ERRATA

p 92 para 2, last sentence: “aim of our study was” for “aim of our study is”

ADDENDUM

p (vii) point 2: the year of publication is 2010

p 41 line 4: the year of publication is 2010

p 91 line 15: delete “ROA” and insert “radiographic OA (ROA)”

p 92 lines 5, 9 and 12: delete “(ref)” and insert reference for “March LM, Bagga H. Epidemiology of osteoarthritis in Australia. Med J Aust. 2004 Mar 1;180(5 Suppl):S6-10.”

p 99 line 4: delete “pound” and insert “~0.5 kg”

p 100, last sentence: delete “which subsequently also reduces or eliminates the need for revision surgery”

p 101: add reference “March LM, Bagga H. Epidemiology of osteoarthritis in Australia. Med J Aust. 2004 Mar 1;180(5 Suppl):S6-10.”

NOVEL APPROACHES TO MUSCULOSKELETAL DISEASE

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Abstract

Osteoarthritis (OA) is the most common musculoskeletal disease, affecting not only articular cartilage but also the subchondral bone and surrounding soft tissues. OA affects ~8% of the Australian population. It is a major cause of disability and poor quality of life. Importantly, there is currently no cure for OA.

Radiography has long been considered the gold standard for measuring OA. However, the use of magnetic resonance imaging (MRI) is increasingly common, given its non-invasive nature, ability to directly visualise articular cartilage *in vivo,* and lack of exposure to radiation. MRI has enabled the study of OA along the disease continuum, from its asymptomatic stages through to established and end-stage disease.

A number of the risk factors that influence OA as well as the underlying pathogenesis of disease are still unclear. Thus this thesis aims to contribute to current knowledge by examining novel relationships in musculoskeletal disease. This thesis includes community-based populations as well as osteoarthritic populations to allow examination of structural changes not only in the presence of disease but also before disease development or at early stages of disease.

Papers 1 and 2 examined the relationship between bone marrow lesions (BMLs) and subchondral bone cysts, and how they influence progression of disease in tibiofemoral OA. BMLs and cysts were found to commonly co-exist, with 98% of participants who had a cyst also having a BML. Importantly, those with both

a BML and cyst had worse structural outcomes than those with a BML only, or those with neither BML nor cyst.

Paper 3 examined the patellofemoral compartment to determine how patellofemoral geometry is associated with knee pain and patella cartilage volume. A more medially inclined patella was associated with reduced pain and increased medial patella cartilage volume. On the other hand, a higher riding patella was associated with detrimental effects on medial patella cartilage.

Paper 4 aimed to better understand the role of obesity in musculoskeletal disease. Gaining ≥ 5% of body weight over ~2 years was associated with incident knee symptoms (pain, stiffness and functional difficulties) compared to remaining stable in weight, whilst losing ≥ 5% of body weight was associated with improved knee symptoms. Similar effects were seen in relation to knee structure, whereby those who gained weight had increased cartilage loss whilst those who lost weight had reduced cartilage loss.

Paper 5 examined the role of obesity in the foot, and describes the differential contributions of different components of body composition. Whilst fat mass was positively associated with foot pain, there was no association between muscle mass and foot pain. Moreover, a gynoid fat distribution was favourable over an android distribution as gynoid fat was associated with reduced foot pain.

Taken together, this thesis attempted to fill some of the gaps in the literature in relation to some more novel risk factors and their relationship with

musculoskeletal disease. Further research is still required to build on the findings in this thesis, with the potential to contribute to the development of more effective prevention strategies.

Publications arising from thesis

1. **Tanamas SK**, Wluka AE, Pelletier JP, Pelletier JM, Abram F, Berry PA, Wang Y, Jones G, Cicuttini FM. Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: a longitudinal study. Rheumatology (Oxford). 2010 Dec; 49(12):2413-9. (IF 4.171)
2. **Tanamas SK**, Wluka AE, Pelletier JP, Martel-Pelletier J, Abram F, Wang Y, Cicuttini FM. 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. Mar 31; 12(2):R58. (IF 4.36)
3. **Tanamas SK**, Teichtahl AJ, Wluka AE, Wang Y, Davies-Tuck M, Urquhart DM, Jones G, Cicuttini FM. The associations between indices of patellofemoral geometry and knee pain and patella cartilage volume: a cross-sectional study. BMC Musculoskeletal Disorders. 2010; 11:87. (IF 1.94)
4. **Tanamas SK**, Wluka AE, Berry P, Menz HB, Strauss BJ, Davies-Tuck M, Proietto J, Dixon JB, Jones G, Cicuttini FM. Relationship between obesity and foot pain and its association with fat mass, fat distribution and muscle mass. Arthritis Care & Research. 2012 Feb; 64(2):262-8. (IF 4.749)
5. **Tanamas SK,** Wluka AE, Davies-Tuck M, Wang Y, Strauss BJ, Proietto J, Dixon JB, Jones G, Forbes A, Cicuttini FM. Weight gain is associated with incident knee pain, stiffness and functional difficulties: a longitudinal study. (Accepted for publication by Arthritis Care & Research, IF 4.749)

