	female	31	.3223	.82352	.14791
	male	31	.1926	.58130	.10440
Joint Eburnation Total Severity	female	31	1.2348	.95077	.17076
	male	31	1.0797	.80326	.14427
Medial Overall Severity	female	31	3.6935	1.63045	.29284
	male	31	3.9800	1.27542	.22907
Lateral Overall Severity	female	31	2.9977	1.36664	.24536
	male	31	2.8045	1.06431	.19116
Overall Joint Severity	female	31	6.6913	1.89858	.34099
	male	31	6.7523	1.84883	.33206
Number of Inferior Lytic Areas	female	31	1.65	1.539	.276
	male	31	2.16	1.635	.294
Number of Inferior Lytic Areas with Sclerotic Border	female	31	1.19	1.558	.280
	male	31	1.55	1.609	.289

Table 3.05
Results of Sex Comparisons for Lesion Severity Scores (Lipping, Porosity, Eburnation, and Overall Severity) on Medial, Lateral, and Total Joints and for Number of Inferior Lytic Areas (Overall and With Sclerotic Border)

Measure	t	df	p	Mean Difference	Std. Error Difference	95% Confidence Level of Difference (lower, upper)
Medial Total Lipping	-1.129	59	.259	-.14624	.12836	(-.40309, .11062)
Lateral Total Lipping	.000	60	1.000	.0000	.12903	(-.25810, 25810)
Joint Lipping Total Severity	-1.013	60	.315	-.22581	.22287	(-.67161, .22000)
Medial Total Porosity	-.644	60	.522	-.07548	.11716	(-.30984, .15888)
Lateral Total Porosity	1.279	60	.206	.09581	.07492	(-.05406, .24567)
Joint Porosity Total Severity	.071	60	.944	.00968	.13650	(-.26336, .28271)
Medial Eburnation Total*	.077	60	.939	.01484	.19181	(-.36940, .39908)
Lateral Eburnation Total	.716	60	.477	.12968	.18104	(-.23246, .49182)
Joint Eburnation Total Severity	.694	60	.490	.15516	.22355	(-.29200, 60232)
Medial Overall Severity	-.770	60	.444	-.28645	.37179	(-1.03014, .45724)
Lateral Overall Severity	.621	60	.537	.19323	.31111	(-.42909, .81554)
Overall Joint Severity	-.128	60	.899	-.06097	.47596	(-1.01304, .89110)
Number of Inferior Lytic Areas	-1.280	60	.206	-.516	.403	(-1.323, .291)
Number of Inferior Lytic Areas with Sclerotic Border	-.882	60	.381	-.355	.402	(-1.160, .450)

p=p-value of independent samples t-test (bold if significant)
*Levene's test for equality of variances was found to be violated for this variable, F (1,60) =4.277, p=.043. Therefore, results for a t-test not assuming homogeneity of variance are reported.

Table 3.06
Summary and results of dichotomous variables' association with sex.

Associations	Sex	Absent/No	Present/Yes	Fisher's Exact Test p-value (2 -sided)
Sex*Xray Osteophytes	Male	0	31	Not calculated*
	Female	0	31	
Sex*Xray JSN	Male	1	30	1.000
	Female	0	31	
Sex *Xray Sclerotic Area	Male	0	31	1.000
	Female	1	30	
Sex*Overall Porosity On/Adjacent to Eburnation	Male	13	18	1.000
	Female	12	19	
Sex*IC Proliferative Lesions	Male	0	31	Not calculated*
	Female	0	31	
Sex*Osteophytes on Tubercles	Male	1	30	1.000
	Female	2	29	
Sex*Enthesophytes in Other IC Areas	Male	2	29	1.000
	Female	1	30	
Sex*IC Eburnation	Male	23	8	.582
	Female	20	11	
Sex*IC Porosity	Male	3	28	1.000
	Female	2	29	
Sex*IC Porosity Extends to Inferior	Male	24	7	.772
	Female	22	9	
Sex*Inferior Dense Trabecular Areas	Male	0	31	1.000
	Female	1	30	
Sex*Inferior Dense Trabeculae Associated with Superior Eburnation	Male	4	27	.508
	Female	7	24	
Sex*Presence of Inferior Lytic Areas	Male	3	28	.301
	Female	7	24	
Sex*Lytic Areas Extend to Superior	Male	21	10	1.000
	Female	22	9	
Sex*Lytic Areas with Sclerotic Border/Interior	Male	8	23	.283
	Female	13	18	

*p-values not calculated because presence of Xray Osteophytes and IC Proliferative Lesions was considered a constant.

As noted in Table 3.03, areas of inferior dense trabeculae were associated with eburnation immediately superior to the dense area in 82.3% of the study specimens. The size of the area of dense trabeculae compared with that of the area of eburnation was scored as: not present; dense trabecular area smaller than that of eburnation; dense trabecular area same size as area of eburnation same size; or dense trabecular area larger than that of eburnation. A summary of

male, female, and overall scores is presented in Table 3.07. Table 3.08 contains the results of independent samples Mann-Whiney U tests comparing male and female differences in these scores. The results indicated that the distribution of dense trabecular patch size compared with associated eburnation size did not differ significantly across sex categories (U=413.5, p=.267).

Overall, 64.5% of the study sample had inferior patches of dense trabeculae that were larger than the associated area of eburnation on the superior (articular) portion of the plateau.

Table 3.07
Male, female, and overall summary of size comparisons of superior eburnation and areas of inferior dense trabeculae

	Not present	Dense trab. smaller than eburnation	Dense trab. same size as eburnation	Dense trab. larger than eburnation	Total
Female	7 (11.3%)	1 (1.6%)	5 (8.1%)	18 (29.0%)	31
Male	4 (6.5%)	1 (1.6%)	4 (6.5%)	22 (35.5%)	31
Total	11 (17.7%)	2 (3.2%)	9 (14.5%)	40 (64.5%)	62

Table 3.08
Summary and results of male and female comparisons of superior eburnation and areas of inferior dense trabeculae

Variable	Sex	N	Mean Rank	Sum of Ranks	Mann-Whitney U	p-value (2 -tailed)
Size of dense trabecular area compared to eburnation	female	31	29.34	909.50	413.50	.267
	male	31	33.66	1043.50		

The diameter of the largest inferior side lytic area was measured and categorized as not present, <2mm, 2-4mm, or > 4mm. Table 3.09 shows the female, male, and overall numbers of each diameter category. Table 3.10 displays the results of independent samples Mann-Whitney U-tests of the distribution of lytic area diameter across sex categories, indicating that the distribution differed in males and females (U=305.00, p=.01).

As shown in Figure 3.1, female specimens were more likely than males not to have inferior lytic areas, or to have the smallest category of lytic area (diameter < 2mm) (11.3% and 16.1% respectively). Male specimens, however, were more likely to score in the largest category of lytic area (diameter > 4mm) (21.0%).

Table 3.09
Male, female, and overall results in diameter of largest inferior lytic area

Diameter of Largest Lytic Area

Sex	Not present	<2 mm	2-4 mm	>4 mm	Total
Female	7 (11.3%)	10 (16.1%)	9 (14.5%)	5 (8.1%)	31
Male	3 (4.8%)	5 (8.1%)	10 (16.1%)	13 (21.0%)	31
Total	10 (16.1%)	15 (24.2%)	19 (30.6%)	18 (29.0%)	62

Table 3.10
Results of male and female differences in diameter of largest inferior lytic area

Variable	Sex	N	Mean Rank	Sum of Ranks	Mann-Whitney U	p-value (2-tailed)
Size of largest lytic area	female	31	25.84	801.00	305.0	.01
	male	31	37.16	1152.00		
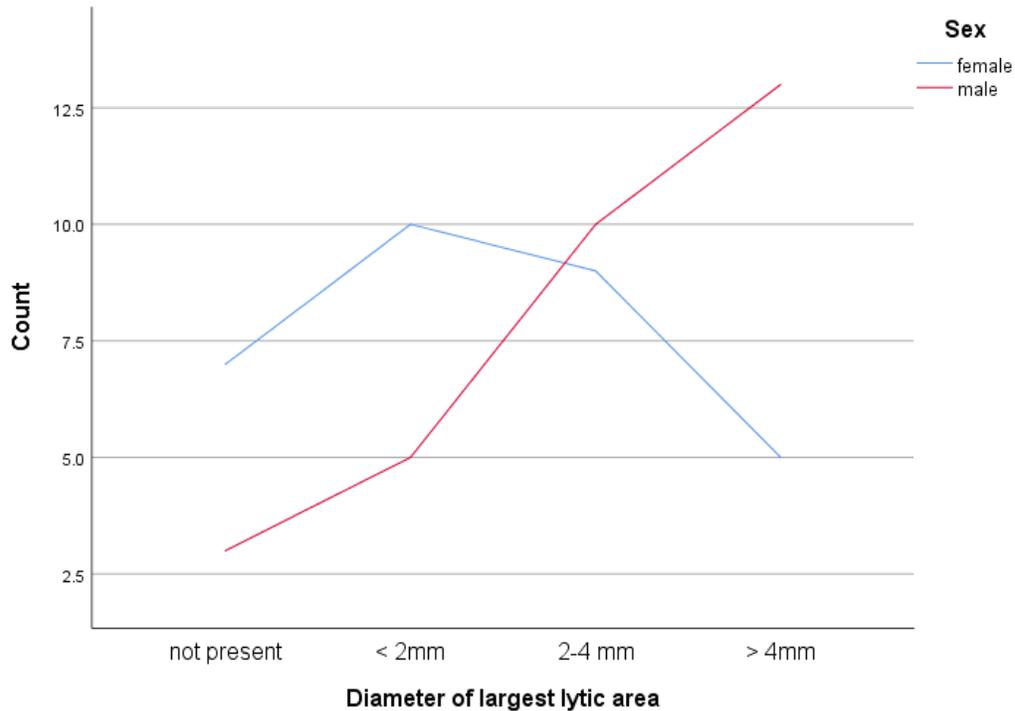
Figure 3.1. **Male and female comparisons in diameter of largest inferior lytic area**

3.4 Correlations

Correlation coefficients were calculated to ascertain the nature and strength of relationships between Overall Joint Severity scores and variables measuring intercondylar and inferior lesions. The types of variable combinations involved (i.e. continuous, ordinal, dichotomous) informed which measure of correlation was used. These are noted in Table 3.11, along with the results.

There was a significant weak positive correlation between Overall Joint Severity and Size of Dense Trabeculae Compared to Eburnation (r_s=.374, N=62, p=.003), and a moderate positive correlation between Overall Joint Severity and Inferior Dense Trabeculae Associated with Superior Eburnation (r_{pb}=.580, N=62, p<.001). Given that eburnation severity scores form a portion of Overall Joint Severity scores, this relationship is not surprising. There was also a moderate positive correlation between Overall Joint Severity and Intercondylar Eburnation (r_{pb}=.482, N=62, p<.001).

Table 3.11

Correlations between Overall Joint Severity scores and measures of intercondylar and inferior lesions

Correlation Variables	N	Correlation Coefficient	p (2-tailed)
Overall Joint Severity/Intercondylar Proliferative Lesions	62	Not calculated*	
Overall Joint Severity/Osteophytes on Tuberosities	62	-.170[+]	.186
Overall Joint Severity/Enthesophytes in Other Intercondylar Areas	62	.158+	.221
Overall Joint Severity/Intercondylar Eburnation	62	.482+	**<.001**
Overall Joint Severity/Intercondylar Porosity	62	.064+	.623
Overall Joint Severity/Inferior Dense Trabecular Areas	62	.120+	.352
Overall Joint Severity/Inferior Dense Trabeculae Associated with Superior Eburnation	62	.580+	**<.001**
Overall Joint Severity/Size of Areas of Dense Trabeculae Compared to Associated Eburnation	62	.374**	**.003**
Overall Joint Severity/Presence of Inferior Lytic Areas	62	.015+	.910
Overall Joint Severity/Number of Inferior Lytic Areas	62	.082[++]	.524
Overall Joint Severity/Number of Inferior Lytic Areas with Sclerotic Borders	62	.075[++]	.563
Overall Joint Severity/Diameter of Largest Lytic Area	62	.012**	.927

*unable to be calculated because all specimens had intercondylar osteophytes; p=correlation p-value (significant values bolded)
**Spearman's Correlation (r_s); [+] Point-biserial Correlation (r_{pb}); [++] Pearson's Correlation (r)

As noted in section 3.1, medial and lateral surface osteophyte scores differed significantly; correlations between these measures and opposite condyle total eburnation severity scores are reported in Table 3.12. Correlations were also calculated between radiographically visible lesions (joint space narrowing, sclerotic cortical bone) and their typically associated physical markers (areas of total cartilage loss and eburnation for the former, and patches of dense trabeculae for the latter). Again, the test used depended upon the nature of the variables and is also noted in Table 3.12.

There was a significant positive association between the presence of radiographically visible joint space narrowing (JSN) and areas of total cartilage loss ($\chi(1)=9.486$, p=.002), as well as a significant moderate positive correlation between areas of total cartilage loss and total joint eburnation severity scores (r_{pb} =.436, N=62, p<.001).

Table 3.12
Correlations between medial and lateral surface osteophytes and opposite condyle eburnation; radiographically visible OA lesions and associated physical markers

Correlation Variables	N	Correlation Coefficient	p-value (2-sided)
Medial Total Eburnation/Lateral Surface Osteophytes	62	-.043*	.739
Lateral Total Eburnation/Medial Surface Osteophytes	62	.196*	.126
Xray JSN/Areas of Total Cartilage Loss	62	9.486+	**.002**
Xray Sclerotic Areas/ Areas of Inferior Dense Trabeculae	62	.017+	.897
Areas of Total Cartilage Loss/Total Joint Eburnation Severity	62	.436++	**<.001**

p=correlation p-value (significant values bolded)
*Spearman's Correlation (r_s); + Chi-square Test for Association (χ); ++ Point-biserial Correlation (r_{pb})

While, as reported in Table 3.12, there was no significant correlation between surface osteophyte presence and opposite condyle eburnation severity, examining the data more closely is enlightening. Tables 3.13 and 3.14 present cross tabulations of medial and lateral surface osteophyte presence, respectively, and opposite condyle eburnation severity scores.

It is interesting to note the pattern of osteophyte presence compared with eburnation severity. For both cross tabulations, it appears that if surface osteophytes are present, they are more likely to be associated with lower opposite condyle eburnation severity scores (.99 or less). For most specimens, a score of .99 is likely to be reflective of a high eburnation degree score (3), coupled with the lowest extent score (.33, or 1/3 or less of condyle). A higher overall score is likely to reflect a higher degree score, meaning that more surface area of the condyle is affected by eburnation. For this sample, surface osteophyte development seems to be inversely proportional to opposite condyle eburnation severity.

Table 3.13
Crosstabulation of medial surface osteophyte presence and lateral condyle eburnation severity scores

Medial Surface Osteophytes	Lateral Eburnation Total Severity Score (Eburnation Degree*Eburnation Extent)						
	.00	.33	.66	.99	2.01	3.00	Total
Not present	46	1	2	2	1	2	54
Barely discernable	4	0	1	0	0	1	6
Clearly present	1	0	1	0	0	0	2
Total	51	1	4	2	1	3	62

Table 3.14
Crosstabulation of lateral surface osteophyte presence and medial condylar eburnation severity scores

Lateral Surface Osteophytes	Medial Eburnation Total Severity Score (Eburnation Degree*Eburnation Extent)							
	.00	.33	.66	.99	1.34	2.01	3.00	Total
Not present	9	1	3	13	1	5	2	34
Barely discernable	4	0	3	0	0	3	0	10
Clearly present	3	1	2	11	0	1	0	18
Total	16	2	8	24	1	9	2	62

3.5 Exploratory Data

Locations were noted for as many lesions and measures as possible. Location frequencies of radiographically visible measures (JSN and sclerosis), areas of total cartilage loss, and areas of inferior dense trabeculae are reported in Tables 3.15-3.17.

For the purposes of providing the most accurate description of location, 'centre' is defined as centre of the condyle's articular surface, 'anterior third' refers to lesions which are completely in the anterior third of the articular surface and may extend to the anterior edge, and 'posterior third' is the posterior corollary of this. 'Medial/lateral third' lesions extend to the edge of the articular surface and are completely in the medial or lateral third of the condyle's articular surface. 'Both condyles' refers to dense trabeculae present on both condyles, in any areas.

Consistent with results for porosity and eburnation severity noted in Section 3.1, the majority of lesions were located on the medial condyle. Radiographically visible joint space narrowing is taken as evidence of areas of complete cartilage loss (Kellgren & Lawrence, 1957). Overall, this appears to be borne out by results for this sample. However, the relationship is not perfect; as

noted, there were a few instances of JSN without corresponding areas of total cartilage loss (Tables 3.15 and 3.16).

Results presented previously indicated that there was not a significant relationship between X-ray visible sclerosis and areas of dense trabeculae. This result appears to be supported by location data, which suggests that while sclerosis was visible mainly on medial or both condyles, dense trabeculae were strongly associated with the medial condyle (87%, cumulatively).

Table 3.15
Location frequencies of X-ray visible measures

Measure	Not present	Medial Condyle	Lateral Condyle	Both Condyles	Total
Xray JSN	1 (1.6%)	54 (87.1%)	5 (8.1%)	2 (3.2%)	62 (100%)
Xray Sclerosis	1 (1.6%)	36 (58.1%)	1 (1.6%)	24 (38.7)	62 (100%)

Table 3.16
Location frequencies of areas of total cartilage loss

Not present	Medial Condyle	Lateral Condyle	Both Condyles	Medial and Intercondylar	Total
6 (9.7%)	45 (72.6%)	6 (9.7%)	3 (4.8%)	2 (3.2%)	62 (100%)

Table 3.17
Location frequencies for areas of inferior dense trabeculae

	Medial Condyle				Lateral Condyle			
Not present	Centre	Medial Third	Anterior Third	Posterior Third	Centre	Lateral Third	Both Condyles	Total
1 (1.6%)	30 (48.4%)	10 (16.1%)	11 (17.7%)	3 (4.8%)	2 (3.2%)	1 (1.6%)	4 (6.5%)	62 (100%)

The presence of enthesophytes in the intercondylar area was a common lesion in this sample, with the majority of these occurring in either both the anterior and posterior portions of the eminence, or anterior only, as detailed in Table 3.18. Eburnation in the intercondylar eminence was far less common, and as previously noted, moderately correlated to overall joint severity. Table 3.19 reports location frequencies for intercondylar eminence eburnation. Of the 19 samples with intercondylar eburnation, 11 (57.9%) had eburnation on the lateral tubercles. Observations

of these 19 samples indicate that in all of cases (4) in which both tubercles were affected, and in one of each of the medial/lateral cases, eburnation on the articular surface of one of the condyles had spread to the intercondylar eminence. In 11 of the remaining cases, articular surface eburnation was confined to the opposite condyle to the affected tubercle.

Table 3.18
Location frequencies for intercondylar eminence enthesophytes

Not present	Anterior	Posterior	Anterior and Posterior	Total
3 (4.8%)	17 (27.4%)	1 (1.6%)	41 (66.1%)	62 (100%)

Table 3.19
Location frequencies for intercondylar eminence eburnation

Not present	Medial Tubercle	Lateral Tubercle	Both Tubercles	Total
43 (69.4%)	4 (6.5%)	11 (17.7%)	4 (6.5%)	62 (100%)

As reported in Section 3.2, there were no significant differences between males and females in the numbers of inferior lytic areas or the numbers of lytic areas with sclerotic borders/interiors. Table 3.20 reports the overall frequencies for numbers of lytic areas.

Of the 118 lytic areas observed, 72.9% had a sclerotic border/interior. As noted in Table 3.21, the majority of specimens with lytic areas had only sclerotic-bordered lesions (30 of 52, or 57.7%), while 21.2% (11 of 52) each had only non-sclerotic lesions, or a mixture of sclerotic and non-sclerotic.

Table 3.20
Numbers of total lytic areas and lytic areas with sclerotic border/interior

Number of Lytic Areas Per Specimen							
	0	1	2	3	4	5	6	Total
Total Lytic Areas Present	10	25	6	9	8	2	2	118
Lytic Areas with Sclerotic Border/Interior	21	22	6	4	7	0	2	86

Table 3.21

Number of specimens with non-sclerotic, sclerotic, and both types of lytic lesions

Non-sclerotic border only	Both sclerotic and non-sclerotic	Sclerotic border only	Total
11 (21.2%)	11 (21.2%))	30 (57.7%))	52 (100%)

Note: 10 specimens (of 62) had no lytic lesions

To most accurately chart the locations of inferior lytic areas, the plateaus were divided into three unequal portions in the sagittal plane and three relatively equal portions in the coronal plane (for a total of nine).On the sagittal plane, the portions were defined as medial (inferior to and matching contours of the medial condyle), lateral (inferior to and matching contours of the lateral condyle), and centre (inferior to the intercondylar area).On the coronal plane, the plateau was divided into three approximately equal bands (anterior, centre, and posterior). The anterior and posterior margins of the tibial tuberosities constituted the borders for the anterior and posterior bands; the centre band was between these. Figure 3.2 shows the location divisions.

Table 3.22 describes the location frequencies of inferior lytic areas. In addition to the nine locations delineated above, lesions were also scored as occurring in multiple areas of each of the sagittal portions, as well as in multiple locations on the plateau, if appropriate.

Tables 3.23 describes location frequencies by portion. Observing the data for the sagittal plane, centre locations accounted for 46.2% of the observed lesions (24 out of 52 observed), while for the coronal plane, the anterior band accounted for 38.5% (20 of 52 observed).
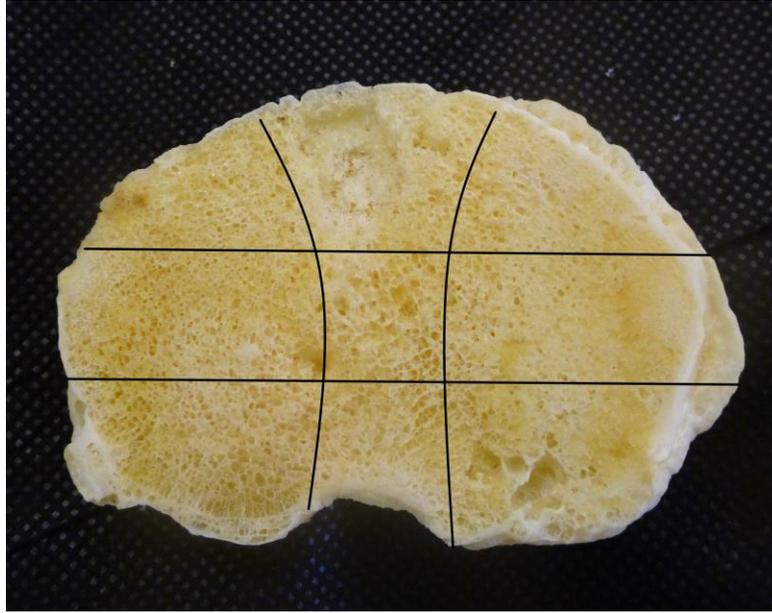
Figure 3.2. **Sagittal and coronal plane divisions for describing locations of inferior lytic areas**

Table 3.22
Location frequencies of inferior lytic areas (per specimen)

Location	Frequency	Percent
Not present	10	16.1%
Anterior centre	11	17.7%
Centre of centre	5	8.1%
Posterior centre	5	8.1%
Multiple locations in centre	3	4.8%
Anterior medial	6	9.7%
Centre medial	1	1.6%
Posterior medial	2	3.2%
Multiple locations in medial	2	3.2%
Anterior lateral	3	4.8%
Centre lateral	1	1.6%
Posterior lateral	1	1.6%
Multiple locations in lateral	1	1.6%
Multiple areas of plateau	11	17.7%
Total	62	100%

Table 3.23
Location category frequencies of interior lytic areas (per specimen)

Location	Frequency (of 52 specimens with lytic areas)	Percent
Sagittal Plane		
Centre	24	46.2%
Medial	11	21.2%
Lateral	6	11.5%
Multiple Locations	11	21.2%
Total	52	100%
Coronal Plane		
Anterior	20	38.5%
Centre	7	13.5%
Posterior	8	15.4%
Multiple Locations	17	32.7%
Total	52	100%

3.6 Study Sample and Cadaver Comparisons

As discussed in the previous chapter, no statistical comparisons between the study and cadaver groups were carried out. The cadaver sample was small (n=3), much older on average than the study sample, and all cadaver specimens had at least some evidence of OA lesions. Two of the cadaver specimens had areas of eburnation; this, by itself, is enough to diagnose OA by paleopathological standards (Rogers & Waldron, 1995; Waldron 2008). Thus, the cadaver group cannot be characterised as a true 'control' sample.

However, observational comparisons can be made. Table 3.24 compares the study sample and cadaver averages in lesion severity scores. Overall, the average severity of the cadaver group on all severity scores is considerably lower than that of the study group. However, the cadaver average is skewed somewhat by the presence of the second cadaver sample; the scores of this specimen would not be out of place in the study group. Compared to the study group averages, the scores of the remaining two cadaver specimens are substantially lower, even with the third specimen's OA diagnosis.

Observing the other items scored (see Tables 2.3 and 3.03), it is interesting to note that both of the cadaver samples with OA diagnoses (Cadaver 2 and 3) also showed the presence of proliferative lesions in the intercondylar area (both had osteophytes on the tuberosities, and

Cadaver 3 had an intercondylar enthesophyte), as did all specimens in the study sample. The cadaver sample with the least evidence of OA (only marginal lipping) had no evidence of these types of lesions. Neither Cadavers 1 nor 3 showed evidence of any of the other measures recorded (scored as 'no' or 'not present'), while Cadaver 2 scored in a manner consistent with that of the study specimens.

Table 3.24
Comparison of study and cadaver samples' lesion severity scores

	Medial Lipping Total Severity	Medial Porosity Total Severity	Medial Eburnation Total Severity	Total Medial Severity	Lateral Lipping Total Severity	Lateral Porosity Total Severity	Lateral Eburnation Total Severity	Total Lateral Severity	Overall Joint Severity
Study Sample Average	2.54	.43	.91	3.84	2.58	.14	.26	2.89	6.72
Cadaver 1	.67	0	0	.67	.67	0	0	.67	1.34
Cadaver 2	3	.99	.33	4.32	1.34	0	0	1.34	5.66
Cadaver 3	1	0	0	1	1	0	.66	1.66	2.66
Cadaver Sample Average	1.56	.33	.11	2.00	1.37	0	.22	1.22	3.22

Chapter 4

Discussion

This chapter will discuss the results of the study and their relationship to current and past clinical and paleopathological research on OA-related lesions. Discussion will centre on results pertaining to each of the four stated research questions, including the examination of findings that fall outside of the realm of the research questions, but are nevertheless relevant to this and future research on the topic. Finally, the study's limitations will be outlined and considered.

4.1 OA-Related Articular Surface Lesions

As noted in Chapter 3, statistical comparisons between the cadaver and study samples were not performed due to limitations in the cadaver samples, which will be discussed later in this chapter. Despite this, articular surface lesion scoring, based on the work of Buikstra and Ubelaker (1994), indicated that all the study sample specimens had some combination of OA lesions (Figure 4.01 shows a typical specimen). This is not overly surprising, given that the sample population was one with both radiographic and symptomatic OA. Marginal osteophytes (lipping) were the most common and severe lesions, with all the study specimens (with the exception of one missing the medial condylar edge) showing definitive evidence of this lesion. Average lipping severity scores were the highest of all lesion severity scores: 2.54 (medial condyle) and 2.48 (lateral condyle) out of a possible score of 3 (see Table 3.10).
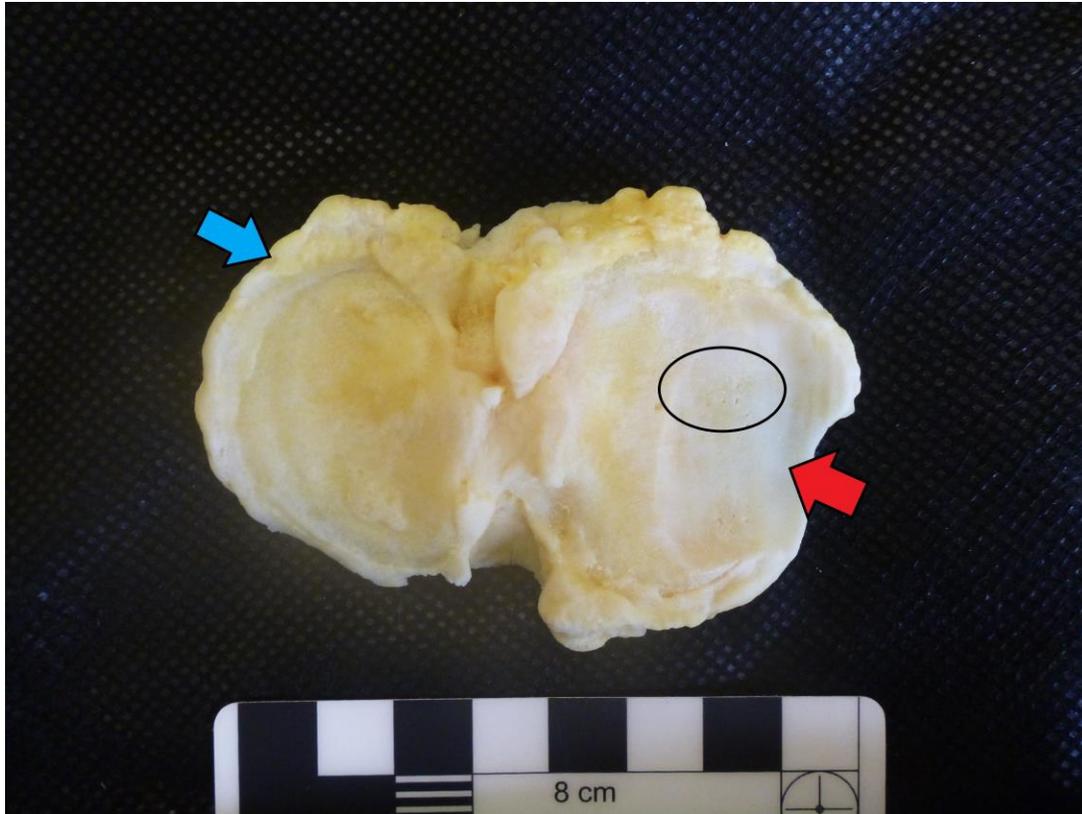
Figure 4.01. **Specimen plateau (left tibia, female, age 59) with articular surface OA lesions. Blue arrow – marginal osteophytes; red arrow – eburnation; black ellipse– porosity. Superior view, anterior oriented to the top of image.**

As one might surmise, there were no significant differences in medial and lateral condyle severity for this score. However, medial condyle severity scores in porosity, eburnation, and overall severity were significantly greater than those of the lateral condyle. This result supports the findings of previous studies indicating that the medial condyle is typically most and/or first affected by OA (e.g., Everhart, Abouljoud, Poland, & Flanigan, 2018; Immonen, Siefring, & Sanders, 2017; Nakagawa, Mukai, Yabumoto, Tarumi, & Nakamura, 2015). Much of this is attributed to the physiology of the femorotibial joint; in a normally aligned joint, the medial condyle absorbs about 60% of the compressive force generated by a typical walking gait (Immonen et al., 2017).

The other significant mediolateral difference was in the presence of surface osteophytes; here, the lesion's distribution on the lateral condyle was higher (see Figure 4.02). Unlike the

condylar differences discussed previously, this result appears to have no previous mention in the literature. Potential implications of the presence of surface osteophytes are discussed more fully in section 4.3**.**

Figure 4.02. **Lateral condyle surface osteophytes, indicated by arrows (left tibia, male, age 56). Superior view, anterior oriented to top of image**

4.2 Lesions Not Included on Bioarchaeological Measures of OA Lesions

The Buikstra and Ubelaker (1994) scale deals with OA-related lesions on the articular surfaces of the bone, in this case the medial and lateral condyles. Early in the process of specimen scoring and observation, it became obvious that that there were consistently-observed lesions or features on the non-articular portions of the plateaus. The necessity of quantifying these observations resulted in the 20 scoring items listed in Table 2.3. These scores reflect lesions and features observed in the intercondylar area and on the inferior (trabecular) side of the cut plateau. The latter, especially, is not usually accessible in archaeological dry bone; if it is visible, it is likely that the bone is too damaged or otherwise degraded to be accurately scored in other measures.

4.2.1 Intercondylar Lesions

These lesions include three main categories: proliferative bone presence (on the intercondylar tubercles and elsewhere in the area), porosity, and eburnation. In terms of the first category, all the study specimens and the two cadaver specimens with diagnostic OA lesions had some proliferative bone growth in the intercondylar area. When this item was delineated into presence of osteophytes on the intercondylar tubercles and proliferative bone in other parts of the area, each was present in 95% of the study specimens, indicating that the majority of the study sample had both lesion types.

It is important to note that in a living individual, the medial and lateral intercondylar tubercles are covered in articular cartilage, while the intercondylar area between them is not; rather, this area serves as an attachment space for the anterior and posterior cruciate ligaments (ACL and PCL), and the anterior and posterior horns of the menisci (Mays & Cooper, 2009; Martini et al., 2015; Robinson et al., 2016). Thus, proliferative bone growth on the tubercles (osteophytes), can be taken as direct evidence of OA, while proliferative bone growth elsewhere in the intercondylar area cannot (Felson & Neogi, 2004). While not included on bioarchaeological measures of OA lesions, intercondylar tubercle osteophytes or 'tibial spiking' are clinically-recognized features of knee OA, and are associated with the development of marginal osteophytes on the articular portions of the tibial plateau (Hayeri et al., 2010; Reiff, Heron, & Stoker, 1991). Indeed, Katsuragi and colleagues (2015) found that intercondylar tubercle and medial tibial condyle osteophytes were among those observed in MRI of knees at pre-radiographic stages of OA. Osteoarthritic bone changes in the femoral and tibial intercondylar areas are difficult to detect with typical radiographic views (Katsuragi et al., 2015). X-rays, however, remain the most common imaging technology in OA diagnostics, due to availability and low cost. While intercondylar tubercle osteophytes are recognized as evidence of OA (Reiff et al., 1991), their lack of inclusion in clinical OA diagnostic criteria may be due to their relative invisibility in traditional imaging technology. Figure 4.03 provides an example of intercondylar tubercle osteophytes.

Figure 4.03. **Intercondylar tubercle osteophytes, indicated by ellipses (right tibia, male, age 57). Superior view, anterior side oriented to top of image.**

In the study sample, proliferative bone in the rest of the intercondylar area was found mainly in the anterior only, or both anterior and posterior (28.8% and 69.5% of the specimens with proliferative bone, respectively). These positions correspond with the insertion points of the ACL and PCL (Figures 4.04 and 4.05), lending credence to the suggestion that these proliferative lesions represent enthesophytes of the two ligaments. Although enthesophytes are not themselves diagnostic of OA, the association between their presence and other types of arthritis has been established in a number of studies (Benjamin et al., 2004; Benjamin, Toumi, Suzuki, Hayashi, & McGonagle, 2009; Emad et al., 2012; Tan et al., 2005). Researchers suggest that the ACL and PCL are members of a class of ligaments referred to as 'enthesis organs' or 'synovial-entheseal complexes', wherein the ligament or tendon attachment site is integrated with the synovium, and may include other features such as bursae, fat pads, or fibrocartilage (Benjamin et al., 2004; Benjamin & McGonagle, 2007). Studies of spondyloarthritis indicate that enthesophytes at these sites may be linked to tensile or mechanical strain on the affected ligaments (Benjamin et al.,

2004, 2009). Inflammation is also implicated as a contributing factor, as it is in psoriasis research that correlates the presence of knee enthesophytes with pre-clinical psoriatic arthritis (Benjamin et al., 2009; Emad et al., 2012). Traditionally, OA has not been thought of as an inflammatory disease, but research has now begun to focus on the influence of synovial and other inflammation on osteophyte development and disease progression (Robinson et al., 2016; Suri & Walsh, 2012; van der Kraan & van den Berg, 2007). As osteophytes and enthesophytes both develop via endochondral ossification, they may also have a similar pathogenic process (Felson & Neogi, 2004; van der Kraan & van den Berg, 2007).

Figure 4.04. **ACL Enthesophyte, indicated by arrow (right tibia, male, age 77). Superior view, anterior side oriented to top of image.**

Figure 4.05. **PCL Enthesophyte, indicated by arrow (left tibia, female, age 75). Superior view, anterior side oriented to top of image.**

In addition to ACL and PCL enthesophytes, the appearance of the third intercondylar tubercle of Parsons (TITP) has also been linked to both ligament strain and OA (Brossmann et al., 1996; Pecina, Bajok, & Pecina, 2001; Yian, Gallo, Hughes, & Kuhn, 2001). This is a variably present bony protuberance in the anterior intercondylar area, near the lateral edge of the medial condyle (Mays & Cooper, 2009). Varying considerably in size when it is present, the TITP is correlated with the insertion points of the anterior meniscal horn and the ACL (Yian et al., 2001). Brossmann and colleagues (1996) assert that TITP development represents a secondary symptom of OA; others stop short of this, instead linking TITP presence and height to ACL injury or frequent, low-grade stress (Mays & Cooper, 2009; Pecina et al., 2001; Yian et al., 2001). As was noted in some detail in Section 1.4.5 of Chapter 1, ACL injury is a risk factor in knee OA, making the appearance of the TITP seemingly more likely. In the absence of acute ACL injury, the increasing misalignment of the OA-affected joint would place additional mechanical stress on both cruciate ligaments, potentially leading to the formation and expansion of both enthesophytes and the TITP.