Publications not directly related to thesis

1. **Tanamas SK,** Wijethilake P, Wluka AE, Davies-Tuck ML, Urquhart DM, Wang Y, Cicuttini FM. Sex hormones and structural changes in osteoarthritis: a systematic review. Maturitas. 2011; 69(2):141-56 (IF 2.286).
2. **Tanamas SK**, Wluka AE, Jones G, Cicuttini FM. Imaging of knee osteoarthritis. (Report). Therapy. 2010; 7(6):635(13).
3. Cicuttini FM, Wluka AE, Urquhart D, **Tanamas SK**, Wang Y. Epidemiology should not be forgotten in osteoarthritis imaging. Osteoarthritis & Cartilage. 2011; 19(9):1165-6 (IF 3.953)

First and foremost I would like to thank my PhD supervisors, Professor Flavia Cicuttini and Dr Anita Wluka for their guidance and support throughout my candidature. Their dedication and hard work has been a great inspiration, and I am very privileged to have had the opportunity to work with such outstanding researchers.

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On a personal note, I would like to thank my parents for their love and guidance, and for all the sacrifices they have made to provide me with the very best opportunities in life. They have inspired me to become the best that I can be and to follow my dreams. I would like to thank my friends for always believing in me. Finally I would like to thank Luke Bartholomew for standing by me with continuous encouragement and unwavering support.

Thank you.

Declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma, except where due reference is made in the text of the thesis.

To the best of my knowledge, this thesis contains no material previously published or written by another person except where due reference is made in the text of the thesis.

Signed

Dated

Monash University

Declaration for thesis based or partially based on conjointly published or unpublished work

General Declaration

In accordance with Monash University Doctorate Regulation 17/ Doctor of Philosophy and Master of Philosophy (MPhil) regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 4 original papers published in peer reviewed journals and 1 unpublished publication. The core theme of the thesis is novel risk factors for musculoskeletal disease. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the School of Public Health and Preventive Medicine under the supervision of Professor Flavia Cicuttini and Dr Anita Wluka.

In the case of chapters 2, 3, 4 and 5 my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
2	Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: a longitudinal study.	Published	Data analysis and interpretation, and manuscript development and preparation
2	The association between subchondral bone cysts and tibial cartilage volume and risk of joint replacement in people with knee osteoarthritis: a longitudinal study.	Published	Data analysis and interpretation, and manuscript development and preparation
3	The associations between indices of patellofemoral geometry and knee pain and patella cartilage volume: a cross-sectional study.	Published	Data collection, data management, data analysis and interpretation, and manuscript development and preparation
4	Weight gain is associated with incident knee pain, stiffness and functional difficulties: a longitudinal study.	Accepted	Data collection, data management, data analysis and interpretation, and manuscript development and preparation
5	Relationship between obesity and foot pain and its association with fat mass, fat distribution and muscle mass.	Published	Subject recruitment, data collection, data management, data analysis, and manuscript development and preparation

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed:

Date:

Chapter 1. Introduction

1.1 Organisation of Thesis

This is a thesis by publication and is organised as follows:

Chapter 1 is the literature review which provides the background relevant to this thesis as well as the aims

Chapters 2-5 present the publications that comprise the main findings of this thesis

Chapter 6 is an overview of the findings in this thesis

Chapter 7 presents the main conclusions of this thesis

1.2 What Is Osteoarthritis?

1.2.1 Definition

Osteoarthritis (OA) is a degenerative condition that is hallmarked by cartilage loss, but is also known to affect the underlying bone and surrounding soft tissues such as tendons, ligaments and muscles. The most widely used definition for OA is that by the American College of Rheumatology (ACR), which states that OA is "a heterogeneous group of conditions that lead to joint symptoms and signs, which are associated with defective integrity of articular cartilage in addition to related changes in the underlying bone margins" (1).

1.2.2 Prevalence

Osteoarthritis is the most common musculoskeletal disease, representing a significant burden to society. The National Health Survey 2007-08 reported approximately 7.8% of Australians living with the disease (2). The prevalence increases with age and is more common in females (33.5%) than in males (21.9%). Compounded with the fact that there is currently no treatment for OA, the prevalence of OA will only continue to rise, fuelled by the increase in life expectancy and the aging of society as well as the obesity epidemic. The proportion of OA that is attributable to obesity is between 8% in China to 50% in the United States, depending on its prevalence in the population (3). Between the years 2000 to 2025, the number of normal weight adults is estimated to decrease from 40.6% to 28.1% and number of obese adults to increase from 20.5% to 33.9%, such that if current trends continue, normal weight adults will

constitute less than a third of the population by 2025 (4). Taken together, this would have a significant impact on the prevalence and incidence of OA.

1.2.3 Burden of Disease

Osteoarthritis is a major cause of disability, psychological distress and poor quality of life. In 2007-08, there were 86,000 hospitalisations with OA as the principal diagnosis, 26% of which involved total knee replacements (5). More than 50,000 knee and hip joint replacements are performed in Australia annually and OA is the most common reason for these (6). Individuals with arthritis experience a lower quality of life when compared to those without arthritis (7). Psychological distress is reportedly much higher in individuals with OA compared to those without the disease (8). OA contributes to more functional limitations, such as dependency in walking and stair climbing, than any other disease (9).

Moreover, despite being considered a chronic, non-fatal condition, the mortality rate for OA has increased from 4.3 per 100,000 population in 1998 to 4.6 per 100,000 population in 2007 (10). Although the association between OA and mortality, independent of age and other confounding factors, has been demonstrated by several studies (11-13), it is acknowledged that OA itself is not likely to be the direct cause of death but rather it is the side-effects of OA medication (10) and surgical procedures for OA that may increase the risk of death (14). Functional limitations associated with OA, such as decreased mobility and physical activity, may further increase the risk of obesity and

cardiovascular diseases, which may also subsequently increase the risk of death (15).

In 2004-05, health expenditure for arthritis and musculoskeletal conditions was the fourth largest at $4.0 billion, of which $1.2 billion (31%) was due to OA alone (5). At $898 million, admitted patient services in hospitals represented the biggest component of this expenditure. In the public sector, total hip and knee replacement procedures cost an average of $14,000 to $29,500 each in 2004-05, which increased to $15,500 to $31,900 in 2006-07 (5).

1.3 Clinical Features of Osteoarthritis

1.3.1 Signs and Symptoms

The signs and symptoms of OA are heterogeneous, with pain as one of the primary symptoms (16). The pain is usually intermittent and is worst during and after weight-bearing activities. It is commonly the first symptom of OA which prompts a visit to the doctor (17). Other symptoms of OA include tenderness and stiffness of the affected joints (6). These symptoms may develop gradually over many years, and may contribute to a range of clinical signs which include altered gait patterns as the patient attempts to protect the painful joint, instability due to ligament laxity or deficiency (18, 19), and joint swelling due to synovitis, synovial effusion, or abnormal bony enlargement. Movement in the affected joints may also be limited and deformities may occur, such as Heberden's nodes in the interphalangeal joints of the hand (18). Another sign of OA is 'crepitus',

thought to arise from the rolling of uneven surfaces across each other and is experienced as a grinding, crackling or crunching sensation (18).

1.3.2 Diagnosis

According to the ACR diagnostic criteria for OA, both radiological and other visible evidence of OA (such as joint swelling), as well as patient-reported symptom is required to make a diagnosis (18, 20). Radiographic evidence of OA includes joint space narrowing (JSN), where the distance between two articulating surfaces is decreased as a result of cartilage loss (21). JSN can progress until there is no longer any space between the two surfaces. Other radiographic features of OA are osteophytes (bony spurs that occur on the surface of subchondral bone (22)), subchondral bone cysts and subchondral sclerosis.

1.3.3 Treatment

There is currently no cure for OA and treatments are predominantly aimed at symptom alleviation. In the early stages of disease, treatment is usually focused on the reduction of pain and stiffness, and on the maintenance and improvement of functional abilities. Eventually as the disease progresses, the goal is to improve quality of life either via non-pharmacological, pharmacological (medication), or surgical means (17). Non-pharmacological methods include exercise (23, 24), weight reduction (25, 26), braces (27), insoles (28), and acupuncture (29). Commonly used medications include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDS), glucosamine and opioids (30), though these may

cause side effects ranging from patient discomfort to morbidity and mortality (31). Once the disease reaches end-stage, surgery can become the only option, though joint replacement surgeries are usually only considered as a last resort when all other treatments have been proven ineffective. Nevertheless, joint replacements may greatly improve quality of life for the patient and restore joint function (30).