Almost ninety-one percent (90.9%) of the study specimens had porosity present in the intercondylar area; in 39% of these cases, the porosity extended to the inferior side of the cut plateau (see Table 3.03). Again, this lesion was present in both cadaver specimens exhibiting OA lesions. As detailed in Section 1.3.4 of Chapter 1, porosity has been tied to subchondral plate thinning early in the OA disease process (Botter et al., 2011; Dedrick et al., 1997; Sniekers et al., 2008), as well as to vascular and nerve invasion of the osteochondral junction (Sniekers et al., 2008; Suri et al., 2007). The intercondylar area in question, however, is not subchondral bone. However, Binks and colleagues (2013) note that there are normal vascular channels adjacent to the ACL and PCL and suggest that these channels form a conduit for the entry of inflammatory tissue and osteoclast activation in cases of OA and inflammatory arthritis. Research by Shibakawa and colleagues (2005) indicates that mechanical stress might be at the root of the formation of some 'reabsorption pits' (i.e. porosity); given the previous discussion of the influence of mechanical strain on the appearance of intercondylar enthesophytes, this may be worthy of future research.

A small number of study specimens (n=19) had eburnation in the intercondylar area; this lesion was located on one or both tubercles (lateral=11; medial=4; both=4) (see Table 3.19). In all cases in which both tubercles were affected, and in one each of the medial/lateral cases, it is evident from examining the dry bone that eburnation originating on one condyle has expanded to the midline of the plateau, eventually affecting the tubercle(s). In the majority of the other cases, eburnation is evident on one condyle, and the opposite-side tubercle is also affected. Figure 4.06 shows an example of this. Nakagawa and colleagues (2015) suggest a sequence for knee OA progression that starts with cartilage loss in the central part of the medial condyle, which expands to the anterior and posterior portions of the condyle. This, coupled with bone attrition in the medial condyle, causes the femorotibial angle to increase. The resulting misalignment leads to lateral femoral cartilage damage by the lateral tubercle; cartilage damage then progresses on the lateral femoral and tibial condyles (Nakagawa et al., 2015). This sequence would explain the eburnation pattern seen in the sample specimens (whether the cartilage loss started on the medial or lateral condyles). In viewing pre-operative radiographs, all the individuals with intercondylar eburnation exhibited obvious joint misalignment due to extreme JSN, which is evidence for cartilage damage and loss.

Figure 4.06. **Lateral intercondylar tubercle with medial condyle eburnation, indicated by ellipse (right tibia, male, age 61). Superior view, anterior side oriented to top of image.**

4.2.2 Inferior Dense Trabeculae

Sixty-one of the 62 sample specimens and the cadaver sample with the most severe OA lesions exhibited areas of what appeared to be noticeably denser trabeculae on the inferior of the plateau (see Figure 4.07). As was noted in the previous chapter, these dense areas are not significantly associated with radiographic evidence for sclerosis; rather, 83.6% of the samples with dense trabeculae also had areas of eburnation immediately superior (see Tables 3.12 and 3.03). Of these 51 specimens, 40 (78.4%) had dense areas larger than the corresponding patch of eburnation, while the two areas were a similar size in 9 (17.6%) cases. Examining data on the 10 specimens with no eburnation associated with dense trabeculae indicates that in four cases, there was full-thickness cartilage loss present in the same location as the dense trabeculae. In another specimen, dense trabeculae were present in both condyles, but cartilage loss was noted only on

the medial condyle. In one other specimen, no complete cartilage loss was present, but radiographic JSN was present on the same condyle as the area of dense trabeculae. Taken together, these data indicate that, for the majority of this sample, subchondral bone changes in the form of dense trabeculae appear to precede the development of eburnation, and possibly full-thickness cartilage loss.

Figure 4.07. **Example of area of inferior dense trabeculae inferior to medial condyle, indicated by ellipse (left tibia, male, age 65). Inferior view, anterior side oriented to top of image.**

While there is no doubt that cartilage degradation and subchondral bone changes are hallmark components of OA, research on the order in which each change occurs is inconclusive (Bobinac et al., 2003; Cox et al., 2013; Felson & Neogi, 2004). Chen and colleagues (2016) suggest that in animal models, changes in trabecular rod thickness may precede cartilage changes in OA. This was previously noted by Cox and colleagues (2013), who attribute an increase in number of trabeculae to the progression of subchondral bone-driven changes at the osteochondral junction. In the present study sample, no microscopic examinations were made, so it is unknown whether the dense trabeculae reflect a localized increase in trabecular volume or rod thickness, a

combination thereof, or another factor altogether. However, other research argues that subchondral bone changes are driven by cartilage damage, even macroscopically invisible damage (Bobinac et al., 2003). One of the study samples with dense trabeculae and no associated eburnation also had no evidence of cartilage loss, and no obvious radiographic JSN. In this case, it would have been interesting to observe the specimen for microscopic cartilage degradation, to further examine the relationship between subchondral bone remodelling and cartilage damage.

4.2.3 Inferior Lytic Areas

Lytic areas, ranging in size from less than 2mm to over 4mm, were present in 83.9% (n=52) of the study sample. Of the total 118 lytic areas, 86 (72.9%) had sclerotic interiors (see Table 3.21). Observations recorded before the plateaus were reduced to dry bone refer to 'spongy-looking' areas on the inferior side of the plateau. These areas did not appear to contain normal trabeculae, instead consisting of homogenous-appearing, structurally poorly-defined tissue, which despite its appearance, was not soft. After the simmering process, this tissue was the same colour and texture as the remaining articular and peri-articular soft tissue and could be easily removed, leaving lytic areas.

These features are unknown in the paleopathological literature, due to the aforementioned issues with trabecular bone exposure. In clinical research, the known OA-related lesions best fitting the location and appearance of these lytic areas are bone marrow lesions (BML). As detailed in Section 1.3.2 of Chapter 1, these are a 'new' OA symptom, becoming evident to researchers only after the advent of MRI technology; subchondral bone cysts (SBC), seemingly related to BML, have been a known OA symptom for decades (Crema et al., 2010a; Li et al., 2013). Appearing in the subchondral bone close to the joint surface, BML contain a mixture of poorly organized trabeculae, sclerotic and necrotic bone, fibrous tissue, bone marrow, and fluid (Eriksen & Ringe, 2012; Hunter et al., 2009; Muratovic et al., 2016). As MRI technology has advanced, researchers have been able to demonstrate that there are at least two subtypes of BML, detectable by different MRI sequences, (Mattap et al., 2018; Muratovic et al., 2016, 2018; Wluka et al., 2015), and that the lesions appear to be associated with areas of mechanical stress and bone remodelling (Crema et al., 2010b; Hunter et al., 2009; Muratovic et al., 2018; Roemer et al., 2010). Researchers suggest that the BML subtypes may reflect different histological components (Mattap et al., 2018; Muratovic et al., 2016, 2018; Wluka et al., 2015). Hunter and colleagues

(2009) note that BML region bone samples appear sclerotic compared to samples taken from a different region of the same bone.

In the study sample, 11 specimens had lytic areas without sclerotic interiors, while another 11 had areas both with and without sclerotic interiors; the remaining 30 had only areas with sclerotic interiors (see Table 3.21). Figures 4.08-4.10 provide examples of each of these. In examining the size of the largest of the lytic areas present, an interesting pattern emerges. The specimens with only non-sclerotic lytic areas did not have any areas falling into the largest category (> 4mm). For the smallest category (< 2mm), 7 of 15 specimens had only non-sclerotic lytic areas. In examining specimens with both sclerotic and non-sclerotic areas, a sclerotic area was the largest in all but one case. The presence of sclerotic bone indicates bone remodelling and healing; in the case of a lytic lesion, a sclerotic interior means that whatever has caused the initial bone destruction is no longer expanding or is expanding slowly enough to allow bone remodelling to take place (Ortner, 2003). In these specimens, it may be that the sclerotic interior areas represent long-standing, stable BML, while the non-sclerotic versions represent newly-formed lesions, arising from active areas of bone remodelling. Given that there may be more than one subtype of BML, the size and sclerotic vs. non-sclerotic interiors may be indicative of BML of different subtypes and etiological mechanisms (Muratovic et al., 2016, 2018; Wluka et al., 2015).

Figure 4.08. Inferior lytic lesions without sclerotic borders/interiors, indicated by arrows (left tibia, female, age 63). Inferior view, anterior side oriented to top of image.

Figure 4.09. Inferior lytic lesions, both sclerotic (ellipse) and non-sclerotic (arrow) (left tibia, male, age 53). Inferior view, anterior side oriented to top of image.

Figure 4.10. **Inferior lytic lesions with sclerotic borders/interiors, indicated by ellipse (right tibia, female, age 63). Inferior view, anterior side oriented to top of image.**

Another interpretation is that some of the lytic areas, especially the small ones, are evidence of angiogenesis, representing vascular channels invading the calcified cartilage zone from the subchondral bone. Tiny blood vessels are accompanied by sympathetic and sensory nerves which may lead to sensations of pain in the normally aneural articular cartilage (Suri et al., 2007). Lytic areas of 19 study specimens extended from the inferior to the superior side of the plateau; all but one of these had a sclerotic interior, again indicating bone remodelling. However, the size of these was not consistently small, suggesting that something other than vascular channels were at play.

As discussed in the previous chapter, locations of lytic areas were also recorded, using both coronal and sagittal planes. Considering the sagittal plane, 46.1% of specimens with lytic areas had those areas only in the centre, or inferior to the intercondylar area, while 21.2% and 11.5% had only lytic areas inferior to the medial and lateral condyles, respectively. Another 21.1% had lytic areas in multiple areas of the inferior plateau (see Table 3.23). These

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percentages are consistent with the results of Chan and colleagues (2016)'s imaging study of what they referred to as subchondral bone cysts in patients undergoing knee replacement surgery. Medial and lateral BML are in weight-bearing areas of the tibial plateau, which is logical in terms of their apparent relationship to mechanical stress; BML in these areas have also been implicated in the progression of articular cartilage damage (Hernandez-Molina et al., 2008; Mattap et al., 2018; Tanamas et al., 2010b; Wluka et al., 2015). Central BML are in a non-weight bearing area, so any mechanical stress would be most likely to involve joint misalignment and ligament strain. Hernandez-Molina and colleagues (2008), finding the majority of central BML beneath the areas of the ACL and PCL, suggest that enthesopathy may be involved in their formation. ACL BML correlate with ACL pathology (Hernandez-Molina et al., 2008). Anterior centre was the most common location among study specimens with centre lytic areas (11 of 24), aligning approximately with the location of the ACL.

The common theme in this discussion of lesions not included in bioarchaeological measures of OA is that these lesions should perhaps be included in measures of OA, or should at least warrant further investigation. The link between inferior areas of dense trabeculae and eburnation and cartilage loss may provide evidence for subchondral bone changes preceding cartilage change in some instances. Inferior lytic areas may be physical evidence of BML or SBC; centrally-located BML are linked to ligament strain and damage. The latter is also associated with enthesophytes in the intercondylar area. These may not be direct evidence of OA by themselves, but taken together can provide a more complete picture of some of the processes involved and underlying etiological mechanisms.

4.3 Male and Female Differences in Lesions or Lesion Patterns

As discussed in Chapter 1, sex, particularly being female, is a known risk factor in the development of OA. Females have a higher incidence of the condition, and experience more rapid symptom progression and pain compared with males at the same level of radiographic OA (Boyan et al., 2012; Cho et al., 2010; Glass et al., 2014; Srikanth et al., 2005). The reasons for these differences are not completely understood, but may involve biomechanical and pain processing differences, as well as post-menopausal hormone changes (Bartley et al., 2016; Boyan et al., 2013; Glass et al., 2014; O'Connor, 2007).

Given the considerable evidence of sex differences in the incidence and experience of OA, it was expected that some male/female differences in OA lesions or lesion patterns might be observed in the current study. For the most part, this was not the case. The two exceptions will be discussed presently, but there were few significant differences between male and female severity scores for articular surface lesions, and sex was not significantly associated with the majority of the non-articular measures.

While these results appear to contradict current research knowledge of sex differences in OA, the design of the study itself may play a part in this conundrum. At the beginning of the participant recruitment portion of the project, the plan was to obtain around 60 tibial plateaus, ideally with approximately equal numbers of males and females. When 62 plateaus had been removed, sample collection was suspended. The fact that the plateaus were evenly split between genders was a random occurrence in sampling. One could claim sample bias, since participants were self-selected, but to the writer's knowledge, no one refused to participate upon being approached. Thus, this particular sample does not reflect any general sex differences in incidence. As there were no data collected on patients' pain level or OA progression, there is no indication of who may have been experiencing more or less pain or debilitation compared to the severity of their bone lesions. This sample reflects the 'end stage' of knee OA, so it is not surprising that there are few differences in bone lesion type or severity. Perhaps doing a similar investigation in an earlier stage of the disease or being able to integrate patients' pain experiences into the data would have produced further insights into male and female differences in OA development and symptomatology.

One of the significant male/female differences in the study involved the distribution of medial articular surface osteophytes. There were no sex differences in the distribution of lateral surface osteophytes, but upon closer inspection of the data, it became obvious that all the study samples with medial surface osteophytes were male (n=8). Surface osteophytes, by definition, form beneath the articular cartilage (Rogers et al., 1997). This particular lesion type has received little attention in the scientific literature; its presence alone is not enough to diagnose OA in dry bone (Rogers & Waldron, 1995), and it is not dealt with directly in clinical OA studies. Logically, the same reawakening of the endochondral ossification process implicated in the formation of marginal osteophytes should govern this formation process as well (van der Kraan & van den Berg, 2007). For this study sample, the presence and severity level of marginal

osteophytes was universally consistent and high, so any attempts at correlating the presence of marginal and surface osteophytes would not be useful.

As discussed in Section 1.3.2 of Chapter 1, there is evidence for some individuals' predisposition towards 'bone forming', resulting in higher bone mineral density (BMD), and more and larger enthesophyte and osteophyte formation (Hardcastle et al., 2014; Mays, 2016; Rogers et al., 1997). Studies in this area tend not to find significant sex differences (Hardcastle, Dieppe, Gregson, Davey Smith, & Tobias, 2015). Some researchers, however, place bone losing/forming on a continuum with osteoporosis and diffuse idiopathic skeletal hyperostosis (DISH) respectively, representing the most extreme examples of each condition. Traditionally, each of those conditions has been identified as more prevalent in females and males, respectively (Hardcastle et al., 2014, 2015; Mays, 2016; Ortner, 2003). It may be that the medial osteophyte-forming males in this sample are 'bone formers'; this is impossible to clarify without an examination of BMD, and osteophytes and entheses in locations other than the tibial plateau. Given the small number of individuals with this lesion, it is also possible that the difference is due to sample size. An interesting outcome related to bone formation is the extraction of sesamoid bones, one quite large, from the PCL of two male specimens after the simmering process (see Figure 4.11). Upon examining mediolateral view X-rays, one of these bones is clearly visible; further examination revealed that 15 other individuals (9 male, 6 female) appear to have sesamoid bones in the same area. Of the 17 specimens with radiographic or physical evidence of sesamoid bones, 11 had surface osteophytes, which initially appeared to lend some credence to the idea of 'bone formers.' However, a further 22 specimens had medial or lateral surface osteophytes and no radiographic evidence of sesamoid bones.

Figure 4.11. **Sesamoid bone removed from PCL (male, age 71).**

The other significant sex difference involves the size distribution of the inferior lytic areas. Females were significantly more likely to not have lytic lesions (7 of 10), or to have the smallest lesions (<2mm; 10 of 15). Males were more likely to have the largest lesions (>4mm; 13 of 18) (see Table 3.09 and Figure 3.1). As discussed in some detail in Section 4.2.3 of this chapter, evidence points to these lesions representing bone evidence of BML or SBC. Since BML are a newly-imaged symptom of OA, research has centred on defining and categorizing these lesions, as well as investigating their etiology (Eriksen & Ringe, 2012; Mattap et al., 2018; Muratovic et al., 2016, 2018). Because the indication that there are potentially multiple subtypes of BML is quite new, research investigating these subtypes and their individual significance is yet to come (Muratovic et al., 2018). As discussed previously, the different sizes of lytic lesions may evidence different types of BML. There were no significant sex differences in sclerotic vs. non-sclerotic lytic areas, so the recency of the BML formation may not be a factor. Interestingly, both vascular channel invasion and BML presence have been correlated with patient-reported pain (Antony et al., 2016; Ip et al., 2011; Mattap et al., 2018; Wluka et al., 2015; Zhang et al.,

2011). Despite research also linking female sex to greater pain, females in this sample were more likely than males to not have inferior lytic areas. However, pain perception and sensitization are considered more likely contributing factors to OA pain in females than physiological/structural symptoms (Bartley et al., 2016; Glass et al., 2014). If this is the case, it might not be unusual to find less evidence of pain-associated bony lesions in females.

4.4 Lesions or Lesion Patterns Associated with Sources of Pain

The current study is consistent with other efforts to correlate patient pain with physical manifestations of OA, in that there are no clearly emerging lesion patterns that may indicate a source of pain. The majority of known OA lesions (i.e., osteophyte presence, porosity, eburnation) are consistently present and in such high percentages that it is difficult to tease apart which of these, if any, might be most pain-related. This is also true for the non-articular lesions noted. Again, this study sample represents 'end-stage' knee OA patients whose pain levels are unknown but assumed to be high.

Despite the lack of a clear and direct link between lesion type/patterns and pain source(s), there are a few potentially pain-related findings arising from the study sample. One, which has already been discussed in some detail, is the consistent appearance of inferior lytic areas in the majority of the study specimens. Whether these constitute evidence of BML or vascular invasion of the articular cartilage is unclear. However, both lesion types have been correlated with patient-reported pain (Mattap et al., 2018; Shibakawa et al., 2005; Anita E Wluka et al., 2015; W. Zhang et al., 2011). To complicate matters, the specimens without inferior lytic areas are not otherwise noticeably different from those with lytic areas, indicating that whatever the lytic areas represent cannot be the sole source of pain.

While cartilage is aneural and avascular, making its degradation an unlikely pain source, ligaments and menisci are enervated (Felson, 2005). Much of the research on intercondylar entheses and enthesophytes (ACL, PCL, TITP, etc.) ties the bone proliferation to ligament strain, degradation, or traumatic injury (Gibson et al., 2012; Mays & Cooper, 2009; Pecina et al., 2001; Yian et al., 2001). Proliferative bone growth consistently observed in the intercondylar area may be evidence of ligament stress and accompanying pain in this sample. The presence of lytic areas inferior to the intercondylar area may support this idea, as intercondylar BML appear to be related to enthesopathy and ligament pathology (Hernandez-

Molina et al., 2008). The enthesophytes, as well as other lesions observed in the intercondylar area (tubercle osteophytes and eburnation), may then impinge upon ligament and meniscus function and structural integrity. Some of these features observed on study plateaus are situated in such a way that it seems likely that the individual(s) experienced at least some degree of ligament functional impairment.

Studies of other types of arthritis suggest that enthesophyte formation is a response to inflammation (Benjamin et al., 2009; Emad et al., 2012; Gibson et al., 2012). There is increasing evidence that OA, once considered a non-inflammatory condition, involves low-grade, chronic inflammation (Robinson et al., 2016). As discussed elsewhere in this study, inflammation of the synovium results in the release of cartilage-degrading enzymes into the synovial fluid (Birn et al., 2014; Guilak et al., 2004; Long et al., 2008; Scanzello et al., 2009). Furthermore, the proinflammatory nature of some adipokines has made the relationship between OA and obesity far more complex than the traditional view of biomechanical overload and joint misalignment (Berenbaum et al., 2013; Sandell, 2009; Sartori-Cintra et al., 2014; Thijssen et al., 2014; Vuolteenaho et al., 2012). Of course, inflammation itself leaves no evidence on dry bone, but some of its purported effects are visible in the form of enthesophytes and evidence of cartilage degradation and loss. In this study, areas of cartilage loss were significantly correlated with radiographic JSN. Previous research suggests that, in addition to cartilage loss, knee JSN may be evidence of meniscal extrusion: painful in itself, but also an arbiter of joint injury and misalignment, leading to further strain on other ligaments, as well as loading-induced cartilage damage (Badlani et al., 2013; Guilak, 2011).

4.5 Study Limitations

This study's limitations mainly pertain to information known about the study sample and several issues with the cadaver sample. In order to ensure the study was of a manageable scale and to maintain complete patient anonymity, only patients' sex and age were known. It would have been interesting and potentially beneficial to be able to integrate patient risk factors (e.g., previous injury, obesity, physical activity level, occupation, etc.) into observations of bone lesions or lesion patterns. In addition, having information on patient experiences of OA progression and pain levels might also provide insight into sources of pain observable on bone. Pain is the main indicator for joint replacement surgery (W. Dust, personal communication, April

21, 2019). The orthopaedic surgeon involved in the study typically sees two distinct patterns of OA pain: a gradual increase in pain over the course of 1-3 years; or minimal symptoms for 1-2 years followed by a rapid increase in pain over the course of about 6 months (W. Dust, personal communication, November 28, 2018). Patients in early stage OA with less severe pain are treated by a family physician; the pain may be present for several years before referral to a surgeon (W. Dust, personal communication, April 21, 2019). Knowing which patients experienced which pattern might be beneficial in associating particular lesion types or patterns to patients' experiences of pain.

Cadaver sample limitations have been briefly mentioned elsewhere in this study. The sample was small (n=3) and elderly (mean age of 92). This will also be an issue for any future studies using a similar design; people with healthy, undamaged joints do not undergo total knee replacement surgery. Therefore, access to control sample joints is restricted to joints donated through planned body bequeathal or other tissue donation programs. The former, especially, tends to represent an older population. More importantly, two of the three cadaver plateaus had sufficient articular surface lesions to warrant an OA diagnosis by paleopathological standards (Rogers & Waldron, 1995; Waldron, 2008). One of these had both articular surface severity and non-articular surface lesion scores that were consistent with scores seen in the study sample.

Despite its small size and lack of practical use as a control, this sample yielded some interesting, yet un-generalizable observations. The one undiagnostic plateau supports the argument that OA is not an inevitable part of aging (Hügle et al., 2012). This 88 year-old had only the beginnings of marginal osteophytes as the sole OA lesion. The oldest cadaver sample (age 97) had complete cartilage loss on the entire medial tibial condyle (this was also matched by cartilage loss on the femoral medial condyle) and on the posterior half of the lateral tibial condyle. After processing, the only evidence of the cartilage loss was a small patch of polish-only eburnation on the posterior lateral edge of the lateral condyle. This is a fascinating result, given the severity and extent of the cartilage loss. One might infer that this individual may not have been mobile, given the opportunity but lack of evidence for bone on bone contact. However, if this is the case, it is interesting that the cartilage loss occurred and continued to expand in the apparent absence of biomechanical load and/or joint misalignment. This may lend evidence to the argument that mechanical stress is not the sole cause of cartilage degeneration, or may be an indication that a lack of mechanical loading is detrimental to cartilage health (Lei et

al., 2016). It is also possible that a slightly different mechanism is at work in the development and progression of OA related to the physiological effects of aging, as compared to pathologically-related OA in younger individuals.

One remaining potential limitation deals with the interpretation of lesions on the inferior (cut) side of the plateaus. In knee replacement surgery, the plateau is cut perpendicular to the tibial shaft, rather than parallel to the articular surface. Thus, the removed plateau is approximately 10 mm thick on the lateral side and only 2-3 mm thick on the medial side (W. Dust, personal communication, April 21, 2019). Depending upon the depth and placement of inferior lesions, the thickness of the plateau may affect the visibility of these lesions.

Chapter 5
Summary and Conclusions

To the best of our knowledge, this is the first study to use paleopathological techniques to analyse OA-related bone lesions in a modern sample known to be experiencing pain. The overall purpose of the research was to observe lesion types, prevalence, and severity with the intention of correlating these with potential pain source(s). Just as the study itself combined the knowledge and techniques of clinical medicine and bioarchaeology, the results and outcomes have implications for current knowledge and future research direction in both disciplines.

5.1 Summary

Tibial plateaus from 62 individuals (31 male; 31 female) undergoing total knee replacement surgery due to OA were examined and scored for the presence of OA-related bone lesions, employing scoring standards used in bioarchaeology (Buikstra & Ubelaker, 1994), as well as clinical radiography standards (Kellgren & Lawrence, 1957) and scoring standards for intercondylar and inferior surface lesions devised for this research. The study focused on four main areas: the presence of macroscopically visible OA-related surface lesions, normally included in bioarchaeological studies; the presence of consistently observed bony lesions not included in bioarchaeological measures of OA lesions; male and female differences in OA-related lesions; and the association of observed lesions or lesion patterns with source(s) of pain.

OA- related articular surface lesions (i.e. marginal osteophytes [lipping], porosity, and eburnation) were strongly present on the majority of the study specimens, with paired t-tests indicating that porosity, eburnation, and overall severity were significantly greater on medial condyles. Surface osteophyte presence, however, was significantly greater on the lateral condyle. The former result is consistent with previous research indicating the medial condyle is most affected by OA (Everhart et al., 2018; Immonen et al., 2017; Nakagawa et al., 2015). No previous research could be found to explain or support the latter result.

The consistent presence of lesions in the non-articular portions of the study plateaus, i.e. the intercondylar area and the inferior (trabecular) side, necessitated the development of additional scoring items (see Table 2.3). A high proportion of the study sample exhibited osteophyte growth ('spiking') on the intercondylar tubercles, a known OA symptom which is

difficult to observe radiographically (Hayeri et al., 2010; Katsuragi et al., 2015; Reiff et al., 1991). In addition, a high percentage of the study sample had proliferative bone growth in the non-articular intercondylar area, mainly in the anterior and posterior portions. While these lesions cannot be interpreted as OA lesions proper, previous studies have linked ACL and PCL enthesophytes and the presence of the third intercondylar tubercle of Parsons (TITP) to both ligament injury/strain and inflammation, as well as OA (Benjamin et al., 2004; Benjamin et al., 2009; Brossmann et al., 1996; Emad et al., 2012; Pecina et al., 2001; Robinson et al., 2016).

All but one of the sample specimens had areas of dense-appearing trabeculae; these areas were strongly associated with areas of eburnation on the superior side, as well as significantly correlated with radiographic joint space narrowing (JSN). This appears to lend support for the view that subchondral bone changes are associated with and may precede cartilage damage (Chen et al., 2016; Cox et al., 2013).

Inferior lytic areas were present in a majority of the sample specimens; 72.9% of these areas had sclerotic interiors. According to their descriptions in clinical literature, bone marrow lesions (BML) or subchondral bone cysts (SBC) appear to be the most likely cause of these lytic areas. Subchondral BML have been linked to concomitant cartilage loss and OA progression, while intercondylar BML, especially those inferior to the ACL and PCL, appear to be associated with enthesopathy and ligament pathology (Hernandez-Molina et al., 2008; Mattap et al., 2018; Tanamas et al., 2010b; Wluka et al., 2015). Size differences in lytic areas may be indicative of BML in different stages of development or different types of BML (Muratovic et al., 2016, 2018; Wluka et al., 2015). Alternatively, the smallest lytic areas (< 2mm) may be evidence of angiogenesis accompanying enervation of the calcified cartilage layer (Suri et al., 2007).

In contrast to research indicating that males and females differ in terms of OA prevalence and progression as well as pain perception (Boyan et al., 2012; Cho et al., 2010; Glass et al., 2014; Srikanth et al., 2005), few significant male/female differences emerged from the current study. One exception to this was the presence of medial condyle surface osteophytes, which were only found in male plateaus. This may be a function of the small sample size, or may indicate a slight male tendency towards bone formation, which has been positively correlated with OA incidence in previous studies (Hardcastle et al., 2014, 2015; Mays, 2016; Rogers et al., 1997). The second male/female difference related to the most prevalent size of inferior lytic areas. Females were significantly more likely to have either no lytic areas or the smallest size thereof,

while males were more likely to have the largest size of lytic areas. As mentioned previously, these lytic areas are believed to be evidence of BML presence, and the size differences may reflect different BML types, BML at different stages of development, or evidence of angiogenesis.

While there were no clear relationships between lesions or lesion patterns and potential sources of pain, some interesting trends emerged that warrant further study. With reference to the potential causes of the inferior lytic areas, both BML and vascular invasion of articular cartilage have been linked to OA pain (Mattap et al., 2018; Shibakawa et al., 2005; Wluka et al., 2015; Zhang et al., 2011). As mentioned previously, intercondylar enthesophytes have been linked to ligament strain and/or damage as well as inflammation, all known to cause varying degrees of pain (Benjamin et al., 2009; Emad et al., 2012; Gibson et al., 2012; Mays & Cooper, 2009; Pecina et al., 2001; Yian et al., 2001). ACL and PCL strain and injury are also associated with the presence of BML in the intercondylar area (Hernandez-Molina et al., 2008). All patients represented by the study sample experienced pain severe enough to seek treatment; in addition, all study samples exhibited lesions likely associated with pain, as evidenced by the previous studies.

5.2 Directions for Future Research

This study's results give rise to several new research possibilities and questions in both clinical medicine and bioarchaeology. Repeating a similar study, but having access to information on patients' lifestyle, potential risk factors, OA progression pattern, and pain perception would enable researchers to both replicate the results of the current study, as well as potentially link lesion patterns to specific risk factor, pain, or OA progression patterns. This, in turn, might assist in delineating different OA origins and their associated etiological mechanisms and disease progression sequences. Using the same research design but different joints (e.g., hip, shoulder) would further validate bioarchaeological measures of OA lesions on modern populations and might provide further information on OA-related bone lesions not included on these measures. The etiology of hip OA, for instance, is far more related to abnormal joint morphology than is knee OA (Ellis et al., 2011; Ganz et al., 2008; Murphy et al., 2016); the lesion types or patterns observed may reflect this difference.

As mentioned previously, the non-articular lesions observed in this study warrant further investigation. The results of this study reveal a link between dense-appearing trabeculae and eburnation or cartilage loss, suggesting that the former may precede total cartilage loss. Observation of trabecular structure at different stages of cartilage damage, both micro- and macroscopic, might clarify the sequence of subchondral bone change and cartilage degeneration, as well as add further information to the study of 'cross-talk' at the subchondral bone plate. The current study suggests that the presence of inferior lytic areas constitutes physical evidence of BML or SBC. Of course, further study is warranted to verify this assertion. Evidence that there are multiple types of BML is recent. Undoubtedly, future studies on these subtypes will further explain the size and apparent developmental differences observed in the sample specimens.

As noted in Chapter 4, previous research on proliferative bone growth (enthesophytes) and BML in the intercondylar area has been linked both to ligament, especially ACL, damage and strain. While ACL injury is a known risk factor for the development of knee OA later in life, more research on the impact of ligament stress and degeneration during the course of OA progression might provide insight into patients' pain experiences and potential therapeutic options. Intercondylar enthesophytes have also been linked to inflammation, as have ligament strain and pain. Research on obesity, synovitis, and injury response all acknowledge the involvement of inflammation on the progression of OA; this is a field of research worth pursuing further, as this study's results appear to provide support for the involvement of inflammation and ligament strain in OA-related bone lesions (and potentially pain).

This study provides several opportunities for further research in bioarchaeology. As noted earlier, the inferior lesions observed are unknown in paleopathological studies simply because trabecular bone is not visible in well-preserved archaeological samples. Using non-destructive imaging technology (i.e., CT, MRI) on OA-affected archaeological bone could provide evidence on whether the dense trabeculae and lytic areas observed in this study are also observed in the bones of ancient OA sufferers. BML are considered a new OA symptom because they were previously unobservable; the presence of lytic areas in archaeological bone would demonstrate that BML may be long-standing symptoms. Due to the typical focus of paleopathological OA studies, the intercondylar lesions observed in this sample are not usually noted. As medical research indicates that intercondylar enthesophytes may be comorbid features, examining archaeological bone for these lesions might indicate whether this has always been the case. OA

appears to have significantly increased in incidence since the beginning of the industrial age (Wallace et al., 2017). A systematic examination of both OA-related and associated lesions on archaeological bone may illuminate different symptom and progression patterns, ultimately revealing differing etiological mechanisms between ancient and modern forms of the condition.

The goal of bioarchaeology is to, as much as is feasible, uncover the lived experience of past peoples. While this study did not provide a clear link between lesion patterns and pain, it did offer a clear portrait of the appearance of tibial plateaus of people known to be experiencing pain. Observing these same lesion patterns on the bones of ancient individuals brings the archaeologist closer to an understanding of those individuals' experiences. Expanding the study to include investigating individuals' coping strategies, whether via pain amelioration techniques or the assistance of family/community members, can assist in providing a more vivid and holistic picture of past lifeways and health practices.

5.3 Concluding Remarks

The current research demonstrates that OA-related bone lesions, whether included in bioarchaeological measures of OA or not, are macroscopically visible on the tibial plateaus of a modern sample known to be experiencing pain. This study also reveals the importance of lesions observed on the non-articular portions of the bone, and their suggested relationship to both clinically-observed OA indicators and potential pain sources. While few male/female differences were noted, those found may indicate sex-based variations in bone formation and symptomatology. As well as with providing insight into OA- related bone lesions, future research arising from this work will benefit both clinical medicine and bioarchaeology's knowledge of OA and its effects on individuals.

In addition to the insights and paths for future research outlined previously, one of the most salient outcomes of this research is the advantage of collaborative, cross-disciplinary research. Here, clinical medicine and bioarchaeology join forces to discover new information on a condition seen in both disciplines; other mutually observed conditions would also benefit from collaborative research. Each discipline brings a unique perspective and set of technical skills to disease research. The outcomes of such research will both benefit modern patients and enhance our understanding of the lived experiences of past peoples.

References Cited

Aho, O. M., Finnilä, M., Thevenot, J., Saarakkala, S., & Lehenkari, P. (2017). Subchondral bone histology and grading in osteoarthritis. *PLoS ONE*, *12*(3), 1–16. https://doi.org/10.1371/journal.pone.0173726

Ajuied, A., Wong, F., Smith, C., Norris, M., Earnshaw, P., Back, D., & Davies, A. (2014). Anterior cruciate ligament injury and radiologic progression of knee osteoarthritis: A systematic review and meta-analysis. *American Journal of Sports Medicine*, *42*(9), 2242–2252. https://doi.org/10.1177/0363546513508376

Akune, T., Muraki, S., Oka, H., Tanaka, S., Kawaguchi, H., Nakamura, K., & Yoshimura, N. (2014). Exercise habits during middle age are associated with lower prevalence of sarcopenia: The ROAD study. *Osteoporosis International*, *25*(3), 1081–1088. https://doi.org/10.1007/s00198-013-2550-z

Alliston, T., Hernandez, C. J., Findlay, D. M., Felson, D. T., & Kennedy, O. D. (2017). Bone marrow lesions in osteoarthritis: What lies beneath. *Journal of Orthopaedic Research*, (October). https://doi.org/10.1002/jor.23844

Andersen, S., Thygesen, L. C., Davidsen, M., & Helweg-Larsen, K. (2012). Cumulative years in occupation and the risk of hip or knee osteoarthritis in men and women: A register-based follow-up study. *Occupational and Environmental Medicine*, *69*(5), 325–330. https://doi.org/10.1136/oemed-2011-100033

Anderson, S.A., & Loeser, R. F. (2010). Why is osteoarthritis an age-related disease? *Best Practice and Research: Clinical Rheumatology*, *24*(1), 15–26. https://doi.org/10.1016/j.berh.2009.08.006

Antony, B., Venn, A., Cicuttini, F., March, L., Blizzard, L., Dwyer, T., … Ding, C. (2016). Correlates of knee bone marrow lesions in younger adults. *Arthritis Research & Therapy*, *18*(1), 31. https://doi.org/10.1186/s13075-016-0938-9

Aref-Eshghi, E., Zhang, Y., Liu, M., Harper, P. E., Martin, G., Furey, A., … Zhai, G. (2015). Genome-wide DNA methylation study of hip and knee cartilage reveals embryonic organ and skeletal system morphogenesis as major pathways involved in osteoarthritis. *BMC Musculoskeletal Disorders*, *16*(1), 1–10. https://doi.org/10.1186/s12891-015-0745-5

Arthritis Alliance of Canada (2011). The impact of arthritis in Canada: today and over 30 years. *The Arthritis Alliance of Canada, 606,*1-52.