1.4 Methods of Imaging Used in Osteoarthritis

1.4.1 Radiography

Radiography is currently considered the gold standard for measuring OA. Its advantages include simplicity, low cost, and clear visualisation of bony features within the joint, such as osteophytes and subchondral sclerosis. Several grading systems for OA assessment have been developed using radiographic features. The two most widely employed systems are the Kellgren-Lawrence (K-L) grading scheme and the Osteoarthritis Research Society International (OARSI) grading system (32, 33). The K-L grading system was developed in 1957 and was the first standardised scoring system for radiographic knee OA that was available. It is commonly used in epidemiological studies and clinical trials to classify participants as having OA (K-L grade $\geq$2) or no OA (K-L grade <2). The OARSI system is also used to grade osteophytes and joint-space, and is commonly used in epidemiological studies and clinical trials.

Radiography has played a great role in furthering our understanding of risk factors for OA. For example, one study found an increased risk of radiographic

OA in persons over the age of 60 (34), whilst another found that rate of incident OA was increased by ~2% annually, particularly in females (35). A female sibling study found a genetic contribution to the risk of radiographic OA in the hand and knee, with an estimated 39% to 65% of OA attributable to genetic factors, independent of known environmental or demographic confounders (36). Obesity has also been associated with both the development and progression of radiographic OA (34, 37, 38).

1.4.1.1 Limitations of Radiography

Despite its advantages, radiography remains greatly limited by its inability to directly visualise soft tissues within the joint. Consequently, assessment of the joint space (joint space width (JSW) or JSN) is used as a surrogate measure of cartilage. JSN can be measured manually with the use of callipers or a simple graded ruler and a micrometric eye piece, or it can be measured with the use of computer software (39). Unfortunately, the use of JSN as an indicator of cartilage loss may be problematic given the presence of structures other than articular cartilage in the joint space. These may result in apparent increases in JSN that, for example, could be a result of meniscal extrusion rather than loss of cartilage itself (40, 41).

There are also reliability issues with using JSN as its measure requires the observer to determine the narrowest point, which is highly observer dependent and can result in large inter-observer variations (42). The measure of JSW is also affected by the alignment and positioning of the knee with respect to the x-ray

and source of radiation (21, 43, 44). Even slight variations in joint flexion or x-ray beam alignment can lead to great variations in the size of the joint space (43).

Furthermore, evidence suggests that radiography is insensitive to structural changes and once radiographic changes are detected significant disease is usually already present. It was found that knees with grade 1 JSN have lost ~11% to 13% of cartilage (45), and that bone marrow lesions (BMLs), meniscal extrusion and tibiofemoral cartilage defects were prevalent in 14%, 4% and up to 62% respectively of subjects without radiographic OA (46-49). This likely relates to the fact that radiographic grading systems predominantly employ ordinal measures which have only a limited number of categories (50). These measures can therefore be crude and insensitive to change, given that small changes to individual structures may not necessarily translate into a change in grade. Consistently, recent findings from the Multicentre Osteoarthritis Study (MOST) demonstrated that in participants with risk factors for OA but without any radiographic structural damage, magnetic resonance imaging (MRI)-detected cartilage lesions, osteophytes, BMLs, and subchondral cysts were common (51).

1.4.2 Magnetic Resonance Imaging

MRI provides excellent tissue contrast and anatomical resolution, allowing *in vivo* visualisation of a joint. Its major advantage over radiography lies in its ability to directly visualise articular cartilage. Other advantages include lack of exposure to radiation which makes it ideal for research studies, as well as its three-dimensional nature of imaging which means that it does not suffer from the reproducibility issues related to repositioning as found with radiography (50).

Although more expensive than radiography, MRI has enabled studies to examine changes to joint structure from early/pre-OA through to established disease. Standard MRI techniques, such as fat-saturated, T1-weighted, spoiled gradient echo sequences and T2-weighted, proton density-weighted fast-spin echo sequences have been used to directly examine changes to knee structure (52). These include examinations of cartilage volume, cartilage defects, subchondral bone changes and meniscal lesions.