Ayral, X., Pickering, E. H., Woodworth, T. G., Mackillop, N., & Dougados, M. (2005). Synovitis: A potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis - Results of a 1 year longitudinal arthroscopic study in 422 patients. *Osteoarthritis and Cartilage*, *13*(5), 361–367. https://doi.org/10.1016/j.joca.2005.01.00

Badlani, J. T., Borrero, C., Golla, S., Harner, C. D., & Irrgang, J. J. (2013). The effects of meniscus injury on the development of knee osteoarthritis: Data from the osteoarthritis initiative. *American Journal of Sports Medicine*, *41*(6), 1238–1244. https://doi.org/10.1177/0363546513490276

Bancroft, L. W., Peterson, J. J., & Kransdorf, M. J. (2004). Cysts , geodes , and erosions. *Radiologic Clinics of North America*, *42*, 73–87. https://doi.org/10.1016/S0033-8389(03)00165-9

Bardakos, N. V., & Villar, R. N. (2009). Predictors of progression of osteoarthritis in femoroacetabular impingement: A radiological study with a minimum of ten years follow-up. *Journal of Bone and Joint Surgery - British Volume*, *91–B*(2), 162–169. https://doi.org/10.1302/0301-620X.91B2.21137

Barrios, J. A., & Strotman, D. E. (2014). A sex comparison of ambulatory mechanics relevant to osteoarthritis in individuals with and without asymptomatic varus knee alignment. *Journal of Applied Biomechanics*, *30*(5), 632–636. https://doi.org/10.1123/JAB.2014-0039

Bartley, E. J., King, C. D., Sibille, K. T., Cruz-Almeida, Y., Riley, J. L., Glover, T. L., … Fillingim, R. B. (2016). Enhanced pain sensitivity among individuals with symptomatic

knee osteoarthritis: potential sex differences in central sensitization. *Arthritis Care and Research*, *68*(4), 472–480. https://doi.org/10.1002/acr.22712

Bay-Jensen, A. C., Slagboom, E., Chen-An, P., Alexandersen, P., Qvist, P., Christiansen, C., … Karsdal, M. A. (2013). Role of hormones in cartilage and joint metabolism: Understanding an unhealthy metabolic phenotype in osteoarthritis. *Menopause*, *20*(5), 578–586. https://doi.org/10.1097/GME.0b013e3182745993

Bedson, J., & Croft, P. R. (2008). The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. *BMC Musculoskeletal Disorders*, *9*, 1–11. https://doi.org/10.1186/1471-2474-9-116

Benjamin, M, Kumai, T., Milz, S., Boszczyk, B. M., Boszczyk, A. A., & Ralphs, J. R. (2002). The skeletal attachment of tendons--tendon "entheses". *Comparative Biochemistry and Physiology. Part A, Molecular & Integrative Physiology*, *133*(4), 931–945. https://doi.org/10.1016/S1095-6433(02)00138-1

Benjamin, M., & McGonagle, D. (2007). Histopathologic changes at "synovio-entheseal complexes" suggesting a novel mechanism for synovitis in osteoarthritis and spondylarthritis. *Arthritis and Rheumatism*, *56*(11), 3601–3609. https://doi.org/10.1002/art.23078

Benjamin, M., Moriggl, B., Brenner, E., Emery, P., McGonagle, D., & Redman, S. (2004). The "enthesis organ" concept: Why enthesopathies may not present as focal insertional disorders. *Arthritis and Rheumatism*, *50*(10), 3306–3313. https://doi.org/10.1002/art.20566

Benjamin, M., Toumi, H., Suzuki, D., Hayashi, K., & McGonagle, D. (2009). Evidence for a distinctive pattern of bone formation in enthesophytes. *Annals of the Rheumatic Diseases*, *68*(6), 1003–1010. https://doi.org/10.1136/ard.2008.091074

Berenbaum, F., Eymard, F., & Houard, X. (2013). Osteoarthritis, inflammation and obesity. *Current Opinion in Rheumatology*, *25*(1), 114–118. https://doi.org/10.1097/BOR.0b013e32835a9414

Binks, D. A., Gravallese, E. M., Bergin, D., Hodgson, R. J., Tan, A. L., Matzelle, M. M., … Radjenovic, A. (2015). Role of vascular channels as a novel mechanism for subchondral bone damage at cruciate ligament entheses in osteoarthritis and inflammatory arthritis. *Annals of the Rheumatic Diseases*, *74*(1), 196–203. https://doi.org/10.1136/annrheumdis-2013-203972

Birn, J., Pruente, R., Avram, R., Eyler, W., Mahan, M., & van Holsbeeck, M. (2014). Sonographic evaluation of hip joint effusion in osteoarthritis with correlation to radiographic findings. *Journal of Clinical Ultrasound : JCU*, *42*(4), 205–211. https://doi.org/10.1002/jcu.22112

Blagojevic, M., Jinks, C., Jeffery, A., & Jordan, K. P. (2010). Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis and Cartilage*, *18*(1), 24–33. https://doi.org/10.1016/j.joca.2009.08.010

Bobinac, D., Spanjol, J., Zoricic, S., & Maric, I. (2003). Changes in articular cartilage and subchondral bone histomorphometry in osteoarthritic knee joints in humans. *Bone*, *32*(3), 284–290. https://doi.org/10.1016/S8756-3282(02)00982-1

Boegård, T., Rudling, O., Petersson, I. F., & Jonsson, K. (1998). Correlation between radiographically diagnosed osteophytes and magnetic resonance detected cartilage defects in the tibiofemoral joint correlation between radiographically diagnosed osteophytes and magnetic resonance detected cartilage defects in the tibiofemoral joint. *Ann Rhuem Dis*, *1*(December 2007), 401–407.

Bosch, P., Moreno-Castilla, C., Zapata-Benabithe, Z., Alemán, I., Lara, V. H., Mansilla, J., … Botella, M. (2014). On porosity of archeological bones I - Textural characterization of pathological Spanish medieval human bones. *Palaeogeography, Palaeoclimatology, Palaeoecology*, *414*, 486–492. https://doi.org/10.1016/j.palaeo.2014.09.018

Botter, S. M., Van Osch, G. J. V. M., Clockaerts, S., Waarsing, J. H., Weinans, H., & Van Leeuwen, J. P. T. M. (2011). Osteoarthritis induction leads to early and temporal subchondral plate porosity in the tibial plateau of mice: An in vivo microfocal computed

tomography study. *Arthritis and Rheumatism*, *63*(9), 2690–2699.
https://doi.org/10.1002/art.30307

Boyan, B. D., Tosi, L., Coutts, R., Enoka, R., Hart, D. A., Nicolella, D. P., … Kohrt, W. (2012).
Sex Differences in Osteoarthritis of the Knee. *Journal of the American Academy of
Orthopaedic Surgeons*, *20*(10), 668–669. https://doi.org/10.5435/JAAOS-20-10-668

Boyan, B. D., Hart, D. A., Enoka, R. M., Nicolella, D. P., Resnick, E., Berkley, K. J., … Kohrt,
W. M. (2013). Hormonal modulation of connective tissue homeostasis and sex differences
in risk for osteoarthritis of the knee. *Biology of Sex Differences*, *4*(1), 1.
https://doi.org/10.1186/2042-6410-4-3

Boyer, K. A., & Andriacchi, T. P. (2016). The nature of age-related differences in knee function
during walking: Implication for the development of knee osteoarthritis. *PLoS ONE*, *11*(12),
1–13. https://doi.org/10.1371/journal.pone.0167352

Brooks, A. T., Andrade, R. E., Middleton, K. R., & Wallen, G. R. (2015). Clinical Medicine
Insights : Arthritis and Musculoskeletal Disorders. *Clinical Medicine Insights: Arthritis and
Musculoskeletal Disorders*, *8*, 1–8. https://doi.org/10.4137/CMAMD.S13849.

Brossmann, J., White, L. M., Stabler, A., Preidler, K. W., Andresen, R., Haghighi, P., & Resnick,
D. (1996). Enlargement of the third intercondylar tubercle of Parsons as a sign
of osteoarthritis of the knee: a paleopathologic and radiographic study. *Radiology*.
https://doi.org/10.1148/radiology.198.3.8628881

Buikstra, J. E., & Ubelaker, D. H. (1994). Standards for data collection from human skeletal
remains. *Arkansas Archaeological Survey Research Series*.
https://doi.org/10.1002/ajhb.1310070519

Burr, D. B., & Gallant, M. A. (2012). Bone remodelling in osteoarthritis. *Nature Reviews
Rheumatology*, *8*(11), 665–673. https://doi.org/10.1038/nrrheum.2012.130

Canadian Institute for Health Information (2018). Hip and knee replacements in Canada, 2016-
2017. *Canadian Joint Replacement Registry Annual Report*, 1-51.

Carrino, J. A., Blum, J., Parellada, J. A., Schweitzer, M. E., & Morrison, W. B. (2006). MRI of bone marrow edema-like signal in the pathogenesis of subchondral cysts. *Osteoarthritis and Cartilage*, *14*, 1081–1085. https://doi.org/10.1016/j.joca.2006.05.011

Chan, K. K. W., Sit, R. W. S., Wu, R. W. K., & Ngai, A. H. Y. (2014). Clinical, radiological and ultrasonographic findings related to knee pain in osteoarthritis. *PLoS ONE*, *9*(3). https://doi.org/10.1371/journal.pone.0092901

Chan, P. B., Wen, C., Yang, W., Yan, C., & Chiu, K. (2016). Phenotype classification of advanced knee osteoarthritis based on occurrence of subchondral bone cysts. *Osteoarthritis and Cartilage*, *24*(2016), S389–S390. https://doi.org/10.1016/j.joca.2016.01.70

Chaudhari, A. M. W., Briant, P. L., Bevill, S. L., Koo, S., & Andriacchi, T. P. (2008). Knee kinematics, cartilage morphology, and osteoarthritis after ACL injury. *Medicine and Science in Sports and Exercise*, *40*(2), 215–222. https://doi.org/10.1249/mss.0b013e31815cbb0e

Chen, Y., Zhou, B., Wang, J., Wang, T., Zhao, W., Cao, X., … Guo, X. (2016). Subchondral trabecular rod loss and trabecular plate stiffening precedes articular cartilage damages in osteoarthritis. *Osteoarthritis and Cartilage*, *24*, S389.

Cho, H. J., Chang, C. B., Yoo, J. H., Kim, S. J., & Kim, T. K. (2010). Gender differences in the correlation between symptom and radiographic severity in patients with knee osteoarthritis. *Clinical Orthopaedics and Related Research*, *468*(7), 1749–1758. https://doi.org/10.1007/s11999-010-1282-z

Cho, H. J., Morey, V., Kang, J. Y., Kim, K. W., & Kim, T. K. (2015). Prevalence and risk factors of spine, shoulder, hand, hip, and knee osteoarthritis in community-dwelling Koreans older than age 65 years. *Clinical Orthopaedics and Related Research*, *473*(10), 3307–3314. https://doi.org/10.1007/s11999-015-4450-3

Cox, L. G. E., Van Donkelaar, C. C., van Rietbergen, B., Emans, P. J., & Ito, K. (2013). Alterations to the subchondral bone architecture during osteoarthritis: Bone adaptation vs

endochondral bone formation. *Osteoarthritis and Cartilage*, *21*(2), 331–338. https://doi.org/10.1016/j.joca.2012.10.013

Crema, M. D., Roemer, F. W., Marra, M. D., Niu, J., Zhu, Y., Lynch, J., … Guermazi, A. (2008). Association with prevalent and incident MRI-detected bone marrow edema-like lesions are strongly associated with subchondral cysts in tatients with or at risk for knee asteoarthritis: The MOST study. *Osteoarthritis and Cartilage*, *16*, S160. https://doi.org/10.1016/S1063-4584(08)60414-8

Crema, M. D., Roemer, F. W., Marra, M. D., Niu, J., Lynch, J. A., Felson, D. T., & Guermazi, A. (2010a). Contrast-enhanced MRI of subchondral cysts in patients with or at risk for knee osteoarthritis: The MOST study. *Eur J Radiol.*, *75*(1), 1–14. https://doi.org/10.1016/j.ejrad.2009.08.009

Crema, M. D., Roemer, F. W., Zhu, Y., Marra, M. D., Niu, J., Zhang, Y., … Guermazi, A. (2010b). Subchondral cystlike lesions develop longitudinally in areas of bone marrow edema–like lesions in patients with or at risk for knee osteoarthritis: Detection with MR Imaging—the MOST study. *Radiology*, *256*(3), 855–862. https://doi.org/10.1148/radiol.10091467

Crubézy, E., Goulet, J., Bruzek, J., Jelinek, J., Rougé, D., & Ludes, B. (2002). Epidemiology of osteoarthritis and enthesopathies in a European population dating back 7700 years. *Joint Bone Spine*, *69*(6), 580–588. https://doi.org/10.1016/S1297-319X(02)00455-4

Dare, D., & Rodeo, S. (2014). Mechanisms of post-traumatic osteoarthritis after ACL injury. *Current Rheumatology Reports*, *16*(10), 1–5. https://doi.org/10.1007/s11926-014-0448-1

Davies, C. M., Guilak, F., Weinberg, J. B., & Fermor, B. (2008). Reactive nitrogen and oxygen species in interleukin-1-mediated DNA damage associated with osteoarthritis. *Osteoarthritis and Cartilage*, *16*(5), 624–630. https://doi.org/10.1016/j.joca.2007.09.012

de Klerk, B. M., Schiphof, D., Groeneveld, F. P. M. J., Koes, B. W., van Osch, G. J. V. M., van Meurs, J. B. J., & Bierma-Zeinstra, S. M. A. (2009). No clear association between female

hormonal aspects and osteoarthritis of the hand, hip and knee: A systematic review. *Rheumatology*, *48*(9), 1160–1165. https://doi.org/10.1093/rheumatology/kep194

Dedrick, D. K., Goulet, R. W., O'Connor, B. L., & Brandt, K. D. (1997). Preliminary report: increased porosity of the subchondral plate in the accelerated canine model of osetoarthritis. *Osteoarthritis and Cartilage*, *5*, 71–74.

Dequeker, J., & Luyten, F. P. (2008). The history of osteoarthritis-osteoarthrosis. *Annals of the Rheumatic Diseases*, *67*(1), 5–10. https://doi.org/10.1136/ard.2007.079764

Ding, C., Cicuttini, F., Scott, F., Glisson, M., & Jones, G. (2003). Sex differences in knee cartilage volume in adults: Role of body and bone size, age and physical activity. *Rheumatology*, *42*(11), 1317–1323. https://doi.org/10.1093/rheumatology/keg374

Driban, J. B., Eaton, C. B., Lo, G. H., Ward, R. J., Lu, B., & McAlindon, T. E. (2014). Association of knee injuries with accelerated knee osteoarthritis progression: data from the Osteoarthritis Initiative. *Arthritis Care & Research*, *66*(11), 1673–1679. https://doi.org/10.1002/acr.22359

Ellis, H. B., Briggs, K. K., & Philippon, M. J. (2011). Innovation in hip arthroscopy: Is hip arthritis preventable in the athlete? *British Journal of Sports Medicine*, *45*(4), 253–258. https://doi.org/10.1136/bjsm.2010.082529

Emad, Y., Ragab, Y., Gheita, T., Anbar, A., Kamal, H., Saad, A., … Rasker, J. J. (2012). Knee enthesitis and synovitis on magnetic resonance imaging in patients with psoriasis without arthritic symptoms. *Journal of Rheumatology*, *39*(10), 1979–1986. https://doi.org/10.3899/jrheum.120301

Eng, J. T. (2016). A bioarchaeological study of osteoarthritis among populations of northern China and Mongolia during the Bronze Age to Iron Age transition to nomadic pastoralism. *Quaternary International*, *405*, 172–185. https://doi.org/10.1016/j.quaint.2015.07.072

Eriksen, E. F., & Ringe, J. D. (2012). Bone marrow lesions: A universal bone response to injury? *Rheumatology International*, *32*(3), 575–584. https://doi.org/10.1007/s00296-011-2141-2

Esser, S., & Bailey, A. (2011). Effects of exercise and physical activity on knee osteoarthritis. *Current Pain and Headache Reports*, *15*(6), 423–430. https://doi.org/10.1007/s11916-011-0225-z

Everhart, J. S., Abouljoud, M. M., Poland, S. G., & Flanigan, D. C. (2018). Medial compartment defects progress at a more rapid rate than lateral cartilage defects in older adults with minimal to moderate knee osteoarthritis (OA): data from the OA initiative. *Knee Surgery, Sports Traumatology, Arthroscopy : Official Journal of the ESSKA*, *0*(0), 0. https://doi.org/10.1007/s00167-018-5202-1

Faccia, K., Waters-Rist, A., Lieverse, A. R., Bazaliiskii, V. I., Stock, J. T., & Katzenberg, M. A. (2016). Diffuse idiopathic skeletal hyperostosis (DISH) in a middle Holocene forager from Lake Baikal, Russia: Potential causes and the effect on quality of life. *Quaternary International*, *405*, 66–79. https://doi.org/10.1016/j.quaint.2015.10.011

Felson, D. T. (2005). The sources of pain in knee osteoarthritis. *Current Opinion in Rheumatology*, *17*(5), 624–628. https://doi.org/10.1097/01.bor.0000172800.49120.97

Felson, D. T. (2006). Osteoarthritis of the Knee. *New England Journal of Medicine*, *354*(23), 2508–2509. https://doi.org/10.1056/NEJMc060815

Felson, D. T., Gale, D. R., Elon Gale, M., Niu, J., Hunter, D. J., Goggins, J., & La Valley, M. P. (2005). Osteophytes and progression of knee osteoarthritis. *Rheumatology*, *44*(1), 100–104. https://doi.org/10.1093/rheumatology/keh411

Felson, D., & Neogi, T. (2004). Osteoarthritis: Is It a Disease of Cartilage or Bone? *Arthritis & Rheumatism*, *50*(2), 341–344. https://doi.org/10.1002/art.20051

Felson, D. T., Niu, J., Yang, T., Torner, J., Lewis, C. E., Aliabadi, P., … Nevitt, M. C. (2013). Physical activity, alignment and knee osteoarthritis: Data from MOST and the OAI. *Osteoarthritis and Cartilage*, *21*(6), 789–795. https://doi.org/10.1016/j.joca.2013.03.001

Findlay, D. M., & Kuliwaba, J. S. (2016). Bone-cartilage crosstalk: A conversation for understanding osteoarthritis. *Bone Research*, *4*(July). https://doi.org/10.1038/boneres.2016.28

Franklin, J., Ingvarsson, T., Englund, M., & Lohmander, L. S. (2009). Sex differences in the association between body mass index and total hip or knee joint replacement resulting from osteoarthritis. *Annals of the Rheumatic Diseases*, *68*(4), 536–540. https://doi.org/10.1136/ard.2007.086868

Franklin, J., Ingvarsson, T., Englund, M., & Lohmander, S. (2010). Association between occupation and knee and hip replacement due to osteoarthritis: A case-control study. *Arthritis Research and Therapy*, *12*(3). https://doi.org/10.1186/ar3033

Friel, N. A., & Chu, C. R. (2013). The role of ACL injury in the development of posttraumatic knee osteoarthritis. *Clinics in Sports Medicine*, *32*(1), 1–12. https://doi.org/10.1016/j.csm.2012.08.017

Garstang, S. V., & Stitik, T. P. (2006). Osteoarthritis: Epidemiology, risk factors, and pathophysiology. *American Journal of Physical Medicine and Rehabilitation*, *85*(11 SUPPL.), 2–11. https://doi.org/10.1097/01.phm.0000245568.69434.1a

Ganz, R., Leunig, M., Leunig-Ganz, K., & Harris, W. H. (2008). The etiology of osteoarthritis of the hip: An integrated mechanical concept. *Clinical Orthopaedics and Related Research*, *466*(2), 264–272. https://doi.org/10.1007/s11999-007-0060-z

Gibson, N., Guermazi, A., Clancy, M., Niu, J., Grayson, P., Aliabadi, P., … Felson, D. T. (2012). Relation of hand enthesophytes with knee enthesopathy: Is osteoarthritis related to a systemic enthesopathy? *Journal of Rheumatology*, *39*(2), 359–364. https://doi.org/10.3899/jrheum.110718

Glass, N., Segal, N. A., Sluka, K. A., Torner, J. C., Nevitt, M. C., Felson, D. T., … Frey-Law, L. A. (2014). Examining sex differences in knee pain: The multicenter osteoarthritis study. *Osteoarthritis and Cartilage*, *22*(8), 1100–1106. https://doi.org/10.1016/j.joca.2014.06.030

Goldring, M. B., & Goldring, S. R. (2010). Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis. *Annals of the New York Academy of Sciences*, *1192*, 230–237. https://doi.org/10.1111/j.1749-6632.2009.05240.x

Goldring, S. R. (2012). Alterations in periarticular bone and cross talk between subchondral bone and articular cartilage in osteoarthritis. *Therapeutic Advances in Musculoskeletal Disease*, *4*(4), 249–258. https://doi.org/10.1177/1759720X12437353

Grynpas, M., Alpert, B., Katz, I., Lieberman, I., & Pritzker, K. (1991). Subchondral bone in osteoarthritis. *Calcified Tissue International*, *49*, 20–26.

Guilak, F. (2011). Biomechanical factors in osteoarthritis. *Best Practice and Research: Clinical Rheumatology*, *25*(6), 815–823. https://doi.org/10.1016/j.berh.2011.11.013

Guilak, F., Fermor, B., Keefe, F. J., Kraus, V. B., Olson, S. A., Pisetsky, D. S., … Weinberg, J. B. (2004). The Role of Biomechanics and Inflammation in Cartilage Injury and Repair. *Clinical Orthopaedics and Related Research*, *423*(423), 17–26. https://doi.org/10.1097/01.blo.0000131233.83640.91

Hall, M., Doherty, S., Courtney, P., Latief, K., Zhang, W., & Doherty, M. (2014). Synovial pathology detected on ultrasound correlates with the severity of radiographic knee osteoarthritis more than with symptoms. *Osteoarthritis and Cartilage*, *22*(10), 1627–1633. https://doi.org/10.1016/j.joca.2014.05.025

Hardcastle, S. A., Dieppe, P., Gregson, C. L., Arden, N. K., Spector, T. D., Hart, D. J., … Tobias, J. H. (2014). Osteophytes, enthesophytes, and high bone mass: A bone-forming triad with potential relevance in osteoarthritis. *Arthritis and Rheumatology*, *66*(9), 2429–2439. https://doi.org/10.1002/art.38729

Hardcastle, S. A., Dieppe, P., Gregson, C. L., Davey Smith, G., & Tobias, J. H. (2015). Osteoarthritis and bone mineral density: are strong bones bad for joints? *BoneKEy Reports*, *4*(January), 1–8. https://doi.org/10.1038/bonekey.2014.119

Harding, G. T., Dunbar, M. J., Hubley-Kozey, C. L., Stanish, W. D., & Astephen Wilson, J. L. (2016). Obesity is associated with higher absolute tibiofemoral contact and muscle forces during gait with and without knee osteoarthritis. *Clinical Biomechanics*, *31*, 79–86. https://doi.org/10.1016/j.clinbiomech.2015.09.017

Hayeri, M. R., Shiehmorteza, M., Trudell, D. J., Hefflin, T., & Resnick, D. (2010). Proximal tibial osteophytes and their relationship with the height of the tibial spines of the intercondylar eminence: Paleopathological study. *Skeletal Radiology*, *39*(9), 877–881. https://doi.org/10.1007/s00256-009-0838-z

Henriksen, M., Hunter, D. J., Dam, E. B., Messier, S. P., Andriacchi, T. P., Lohmander, L. S., … Christensen, R. (2013). Is increased joint loading detrimental to obese patients with knee osteoarthritis? A secondary data analysis from a randomized trial. *Osteoarthritis and Cartilage*, *21*(12), 1865–1875. https://doi.org/10.1016/j.joca.2013.10.003

Hernandez-Molina, G., Guermazi, A., Niu, J., Gale, D., Goggins, J., Amin, S., & Felson, D. T. (2008). Central bone marrow lesions in symptomatic knee osteoarthritis and their relationship to anterior cruciate ligament tears and cartilage loss. *Arthritis and Rheumatism*, *58*(1), 130–136. https://doi.org/10.1002/art.23173

Huber, M., Trattnig, S., & Lintner, F. (2000). Anatomy, biochemistry, and physiology of articular cartilage : Investigative radiology. *Investigative Radiology*, *35*(10), 573–580. Retrieved from https://journals.lww.com/investigativeradiology/Abstract/2000/10000/Anatomy,_Biochemistry,_and_Physiology_of_Articular.3.aspx

Hügle, T., Geurts, J., Nüesch, C., Müller-Gerbl, M., & Valderrabano, V. (2012). Aging and osteoarthritis: An inevitable encounter? *Journal of Aging Research*, *2012*. https://doi.org/10.1155/2012/950192

Hunter, D. J., & Felson, D. T. (2006). Clinical Review: Osteoarthritis. *BMJ*, *332*(7542), 1–4. Retrieved from http://www.bmj.com/highwire/filestream/343033/field_highwire_article_pdf/0/639

Hunter, D. J., Gerstenfeld, L., Bishop, G., Davis, A. D., Mason, Z. D., Einhorn, T. A., …
Morgan, E. F. (2009). Bone marrow lesions from osteoarthritis knees are characterized by
sclerotic bone that is less well mineralized. *Arthritis Research & Therapy*, *11*(1), R11.
https://doi.org/10.1186/ar2601

Hussain, S. M., Cicuttini, F. M., Bell, R. J., Robinson, P. J., Davis, S. R., Giles, G. G., … Wang,
Y. (2014). Incidence of total knee and hip replacement for osteoarthritis in relation to
circulating sex steroid hormone concentrations in women. *Arthritis and Rheumatology*,
66(8), 2144–2151. https://doi.org/10.1002/art.38651

Iagnocco, A. (2014). Ultrasound in osteoarthritis. *Clinical and Experimental Rheumatology*,
32(SUPPL.80), 48–52. https://doi.org/10.1016/B978-1-4377-0127-2.10014-0

Iijima, H., Aoyama, T., Tajino, J., Ito, A., Nagai, M., Yamaguchi, S., … Kuroki, H. (2016).
Subchondral plate porosity colocalizes with the point of mechanical load during ambulation
in a rat knee model of post-traumatic osteoarthritis. *Osteoarthritis and Cartilage*, *24*(2),
354–363. https://doi.org/10.1016/j.joca.2015.09.001

Imhof, H., Sulzbacher, I., Grampp, S., Czerny, C., Youssefzadeh, S., & Kainberger, F. (2000).
Subchondral bone and cartilage disease. *Investigative Radiology*, *35*(10), 581–588.
https://doi.org/10.1097/00004424-200010000-00004

Immonen, J., Siefring, C., & Sanders, L. (2017). Osteoarthritis of the Anterior Cruciate Ligament
and Medial Tibial Plateau: A Cadaveric Study. *Cartilage*, 194760351771381.
https://doi.org/10.1177/1947603517713817

Ip, S., Sayre, E. C., Guermazi, A., Nicolaou, S., Wong, H., Thorne, A., … Cibere, J. (2011).
Frequency of bone marrow lesions and association with pain severity: Results from a
population-based symptomatic knee cohort. *Journal of Rheumatology*, *38*(6), 1079–1085.
https://doi.org/10.3899/jrheum.100587

Ishimori, M.L., Altman, R.D., Cohen, M.J., Cui, J., Guuo, X., Rotter, J.I. & Weisman, M.H.. (2010). Heritability patterns in hand osteoarthritis: The GHOST study. *Osteoarthritis and Cartilage*, *18*, S167–S168. Retrieved from http://arthritis-research.com/content/12/5/R180

Jones, G., Glisson, M., Hynes, K., & Cicuttini, F. (2000). Sex and site differences in cartilage development: A possible explanation for variations in knee osteoarthritis in later life. *Arthritis & Rheumatism*, *43*(11), 2543–2549.

Jurmain, R. D., & Kilgore, L. (1995). Skeletal evidence of osteoarthritis: A palaeopathological perspective. *Annals of the Rheumatic Diseases*, *54*(6), 443–450. https://doi.org/10.1136/ard.54.6.443

Katsuragi, J., Sasho, T., Yamaguchi, S., Sato, Y., Watanabe, A., Akagi, R., … Takahashi, K. (2015). Hidden osteophyte formation on plain X-ray is the predictive factor for development of knee osteoarthritis after 48 months - data from the Osteoarthritis Initiative. *Osteoarthritis and Cartilage*, *23*(3), 383–390. https://doi.org/10.1016/j.joca.2014.11.026

Keen, H. I., & Conaghan, P. G. (2009). Ultrasonography in osteoarthritis. *Radiologic Clinics of North America*, *47*(4), 581–594. https://doi.org/10.1016/j.rcl.2009.04.007

Kellgren, J. H., & Lawrence, J. S. (1957). Radiological assessment of osteo-arthrosis. *Ann. Rheum. Dis.*, *16*, 494–502. https://doi.org/doi: 10.1136/ard.16.4.494

Kerkhof, H. J. M., Bierma-Zeinstra, S. M. A., Arden, N. K., Metrustry, S., Castano-Betancourt, M., Hart, D. J., … Van Meurs, J. B. J. (2014). Prediction model for knee osteoarthritis incidence, including clinical, genetic and biochemical risk factors. *Annals of the Rheumatic Diseases*, *73*(12), 2116–2121. https://doi.org/10.1136/annrheumdis-2013-203620

Khan, H. I., Aitken, D., Chou, L., McBride, A., Ding, C., Blizzard, L., … Jones, G. (2015). A family history of knee joint replacement increases the progression of knee radiographic osteoarthritis and medial tibial cartilage volume loss over 10 years. *Osteoarthritis and Cartilage*, *23*(2), 203–209. https://doi.org/10.1016/j.joca.2014.11.016

Koelling, S., & Miosge, N. (2010). Sex differences of chondrogenic progenitor cells in late stages of osteoarthritis. *Arthritis and Rheumatism*, *62*(4), 1077–1087. https://doi.org/10.1002/art.27311

Koonce, R. C., & Bravman, J. T. (2013). Obesity and osteoarthritis: More than just wear and tear. *Journal of the American Academy of Orthopaedic Surgeons* , *21*(3), 161–169. https://doi.org/10.5435/JAAOS-21-03-161

Kwee, R. M., Wirth, W., Hafezi-Nejad, N., Zikria, B. A., Guermazi, A., & Demehri, S. (2016). Role of physical activity in cartilage damage progression of subjects with baseline full-thickness cartilage defects in medial tibiofemoral compartment: data from the Osteoarthritis Initiative. *Osteoarthritis and Cartilage*, *24*(11), 1898–1904. https://doi.org/10.1016/j.joca.2016.06.009

Lanyon, P., Muir, K., Doherty, S., Doherty, M., Lanyon, P., Muir, K., … Doherty, M. (2000). Assessment of a genetic contribution to osteoarthritis of the hip: Sibling study. *BMJ: British Medical Journal*, *321*(7270), 1179–1183.

Laxafoss, E., Jacobsen, S., Gosvig, K. K., & Sonne-Holm, S. (2010). Case definitions of knee osteoarthritis in 4,151 unselected subjects: Relevance for epidemiological studies: The Copenhagen osteoarthritis study. *Skeletal Radiology*, *39*(9), 859–866. https://doi.org/10.1007/s00256-009-0856-x

Lee, R., & Kean, W. F. (2012). Obesity and knee osteoarthritis. *Inflammopharmacology*, *20*(2), 53–58. https://doi.org/10.1007/s10787-011-0118-0

Lefévre-Colau, M. M., Nguyen, C., Haddad, R., Delamarche, P., Paris, G., Palazzo, C., … Roren, A. (2016). Is physical activity, practiced as recommended for health benefit, a risk factor for osteoarthritis? *Annals of Physical and Rehabilitation Medicine*, *59*(3), 196–206. https://doi.org/10.1016/j.rehab.2016.02.007

Li, G., Yin, J., Gao, J., Cheng, T. S., Pavlos, N. J., Zhang, C., & Zheng, M. H. (2013).
Subchondral bone in osteoarthritis: Insight into risk factors and microstructural changes.
Arthritis Research and Therapy, *15*(6). https://doi.org/10.1186/ar4405

Lieverse, A. R., Mack, B., Bazaliiskii, V. I., & Weber, A. W. (2016). Revisiting osteoarthritis in
the Cis-Baikal: Understanding behavioral variability and adaptation among middle
Holocene foragers. *Quaternary International*, *405*, 160–171.
https://doi.org/10.1016/j.quaint.2015.03.019

Lieverse, A. R., Weber, A. W., Bazaliiskii, V. I., Goriunova, O. I., & Savel'ev, N. A. (2007).
Osteoarthritis in Siberia's Cis-Bailkal: Skeletal indicators of hunter-gatherer adaptation and
cultural change. *American Journal of Physical Anthropology*, *132*, 1–16.
https://doi.org/10.1002/ajpa

Lin, W., Alizai, H., Joseph, G. B., Srikhum, W., Nevitt, M. C., Lynch, J. A., … Link, T. M.
(2013). Physical activity in relation to knee cartilage T2 progression measured with 3tmri
over a period of 4 years: Data from the osteoarthritis initiative. *Osteoarthritis and
Cartilage*, *21*(10), 1558–1566. https://doi.org/10.1016/j.joca.2013.06.022

Loeser, R. F., Goldring, S. R., Scanzello, C. R., & Goldring, M. B. (2012). Osteoarthritis: A
disease of the joint as an organ. *Arthritis and Rheumatism*, *64*(6), 1697–1707.
https://doi.org/10.1002/art.34453

Long, D., Blake, S., Song, X.-Y., Lark, M., & Loeser, R. (2008). Human articular chondrocytes
produce IL-7 and respond to IL-7 with increased production of matrix metalloproteinase-13.
Arthritis Research & Therapy, *10*(R23). https://doi.org/10.1186/ar2376

Lotz, M. K., & Caramés, B. (2011). Autophagy and cartilage homeostasis mechanisms in joint
health, aging and OA. *Nature Reviews Rheumatology*, *7*(10), 579–587.
https://doi.org/10.1038/nrrheum.2011.109

Lyons, T. J., McClure, S. F., Stoddart, R. W., & McClure, J. (2006). The normal human
chondro-osseous junctional region: Evidence for contact of uncalcified cartilage with

subchondral bone and marrow spaces. *BMC Musculoskeletal Disorders*, *7*, 1–8. https://doi.org/10.1186/1471-2474-7-52

MacGregor, A. J., Li, Q., Spector, T. D., & Williams, F. M. K. (2009). The genetic influence on radiographic osteoarthritis is site specific at the hand, hip and knee. *Rheumatology*, *48*(3), 277–280. https://doi.org/10.1093/rheumatology/ken475

MacGregor, A. J., & Spector, T. D. (1999). Twins and the genetic architecture of osteoarthritis. *Rheumatology*, *38*(7), 583–588. https://doi.org/10.1093/rheumatology/38.7.583

Mack, B. P. (2016). *Osteoarthritis in Middle Holocene Hunter-Gatherers from the Cis-Baikal Region of Siberia, Russia*. University of Saskatchewan.

Mahjoub, M., Berenbaum, F., & Houard, X. (2012). Why subchondral bone in osteoarthritis? the importance of the cartilage bone interface in osteoarthritis. *Osteoporosis International*, *23*(8 SUPPL). https://doi.org/10.1007/s00198-012-2161-0

Mansilla, J., Moreno-Castilla, C., Bosch, P., Alemán, I., Pijoan, C., & Botella, M. (2014). On porosity of archeological bones II. Textural characterization of Mesoamerican human bones. *Palaeogeography, Palaeoclimatology, Palaeoecology*, *414*, 493–499. https://doi.org/10.1016/j.palaeo.2014.08.029

Martín-Millán, M., & Castañeda, S. (2013). Estrogens, osteoarthritis and inflammation. *Joint Bone Spine*, *80*(4), 368–373. https://doi.org/10.1016/j.jbspin.2012.11.008

Martini F.H., Timmons, M.J., & Tallitsch, R.B. (2015). *Human Anatomy* (8th ed.). San Francisco: Pearson Benjamin Cummings.

Mattap, S. M., Aitken, D., Wills, K., Laslett, L., Ding, C., Pelletier, J.-P., … kelr, G. (2018). How do MRI-detected subchondral bone marrow lesions (BMLs) on two different MRI sequences correlate with clinically important outcomes? *Calcified Tissue International*, 1–13. https://doi.org/10.1007/s00223-018-0402-8

Mays, S. (2016). Bone-formers and bone-losers in an archaeological population. *American Journal of Physical Anthropology*, *159*(4), 577–584. https://doi.org/10.1002/ajpa.22912

Mays, S., & Cooper, L. (2009). A Paleopathological Investigation of the Third Intercondylar Tubercle of Parsons. *International Journal of Osteoarchaeology*, *19*, 735–741. https://doi.org/10.1002/oa.994

McErlain, D. D., Ulici, V., Darling, M., Gati, J. S., Pitelka, V., Beier, F., & Holdsworth, D. W. (2012). An in vivo investigation of the initiation and progression of subchondral cysts in a rodent model of secondary osteoarthritis. *Arthritis Research & Therapy*, *14*(1), R26. https://doi.org/10.1186/ar3727

McGonagle, D., Tan, A. L., Carey, J., & Benjamin, M. (2010). The anatomical basis for a novel classification of osteoarthritis and allied disorders. *Journal of Anatomy*, *216*(3), 279–291. https://doi.org/10.1111/j.1469-7580.2009.01186.x

Messier, S. P., Mihalko, S. L., Legault, C., Miller, G. D., Nicklas, B. J., DeVita, P., … Loeser, R. F. (2013). Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: The IDEA randomized clinical trial. *JAMA - Journal of the American Medical Association*, *310*(12), 1263–1273. https://doi.org/10.1001/jama.2013.277669

Mezhov, V., Ciccutini, F. M., Hanna, F. S., Brennan, S. L., Wang, Y. Y., Urquhart, D. M., & Wluka, A. E. (2014). Does obesity affect knee cartilage? A systematic review of magnetic resonance imaging data. *Obesity Reviews*, *15*(2), 143–157. https://doi.org/10.1111/obr.12110

Minafra, L., Bravatà, V., Saporito, M., Cammarata, F. P., Forte, G. I., Caldarella, S., … Boniforti, F. (2014). Genetic, clinical and radiographic signs in knee osteoarthritis susceptibility. *Arthritis Research and Therapy*, *16*(2), 1–10. https://doi.org/10.1186/ar4535

Mitani, Y. (2017). Gender-related differences in lower limb alignment, range of joint motion, and the incidence of sports injuries in Japanese university athletes. *Journal of Physical Therapy Science*, *29*(1), 12–15. https://doi.org/10.1589/jpts.29.12

Mork, P. J., Holtermann, A., & Nilsen, T. I. L. (2012). Effect of body mass index and physical exercise on risk of knee and hip osteoarthritis: Longitudinal data from the Norwegian HUNT Study. *Journal of Epidemiology and Community Health*, *66*(8), 678–683. https://doi.org/10.1136/jech-2011-200834

Muraki, S., Oka, H., Akune, T., En-yo, Y., Yoshida, M., Nakamura, K., … Yoshimura, N. (2011). Association of occupational activity with joint space narrowing and osteophytosis in the medial compartment of the knee: The ROAD study (OAC5914R2). *Osteoarthritis and Cartilage*, *19*(7), 840–846. https://doi.org/10.1016/j.joca.2011.03.008

Muratovic, D., Cicuttini, F., Wluka, A., Findlay, D., Wang, Y., Otto, S., … Kuliwaba, J. (2016). Bone marrow lesions detected by specific combination of MRI sequences are associated with severity of osteochondral degeneration. *Arthritis Research and Therapy*, *18*(1), 1–11. https://doi.org/10.1186/s13075-016-0953-x

Muratovic, D., Findlay, D. M., Cicuttini, F. M., Wluka, A. E., Lee, Y. R., & Kuliwaba, J. S. (2018). Bone matrix microdamage and vascular changes characterize bone marrow lesions in the subchondral bone of knee osteoarthritis. *Bone*, *108*, 193–201. https://doi.org/10.1016/j.bone.2018.01.012

Murphy, N. J., Eyles, J. P., & Hunter, D. J. (2016). Hip Osteoarthritis: Etiopathogenesis and Implications for Management. *Advances in Therapy*, *33*(11), 1921–1946. https://doi.org/10.1007/s12325-016-0409-3

Muthuri, S. G., McWilliams, D. F., Doherty, M., & Zhang, W. (2011). History of knee injuries and knee osteoarthritis: A meta-analysis of observational studies. *Osteoarthritis and Cartilage*, *19*(11), 1286–1293. https://doi.org/10.1016/j.joca.2011.07.015

Nakagawa, Y., Mukai, S., Yabumoto, H., Tarumi, E., & Nakamura, T. (2015). Cartilage Degeneration and Alignment in Severe Varus Osteoarthritis. *Cartilage*, *6*(4), 208–215. https://doi.org/10.1177/1947603515595501

Neogi, T., Felson, D., Niu, J., Nevitt, M., Lewis, C. E., Aliabadi, P., … Zhang, Y. (2009). Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. *BMJ: British Medical Journal*, *339*(aug21 1), b2844–b2844. https://doi.org/10.1136/bmj.b2844

Nguyen, A.-D., & Shultz, S. J. (2007). Sex differences in clinical measures of lower extremity alignment. *Journal of Orthopaedic & Sports Physical Therapy*, *37*(7), 389–398. https://doi.org/10.2519/jospt.2007.2487

Nicolella, D. P., O'Connor, M. I., Enoka, R. M., Boyan, B. D., Hart, D. A., Resnick, E., … Kohrt, W. M. (2012). Mechanical contributors to sex differences in idiopathic knee osteoarthritis. *Biology of Sex Differences*, *3*(1), 1–11. https://doi.org/10.1186/2042-6410-3-28

O'Connor, M. I. (2007). Sex differences in osteoarthritis of the hip and knee. *The Journal of the American Academy of Orthopaedic Surgeons*, *15 Suppl 1*(October), S22-5. https://doi.org/10.5435/00124635-200700001-00007

Ortner, D.J. (2003). *Identification of pathological conditions in human skeletal remains.* San Deigo CA: Academic Press.

Outerbridge, R. E. (1961). Etiology of chondromalacia patellae. *J Bone Joint Surg Br*, *43*, 752–757.

Owens, B. D., Duffey, M. L., Nelson, B. J., DeBerardino, T. M., Taylor, D. C., & Mountcastle, S. B. (2007). The incidence and characteristics of shoulder instability at the United States Military Academy. *American Journal of Sports Medicine*, *35*(7), 1168–1173. https://doi.org/10.1177/0363546506295179

Palazzo, C., Nguyen, C., Lefevre-Colau, M. M., Rannou, F., & Poiraudeau, S. (2016). Risk factors and burden of osteoarthritis. *Annals of Physical and Rehabilitation Medicine*, *59*(3), 134–138. https://doi.org/10.1016/j.rehab.2016.01.006

Pan, F., Khan, H., Ding, C., Winzenberg, T., Martel-Pelletier, J., Pelletier, J. P., … Jones, G. (2015). Familial effects on structural changes relevant to knee osteoarthritis: A prospective cohort study. *Osteoarthritis and Cartilage*, *23*(4), 559–564. https://doi.org/10.1016/j.joca.2015.01.004

Pearle, A. D., Warren, R. F., & Rodeo, S. A. (2005). Basic science of articular cartilage and osteoarthritis. *Clinics in Sports Medicine*, *24*(1), 1–12. https://doi.org/10.1016/j.csm.2004.08.007

Pecina, M., Bajok, I., & Pecina, H. I. (2001). Tuberculum intercondylare tibiae tertium as a predictive factor for anterior cruciate, *American Journal of Sports, 29*(6), 709–711.

Perry, B. D., Levinger, P., Serpiello, F. R., Caldow, M. K., Cameron-Smith, D., Bartlett, J. R., … McKenna, M. J. (2013). The effects of osteoarthritis and age on skeletal muscle strength, Na+-K+-ATPase content, gene and isoform expression. *Journal of Applied Physiology*, *115*(10), 1443–1449. https://doi.org/10.1152/japplphysiol.00789.2013

Phinyomark, A., Osis, S. T., Hettinga, B. A., Kobsar, D., & Ferber, R. (2016). Gender differences in gait kinematics for patients with knee osteoarthritis. *BMC Musculoskeletal Disorders*, *17*(1), 1–12. https://doi.org/10.1186/s12891-016-1013-z

Prieto-Alhambra, D., Judge, A., Javaid, M. K., Cooper, C., Diez-Perez, A., & Arden, N. K. (2014). Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: Influences of age, gender and osteoarthritis affecting other joints. *Annals of the Rheumatic Diseases*, *73*(9), 1659–1664. https://doi.org/10.1136/annrheumdis-2013-203355

Radin, E. L., & Rose, R. M. (1986). Role of subchondral bone in the initiation and progression of cartilage damage. *Clinical Orthopaedics and Related Research*. https://doi.org/10.1097/00003086-198612000-00005

Raynauld, J. P., Martel-Pelletier, J., Berthiaume, M. J., Abram, F., Choquette, D., Haraoui, B., …
Pelletier, J. P. (2008). Correlation between bone lesion changes and cartilage volume loss in
patients with osteoarthritis of the knee as assessed by quantitative magnetic resonance
imaging over a 24-month period. *Annals of the Rheumatic Diseases*, *67*(5), 683–688.
https://doi.org/10.1136/ard.2007.073023

Reiff, D. B., Heron, C. W., & Stoker, D. J. (1991). Spiking of the tubercles of the intercondylar
eminence of the tibial plateau in osteoarthritis. *British Journal of Radiology*.
https://doi.org/10.1259/0007-1285-64-766-915

Reina, N., Cavaignac, E., Pailhé, R., Pailliser, A., Bonnevialle, N., Swider, P., & Laffosse, J. M.
(2017). BMI-related microstructural changes in the tibial subchondral trabecular bone of
patients with knee osteoarthritis. *Journal of Orthopaedic Research*, *35*(8), 1653–1660.
https://doi.org/10.1002/jor.23459

Revell, P. A., Mayston, V., Lalor, P., & Mapp, P. (1988). The synovial membrane in
osteoarthritis: A histological study including the characterisation of the cellular infiltrate
present in inflammatory osteoarthritis using monoclonal antibodies. *Annals of the
Rheumatic Diseases*, *47*(4), 300–307. https://doi.org/10.1136/ard.47.4.300

Richmond, R. S., Carlson, C. S., Register, T. C., Shanker, G., & Loeser, R. F. (2000). Functional
estrogen receptors in adult articular cartilage: Estrogen replacement therapy increases
chondrocyte synthesis of proteoglycans and insulin-like growth factor binding protein 2.
Arthritis & Rheumatism, *43*(9), 2081–2090. https://doi.org/10.1002/1529-0131(200009)43:9

Riyazi, N., Meulenbelt, I., Kroon, H. M., Ronday, K. H., Hellio Le Graverand, M. P., Rosendaal,
F. R., … Kloppenburg, M. (2005). Evidence for familial aggregation of hand, hip, and spine
but not knee osteoarthritis in siblings with multiple joint involvement: The GARP study.
Annals of the Rheumatic Diseases, *64*(3), 438–443. https://doi.org/10.1136/ard.2004.024661

Robinson, W. H., Lepus, C. M., Wang, Q., Raghu, H., Mao, R., Lindstrom, T. M., & Sokolove,
J. (2016). Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis.
Nature Reviews Rheumatology, *12*(10), 580–592. https://doi.org/10.1038/nrrheum.2016.136

Roemer, F. W., Jarraya, M., Niu, J., Silva, J. R., Frobell, R., & Guermazi, A. (2015). Increased risk for radiographic osteoarthritis features in young active athletes: A cross-sectional matched case-control study. *Osteoarthritis and Cartilage*, *23*(2), 239–243. https://doi.org/10.1016/j.joca.2014.11.011

Roemer, F. W., Neogi, T., Nevitt, M. C., Felson, D. T., Zhu, Y., Zhang, Y., … Guermazi, A. (2010). Subchondral bone marrow lesions are highly associated with, and predict subchondral bone attrition longitudinally: the MOST study. *Osteoarthritis and Cartilage*, *18*(1), 47–53. https://doi.org/10.1016/j.joca.2009.08.018

Rogers, J., Shepstone, L., & Dieppe, P. (1997). Bone Formers: Osteophyte and Enthesophyte Formation are Positively Associated. *Annals of the Rheumatic Diseases*, *56*, 85–90.

Rogers, J. & Waldron, T. (1995). *A field guide to joint disease in archaeology.* Chichester UK: John Wiley & Sons.

Rogers, J., Waldron, T., Dieppe, P., & Watt, I. (1987). Arthropathies in palaeopathology: the basis of classification according to most probably cause. *Journal of Archaeological Science*, *14*,179–193.

Rossignol, M., Leclerc, A., Hilliquin, P., Allaert, F., Rozenberg, S., Valat, J.-P., … Fautrel, B. (2003). Primary osteoarthritis and occupations : A national cross sectional survey of 10 412 symptomatic patients. *Occupational and Environmental Medicine*, *60*, 882–887.

Rothschild, B. M. (1997). Porosity: A curiosity without diagnostic significance. *American Journal of Physical Anthropology*, *104*(July 1996), 529–533.

Runhaar, J., Koes, B. W., Clockaerts, S., & Bierma-Zeinstra, S. M. A. (2011). A systematic review on changed biomechanics of lower extremities in obese individuals: A possible role in development of osteoarthritis. *Obesity Reviews*, *12*(12), 1071–1082. https://doi.org/10.1111/j.1467-789X.2011.00916.x

Salih, S., & Sutton, P. (2013). Obesity, knee osteoarthritis and knee arthroplasty: a review. *BMC Sports Sci Med Rehabil*, *5*, 25. https://doi.org/10.1186/2052-1847-5-25

Sandell, L. J. (2009). Obesity and osteoarthritis: Is leptin the link? *Arthritis and Rheumatism*, *60*(10), 2858–2860. https://doi.org/10.1002/art.24862

Sartori-Cintra, A. R., Aikawa, P., & Cintra, D. E. C. (2014). Obesity versus osteoarthritis: Beyond the mechanical overload. *Einstein (São Paulo)*, *12*(3), 374–379. https://doi.org/10.1590/s1679-45082014rb2912

Sasho, T., Akagi, R., Tahara, M., Katsuragi, J., Nakagawa, R., Enomoto, T., … Watanabe, A. (2017). Osteophyte formation on medial wall of the intercondylar notch of femur is an early sign of osteoarthritic knee development using osteoarthritis initiative data. *Osteoarthritis and Cartilage*, *25*(2017), S33. https://doi.org/10.1016/j.joca.2017.02.066

Scanzello, C. R., & Goldring, S. R. (2012). The role of synovitis in osteoarthritis pathogensis. *Bone*, *51*, 249–157. https://doi.org/10.1177/1759720X10378373

Scanzello, C. R., Umoh, E., Pessler, F., Diaz-Torne, C., Miles, T., DiCarlo, E., … Crow, M. K. (2009). Local cytokine profiles in knee osteoarthritis: elevated synovial fluid interleukin-15 differentiates early from end-stage disease. *Osteoarthritis and Cartilage*, *17*(8), 1040–1048. https://doi.org/10.1016/j.joca.2009.02.011

Scuderi, G. R. (2006). The basic principles. In G. R. Scuderi & A. J. Tria, Jr. (Eds.) *Knee Arthroplasty Handbook* (pp. 1-6). New York NY: Springer.

Sharma, A. R., Jagga, S., Lee, S. S., & Nam, J. S. (2013). Interplay between cartilage and subchondral bone contributing to pathogenesis of osteoarthritis. *International Journal of Molecular Sciences*, *14*(10), 19805–19830. https://doi.org/10.3390/ijms141019805

Shibakawa, A., Yudoh, K., Masuko-Hongo, K., Kato, T., Nishioka, K., & Nakamura, H. (2005). The role of subchondral bone resorption pits in osteoarthritis: MMP production by cells derived from bone marrow. *Osteoarthritis and Cartilage*, *13*(8), 679–687. https://doi.org/10.1016/j.joca.2005.04.010

Silverwood, V., Blagojevic-Bucknall, M., Jinks, C., Jordan, J. L., Protheroe, J., & Jordan, K. P. (2015). Current evidence on risk factors for knee osteoarthritis in older adults: A systematic

review and meta-analysis. *Osteoarthritis and Cartilage*, *23*(4), 507–515. https://doi.org/10.1016/j.joca.2014.11.019

Simon, D., Mascarenhas, R., Saltzman, B. M., Rollins, M., Bach, B. R., & MacDonald, P. (2015). The relationship between anterior cruciate ligament injury and osteoarthritis of the knee. *Advances in Orthopedics*, *2015*. https://doi.org/10.1155/2015/928301

Skousgaard, S. G., Hjelmborg, J., Skytthe, A., Brandt, L. P. A., Möller, S., & Overgaard, S. (2015). Probability and heritability estimates on primary osteoarthritis of the hip leading to total hip arthroplasty: A nationwide population based follow-up study in Danish twins. *Arthritis Research and Therapy*, *17*(1). https://doi.org/10.1186/s13075-015-0854-4

Skousgaard, S. G., Skytthe, A., Möller, S., Overgaard, S., & Brandt, L. P. A. (2016). Sex differences in risk and heritability estimates on primary knee osteoarthritis leading to total knee arthroplasty: A nationwide population based follow up study in Danish twins. *Arthritis Research and Therapy*, *18*(1). https://doi.org/10.1186/s13075-016-0939-8

Smith, M. D. (2011). The normal synovium. *The Open Rheumatology Journal*, *5*(1), 100–106. https://doi.org/10.2174/1874312901105010100

Sniekers, Y. H., Intema, F., Lafeber, F. P. J. G., Van Osch, G. J. V. M., Van Leeuwen, J. P. T. M., Weinans, H., & Mastbergen, S. C. (2008). A role for subchondral bone changes in the process of osteoarthritis; A micro-CT study of two canine models. *BMC Musculoskeletal Disorders*, *9*, 1–11. https://doi.org/10.1186/1471-2474-9-20

Sofat, N., Ejindu, V., & Kiely, P. (2011). What makes osteoarthritis painful? The evidence for local and central pain processing. *Rheumatology*, *50*(12), 2157–2165. https://doi.org/10.1093/rheumatology/ker283

Song, J., Lindquist, L. A., Chang, R. W., Semanik, P. A., Ehrlich-Jones, L. S., Lee, J., … Dunlop, D. D. (2015). Sedentary behavior as a risk factor for physical frailty independent of moderate activity: Results from the osteoarthritis initiative. *American Journal of Public Health*, *105*(7), 1439–1445. https://doi.org/10.2105/AJPH.2014.302540

Spector, T. D., Cicuttini, F., Baker, J., Loughlin, J., Hart, D., Bmj, S., … Hart, D. (1996). Genetic influences on osteoarthritis in women : A twin study. *BMJ: British Medical Journal*, *312*(7036), 940–944.

Srikanth, V. K., Fryer, J. L., Zhai, G., Winzenberg, T. M., Hosmer, D., & Jones, G. (2005). A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis and Cartilage*, *13*(9), 769–781. https://doi.org/10.1016/j.joca.2005.04.014

Stecher, R. M., & Hersh, A.H. (1944). Heberden's nodes: The mechanism of inheritance of hypertrophic arthritis of the fingers. *J Clin Invest*, *23*, 699–704.

Sulsky, S. I., Carlton, L., Bochmann, F., Ellegast, R., Glitsch, U., Hartmann, B., … Sun, Y. (2012). Epidemiological evidence for work load as a risk factor for osteoarthritis of the hip: A systematic review. *PLoS ONE*, *7*(2). https://doi.org/10.1371/journal.pone.0031521

Suri, S., Gill, S. E., De Camin, S. M., Wilson, D., McWilliams, D. F., & Walsh, D. A. (2007). Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. *Annals of the Rheumatic Diseases*, *66*(11), 1423–1428. https://doi.org/10.1136/ard.2006.063354

Suri, S., & Walsh, D. A. (2012). Osteochondral alterations in osteoarthritis. *Bone*, *51*(2), 204–211. https://doi.org/10.1016/j.bone.2011.10.010

Tan, A. L., Grainger, A. J., Tanner, S. F., Shelley, D. M., Pease, C., Emery, P., & McGonagle, D. (2005). High-resolution magnetic resonance imaging for the assessment of hand osteoarthritis. *Arthritis and Rheumatism*, *52*(8), 2355–2365. https://doi.org/10.1002/art.21210

Tanamas, S. K., Wluka, A. E., Pelletier, J., Martel-Pelletier, J., Abram, F., Wang, Y., & Cicuttini, F. M. (2010a). The association between subchondral bone cysts and tibial cartilage volume and risk of joint replacement in people with knee osteoarthritis : a longitudinal study. *Arthritis Research & Therapy*, *12*, R:58.

Tanamas, S. K., Wluka, A. E., Pelletier, J. P., Pelletier, J. M., Abram, F., Berry, P. A., … Cicuttini, F. M. (2010b). Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: A longitudinal study. *Rheumatology*, *49*(12), 2413–2419. https://doi.org/10.1093/rheumatology/keq286

Teichtahl, A. J., Wang, Y., Heritier, S., Wluka, A. E., Strauss, B. J., Proietto, J., … Cicuttini, F. M. (2016). The interaction between physical activity and amount of baseline knee cartilage. *Rheumatology*, *55*(7), 1277–1284. https://doi.org/10.1093/rheumatology/kew045

Teichtahl, A. J., Wang, Y., Wluka, A. E., & Cicuttini, F. M. (2008). Obesity and knee osteoarthritis: New insights provided by body composition studies. *Obesity*, *16*(2), 232–240. https://doi.org/10.1038/oby.2007.30

Teichtahl, A. J., Wluka, A. E., Proietto, J., & Cicuttini, F. M. (2005). Obesity and the female sex, risk factors for knee osteoarthritis that may be attributable to systemic or local leptin biosynthesis and its cellular effects. *Medical Hypotheses*, *65*(2), 312–315. https://doi.org/10.1016/j.mehy.2005.02.026

Thijssen, E., Van Caam, A., & Van Der Kraan, P. M. (2014). Obesity and osteoarthritis, more than just wear and tear: Pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. *Rheumatology (United Kingdom)*, *54*(4), 588–600. https://doi.org/10.1093/rheumatology/keu464

Thomas, A. C., Hubbard-Turner, T., Wikstrom, E. A., & Palmieri-Smith, R. M. (2017). Epidemiology of Posttraumatic Osteoarthritis. *Journal of Athletic Training*, *52*(6), 491–496. https://doi.org/10.4085/1062-6050-51.5.08

Thompson, M. C. (2015). *Preparing Skeletons for Research and Teaching from Preserved Human Specimens*. California State University, East Bay.

Tillman, M.D.; Bauer, J.A.; Cauraugh, J.H.; Trimble, M. H. (2005). Differences in lower extremity alignment between males and females: Potentail predisposing factors for knee injury. *Journal of Sports Medicine and Physical Fitness*, *45*(3), 355–359.

Tochigi, Y., Buckwalter, J. A., Martin, J. A., Hillis, S. L., Zhang, P., Vaseenon, T., … Brown, T. D. (2011). Distribution and progression of chondrocyte damage in a whole-organ model of human ankle intra-articular fracture. *Journal of Bone and Joint Surgery - Series A*, *93*(6), 533–539. https://doi.org/10.2106/JBJS.I.01777

Valderrabano, V., Hintermann, B., Horisberger, M., & Tak, S. F. (2006). Ligamentous posttraumatic ankle osteoarthritis. *American Journal of Sports Medicine*, *34*(4), 612–620. https://doi.org/10.1177/0363546505281813

van der Kraan, P. M., & van den Berg, W. B. (2007). Osteophytes: relevance and biology. *Osteoarthritis and Cartilage*, *15*(3), 237–244. https://doi.org/10.1016/j.joca.2006.11.006

Van Meer, B. L., Meuffels, D. E., Van Eijsden, W. A., Verhaar, J. A. N., Bierma-Zeinstra, S. M. A., & Reijman, M. (2015). Which determinants predict tibiofemoral and patellofemoral osteoarthritis after anterior cruciate ligament injury? A systematic review. *British Journal of Sports Medicine*, *49*(15), 975–983. https://doi.org/10.1136/bjsports-2013-093258

van Meurs, J. B. J. (2017). Osteoarthritis year in review 2016: genetics, genomics and epigenetics. *Osteoarthritis and Cartilage*, *25*(2), 181–189. https://doi.org/10.1016/j.joca.2016.11.011

Verweij, L. M., Van Schoor, N. M., Deeg, D. J. H., Dekker, J., & Visser, M. (2009). Physical activity and incident clinical knee osteoarthritis in older adults. *Arthritis Care and Research*, *61*(2), 152–157. https://doi.org/10.1002/art.24233

Visotsky, J. L., Basamania, C., Seebauer, L., Rockwood, C., & Jensen, K. (2004). Cuff tear arthropathy : Pathogenesis, classification , and algorithm for treatment pathomechanics. *Journal of Bone and Joint Surgery - Series A*, *86*(Supplement 2), 35–40.

Vuolteenaho, K., Koskinen, A., Moilanen, T., & Moilanen, E. (2012). Leptin levels are increased and its negative regulators, SOCS-3 and sOb-R are decreased in obese patients with osteoarthritis: A link between obesity and osteoarthritis. *Annals of the Rheumatic Diseases*, *71*(11), 1912–1913. https://doi.org/10.1136/annrheumdis-2011-201242

Waldron, T. (2008). *Paleopathology.* New York NY: Cambridge University Press.

Wallace, I. J., Worthington, S., Felson, D. T., Jurmain, R. D., Wren, K. T., Maijanen, H., …
Lieberman, D. E. (2017). Knee osteoarthritis has doubled in prevalence since the mid-20th
century. *Proceedings of the National Academy of Sciences of the United States of America*,
114(35), 9332–9336. https://doi.org/10.1073/pnas.1703856114

Wang, F., Ying, Z., Duan, X., Tan, H., Yang, B., Guo, L., … Yang, L. (2009).
Histomorphometric analysis of adult articular calcified cartilage zone. *Journal of Structural
Biology*, *168*(3), 359–365. https://doi.org/10.1016/j.jsb.2009.08.010

Weinans, H., Siebelt, M., Agricola, R., Botter, S. M., Piscaer, T. M., & Waarsing, J. H. (2012).
Pathophysiology of peri-articular bone changes in osteoarthritis. *Bone*, *51*(2), 190–196.
https://doi.org/10.1016/j.bone.2012.02.002

Wen, C., & Lohmander, L. S. (2014). Does post-injury ACL reconstruction prevent future OA?
Nature Reviews Rheumatology, *10*(10), 577–578. https://doi.org/10.1038/nrrheum.2014.120

Williams, C. J. (2007). The genetics of osteoarthritis. *Expert Review of Clinical Immunology*,
3(4), 503–516. https://doi.org/10.1586/1744666X.3.4.503

Willy, R. W., Manal, K. T., Witvrouw, E. E., & Davis, I. S. (2012). Are mechanics different
between male and female runners with patellofemoral pain? *Medicine and Science in Sports
and Exercise*, *44*(11), 2165–2171. https://doi.org/10.1249/MSS.0b013e3182629215

Wluka, A. E., Davis, S. R., Bailey, M., Stuckey, S. L., & Cicuttini, F. M. (2001). Users of
oestrogen replacement therapy have more knee cartilage than non-users. *Annals of the
Rheumatic Diseases*, *60*(4), 332–336. https://doi.org/10.1136/ard.60.4.332

Wluka, A. E., Teichtahl, A. J., Maulana, R., Liu, B. M., Wang, Y., Giles, G. G., … Cicuttini, F.
M. (2015). Bone marrow lesions can be subtyped into groups with different clinical
outcomes using two magnetic resonance imaging (MRI) sequences. *Arthritis Research and
Therapy*, *17*(270). https://doi.org/10.1186/s13075-015-0780-5

Woods, R. J. (1995). *Biomechanics and Osteoarthritis of the Knee*. Ohio State University.

Xu, L., Li, Z., Lei, L., Zhou, Y. Z., Deng, S. Y., He, Y. Bin, & Ni, G. X. (2016). Spatial and temporal changes of subchondral bone proceed to articular cartilage degeneration in rats subjected to knee immobilization. *Microscopy Research and Technique*, *79*(3), 209–218. https://doi.org/10.1002/jemt.22620

Yian, E. H., Gallo, L., Hughes, R. E., & Kuhn, J. E. (2001). The relationship between Parson's tubercle and the insertion of the anterior horn of the medial meniscus. *Arthroscopy*, *17*(7), 737–740. https://doi.org/10.1053/jars.2001.25252

Yusuf, E., Kortekaas, M. C., Watt, I., Huizinga, T. W. J., & Kloppenburg, M. (2011). Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? a systematic review. *Annals of the Rheumatic Diseases*, *70*(1), 60–67. https://doi.org/10.1136/ard.2010.131904

Zhang, Y., Nevitt, M., Niu, J., Lewis, C., Torner, J., Guermazi, A., … Felson, D. T. (2011). Fluctuation of knee pain and changes in bone marrow lesions, effusions, and synovitis on magnetic resonance imaging. *Arthritis and Rheumatism*, *63*(3), 691–699. https://doi.org/10.1002/art.30148

Zingman, A., Li, H., Sundem, L., DeHority, B., Geary, M., Fussel, T., … Elfar, J. (2017). Shoulder arthritis secondary to rotator cuff tear: A reproducible murine model and histopathologic scoring system. *Journal of Orthopaedic Research*, *35*(3), 506–514. https://doi.org/10.1002/jor.23383

APPENDIX A

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Approval

PRINCIPAL INVESTIGATOR Angela R Lieverse	DEPARTMENT Archaeology & Anthropology	Bio # 17-108

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
University of Saskatchewan
Saskatoon SK

STUDENT RESEARCHER(S)
Maryann Scott

FUNDER(S)
CANADIAN INSTITUTES OF HEALTH RESEARCH (CIHR)

TITLE
Protocol: The Pathophysiology of Osteoarthritis

| ORIGINAL REVIEW DATE
21-Apr-2017 | APPROVED ON
08-May-2017 | APPROVAL OF
Application for Biomedical Research Ethics Review,
rec'd 02-May-2017
Participant Information and Consent Form, rec'd 02-May-2017
Master List, rec'd 02-May-2017
Study Data List, rec'd 02-May-2017
Consent for Organ/Tissue Donation, rec'd 05-April-2017
McMaster Chart Review Tutorial, Certificate of Completion for
Maryann Scott, rec'd 05-April-2017
TCPS 2: CORE Certificate of Completion for Maryann Scott, rec'd
05-April-2017 | EXPIRY DATE
07-May-2018 |

Delegated Review ☒   Full Board Meeting ☐

IRB 1 Registration #00001471 ☐   IRB 2 Registration #00008358 ☐   Not Applicable ☒

CERTIFICATION
The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named research study. The study was found to be acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face) meeting. If a protocol has been reviewed at a full board meeting, a subsequent study of the same protocol may be reviewed through the delegated review process. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://research.usask.ca/for-researchers/ethics/index.php.

REB ATTESTATION
In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board is

Please send all correspondence to: Research Services and Ethics Office
Room 223 Thorvaldson Building
110 Science Place
Saskatoon SK Canada S7N 5C9

UNIVERSITY OF SASKATCHEWAN

Certificate of Approval
Study Amendment

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Angela R Lieverse	Archaeology & Anthropology	17-108

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
University of Saskatchewan
Saskatoon SK

STUDENT RESEARCHER(S)
Maryann Scott

FUNDER(S)
CANADIAN INSTITUTES OF HEALTH RESEARCH (CIHR)

TITLE
The Pathophysiology of Osteoarthritis

APPROVAL OF		APPROVED ON	CURRENT EXPIRY DATE
Revised Participant Information and Consent Form, rec'd 24-Oct-2017		25-Oct-2017	09-May-2018

Delegated Review ☒   Full Board Meeting ☐

IRB 1 Registration #00001473 ☐   IRB 2 Registration #00008358 ☐   Not Applicable ☒

CERTIFICATION
The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named research study. The study was found to be acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face) meeting. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval indicates the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://research.usask.ca/for-researchers/ethics/index.php.

REB ATTESTATION
In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part A of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board is constituted and operates in accordance with the current version of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2 2014)*

Ildiko Badea, Vice-Chair
University of Saskatchewan
Biomedical Research Ethics Board

UNIVERSITY OF SASKATCHEWAN

Certificate of Approval
Study Amendment

PRINCIPAL INVESTIGATOR	DEPARTMENT	REB #
Angela R Lieverse	Archaeology & Anthropology	17-108

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED-OUT
University of Saskatchewan
Saskatoon SK

STUDENT RESEARCHER(S)
Maryann Scott

FUNDER(S)
CANADIAN INSTITUTES OF HEALTH RESEARCH (CIHR)

TITLE
The Pathophysiology of Osteoarthritis

APPROVAL OF	APPROVED ON	CURRENT EXPIRY DATE
Revision of Source of Biological Materials	11-Apr-2018	07-May-2018

Delegated Review ☒   Full Board Meeting ☐

IRB 1 Registration #00001471 ☐   IRB 2 Registration #00008358 ☐   Not Applicable ☒

CERTIFICATION
The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named research study. The study was found to be acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face) meeting. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://research.usask.ca/for-researchers/ethics/index.php.

REB ATTESTATION
In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board is constituted and operates in accordance with the current version of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS 2 2014).

Ildiko Badea, Vice-Chair
Biomedical Research Ethics Board
University of Saskatchewan

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Saskatoon SK Canada S7N 4J8

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Re-Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Angela R Lieverse	Archaeology & Anthropology	27-108

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
University of Saskatchewan
Saskatoon SK

STUDENT RESEARCHER(S)
Maryana Scott

FUNDER(S)
CANADIAN INSTITUTES OF HEALTH RESEARCH (CIHR)

TITLE
: The Pathophysiology of Osteoarthritis

RE-APPROVED ON	EXPIRY DATE
19-Apr-2018	17-Apr-2019

Delegated Review ☒   Full Board Meeting ☐

IRB 1 Registration #00001471 ☐   IRB 2 Registration #00008358 ☐   Not Applicable ☒

CERTIFICATION

The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named research study. The study was found to be acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change in the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL

The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face) meeting. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit https://research.usask.ca/researchers/ethics1.php.

REB ATTESTATION

In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board is constituted and operates in accordance with the current version of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS 2 2014).

Gordon McKay, PhD., Chair
Biomedical Research Ethics Board
University of Saskatchewan

Please send all correspondence to: Research Services and Ethics Office
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APPENDIX B

PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: The Pathophysiology of Osteoarthritis

PRINCIPAL INVESTIGATOR: Dr. Angela Lieverse

STUDENT RESEARCHER: Maryann Scott

COMMITTEE MEMBERS: Dr. William Dust, Dr. Ernie Walker, Dr. David Cooper

SPONSOR: Department of Archaeology and Anthropology, University of Saskatchewan

CONTACT PHONE NUMBER: 306 (955-5484) or maryann.scott@usask.ca

INTRODUCTION:
You are invited to take part in this research because you will be undergoing knee replacement surgery due to osteoarthritis. This surgery results in the removal of bone and tissue that would usually be discarded.

We are asking for your permission to use the bone and tissue that will be removed for this research study. Your participation is voluntary. It is up to you to decide whether or not you wish to take part. If you wish to participate, you will be asked to sign this form. If you do decide to take part in this study, you are still free to withdraw at any time and without giving any reasons for your decision.

If you do not wish to participate, you will not lose the benefit of any medical care to which you are entitled or are presently receiving. It will not affect your relationship with your orthopaedic surgeon, Dr. Dust, or the researchers.

Please take time to read the following information carefully. You can ask the researcher to explain any words or information that you do not clearly understand. You may ask as many questions as you need. Please feel free to discuss this with your family, friends or family physician before you decide.

WHO IS CONDUCTING THE STUDY?
This study is being conducted by the student researcher as part of a Master of Arts thesis in the Department of Archaeology and Anthropology. The researcher, supervisory committee members, and participants will not receive any financial compensation.

WHO CAN PARTICIPATE IN THE STUDY?
Anyone who is undergoing knee replacement surgery due to osteoarthritis can participate. People who are undergoing knee replacement surgery for other reasons, or have bone diseases besides or in addition to osteoarthritis are not eligible to participate.

WHY IS THIS STUDY BEING DONE?
This study is being done to learn more about osteoarthritis. The fact that people with osteoarthritis experience pain as part of the condition is well known, but thus far, clinical research has not discovered what causes this pain. Osteoarthritis is an old disease; archaeologists who study ancient diseases are able to see evidence of osteoarthritis on the dry bones of people who lived thousands of years ago. This study will look at the evidence of osteoarthritis on the bones of modern people who are experiencing osteoarthritis pain, in order to see if there are any common bone lesions which may be related to pain. There is also evidence that males and females experience osteoarthritis differently; the study will also see if there are sex differences in the bone evidence.

WHAT DOES THE STUDY INVOLVE?
The bone and tissue removed during knee replacement surgery is usually discarded. The research involves collecting only these discarded tissues. There will be no change to your knee replacement surgery or your postoperative care due to your involvement in this study.

The study will involve examining the condition of the cartilage remaining on the removed bone, then removing soft tissue to leave only dry bone. This bone will then be examined for lesions related to osteoarthritis; these will be counted and categorized. Imaging techniques such as X-ray or CT scans may be carried out on the bone.

Your pre-operative X-ray reports will also be examined as part of the study, in order to compare the evidence of osteoarthritis seen on the X-rays with the bone evidence. If you have undergone other imaging tests, such as CT or MRI, these reports will be examined as well. Before these reports are passed on to the student researcher, Dr. Dust or your orthopaedic surgeon will remove all identifying information except your age and sex. The report will be assigned a number, which will also be assigned to the removed bone. Only Dr. Dust will have information linking your personal information to the X-ray report and bone numbers. This information will be kept separate from your medical records.

It is possible that your bone sample may be useful for future instructional and/or teaching related purposes. We would like to ask your permission to have your sample stored indefinitely and used for this purpose after this research project has concluded. This is optional and you may choose, at the end of this consent form, whether or not you would like your samples used for this purpose. If you do not want your bone sample used for teaching purposes, it will be returned to Dr. Dust's office for destruction after the study has been completed.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?
If you choose to participate in this study, there are no direct benefits to you. It is hoped the information gained from this study will give more information on the causes of pain in osteoarthritis, and benefit individuals with the condition in the future. The study results may also help archaeologists better understand the experiences of past people who had osteoarthritis.

WHAT HAPPENS IF I DECIDE TO WITHDRAW?

Your participation in this research is voluntary. You may withdraw from this study at any time. You do not have to provide a reason. There will be no penalty or loss of benefits if you choose to withdraw. Your future medical care will not be affected.

Should you choose to withdraw from the study, your bone sample will be returned to Dr. Dust's office for destruction. Your X-ray or other imaging reports will be erased from the researcher's files. Depending upon the progress of the study, the data gathered from your sample may have already been aggregated and therefore no longer identifiable or able to be removed.

WILL MY PARTICIPATION BE KEPT CONFIDENTIAL?
In Saskatchewan, the *Health Information Protection Act (HIPA)* defines how the privacy of your personal health information must be maintained so that your privacy will be respected.

Your name will not be used in the study records. Your samples, X-ray reports, and the study records will be identified by a number only. They will be kept for 5 years in a secure area in the Department of Archaeology and Anthropology at the University of Saskatchewan. Tissue samples and results of the study without your name or other information that could identify you will be combined with information from other participants for analysis. Your participation, the results and the consent form, which will be kept separate from the results, will be kept in a secure file **apart from your medical records.** If the results of this study are presented in a meeting, or published, your identity will not be disclosed. Indeed, the researchers will not know your identity.

No information that discloses your identity will be released or published without your specific consent. Some authorities have a duty to check your study records to make sure all the information is correct. Your study records may be inspected in the presence of the investigator or his/her qualified designate by representatives of University of Saskatchewan Research Ethics Board for the purpose of monitoring the research. However, no records, which identify you by name or initials, will be allowed to leave Dr. Dust's office.

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?
If you have any questions or desire further information about this study before or during participation, you can contact Maryann Scott at (306) 955-5484 or Dr. Angela Lieverse at (306) 966-7097.

If you have any concerns about your rights as a research participant and/or your experiences while participating in this study, contact the Chair of the University of Saskatchewan Research Ethics Board, at 306-966-2975 (out of town calls: 1-888-966-2975). The Research Ethics Board is a group of individuals (scientists, physicians, ethicists, lawyers and members of the community) that provide an independent review of human research studies. This study has been reviewed and approved on ethical grounds by the University of Saskatchewan Research Ethics Board.

CONSENT TO PARTICIPATE

- I have read the information in this consent form.
- I understand the purpose and procedures and the possible risks and benefits of the study.
- I was given sufficient time to think about it.
- I had the opportunity to ask questions and have received satisfactory answers.

- I am free to withdraw from this study at any time for any reason and the decision to stop taking part will not affect my future medical care.
- I have been informed there is no guarantee that this study will provide any benefits to me.
- I understand that by signing this document I do not waive any of my legal rights.
- I will be given a signed and dated copy of this consent form.
- I give permission for the use and disclosure of my de-identified personal health information collected for the research purposes described in this form.
- I give permission for the access of my identifiable personal health information for the research purposes described in this form.

OPTIONAL: It is possible that any remaining portions of the bone tissue sample may be useful in future teaching related activities. My identity will always remain entirely unknown to the instructor and students. I agree that my bone sample can be used for any future teaching, without contacting me again. By not agreeing, any remaining bone tissues will be destroyed when they are no longer needed for this project's purposes. (please tick one of the following options)

Agree ☐ Disagree ☐

Name of Participant

Name of person obtaining consent

Signature of Participant

Signature of person obtaining consent

Date

Date