A recent systematic review of the diagnostic performance of MRI in identifying early and advanced OA (53) reported that whilst there was a significant range in sensitivities (26% to 96%), specificities (50% to 100%) and accuracies (49% to 94%), the majority of the high level of evidence studies reported sensitivities over 80%, specificities over 90% and accuracies over 85%. This is supported by the findings of another systematic review which demonstrated that structural change in OA can be measured reliably using both quantitative and semi-quantitative measures, and with good responsiveness on MRI (54). As such, given the exposure to radiation and poor utility of radiography in identifying early structural changes, MRI may offer a more superior diagnostic tool for identifying early structural damage, particularly as imaging technology continues to improve (53). Indeed MRI is now recommended by the OARSI working group for clinical trials that involve the assessment of cartilage morphology (55).

1.4.2.1 Limitations of MRI

MRI remains limited by its long imaging time, the need of expert input to adequately utilise the technology (particularly in choosing pulse sequences), the

need to be aware of artefacts during image interpretations, and the potential contraindication to MRI in some patients, such as the presence of a pacemaker and pregnancy (56).

1.5 Knee Osteoarthritis

Osteoarthritis can affect both weight bearing joint (such as the hips, knee, and the first metatarsophalangeal joint) and non-weight bearing joints (such as the interphalangeal joints and the shoulder). However, the knee is the most commonly affected joint in OA. The knee joint consists of three separate compartments: two compartments in the tibiofemoral joint (medial and lateral tibiofemoral compartments) and one in the patellofemoral joint (patellofemoral compartment).

Although it is common for OA to co-exist in both the tibiofemoral and patellofemoral compartments (57, 58), it is possible for the compartments to be affected independently. In a middle-aged population with knee pain, 40% of subjects reportedly had combined tibiofemoral and patellofemoral OA, whilst 24% and 4% had isolated patellofemoral and tibiofemoral OA respectively (57). Despite commonly existing together, the disease pattern can differ between tibiofemoral and patellofemoral OA in that they do not necessarily share common risk factors. Furthermore, tibiofemoral disease is more common in the medial compartment while patellofemoral disease is more common in the lateral compartment (59-61). This is not surprising given that the two joints differ in both structure and function. The tibiofemoral joint is formed by the articulation of the femoral and tibial condyles. It is a hinged joint, which allows knee flexion

and extension, as well as inward and outward rotation of the tibia when the knee is in the flexed position. The patellofemoral joint is formed by the articulation of the posterior surface of the patella along the anterior surface of the femoral condyle heads. It is a saddle joint which allows superior and inferior glide of the patella associated with knee extension and flexion.

Of note, OA was traditionally thought to be a disease of the tibiofemoral compartment, which may at least in part explain why a large body of work related to knee OA has been done in relation to the tibiofemoral compartment. Earlier assessment of OA was also done using anteroposterior x-ray views (35, 62), which restricted assessment to the tibiofemoral compartment. However more recently the incorporation of skyline and lateral x-ray views has enabled the study of the involvement of the patellofemoral compartment (63, 64).

1.6 Risk Factors for Knee Osteoarthritis

There are many risk factors that have been shown to be associated with the incidence and prevalence of OA. Evidence suggests that factors that influence the development and progression of disease may differ given the different processes involved. For example, studies of OA progression in different communities have shown that whilst the disease may remain stable for many years in some patients, it can progress very quickly in others (35, 65-68). Whilst there are many more risk factors for OA, for the purposes of this thesis I will only discuss those that are relevant to the work presented in this thesis. Briefly, other risk factors for OA include ethnicity (69), genetics (36), trauma (70), meniscal pathology (71), occupation (72), muscle weakness (73), hormonal

status, bone density (74) and nutritional factors (75). Some of these have been discussed in the following papers, which have been included in the appendices:

***Tanamas SK**, Wluka AE, Jones G, Cicuttini FM. Imaging of knee osteoarthritis. (Report). Therapy. 2010;7(6):635(13).*

***Tanamas SK,** Wijethilake P, Wluka AE, Davies-Tuck ML, Urquhart DM, Wang Y, Cicuttini FM. Sex hormones and structural changes in osteoarthritis: a systematic review. Maturitas. 2011; 69(2):141-56.*

1.6.1 Age

Although OA can affect a person at any age, it is more common in older adults. The average age of onset for OA is around 45 years, however there is suggestion that osteoarthritic changes to the joint begin from the age of 30 and continue to rise (76). Age has been correlated with both the incidence and progression of OA (34, 35). It is estimated that around 80% of the population over the age of 65 years has some radiographic evidence of OA (77).

How age is related to increased risk of OA is unclear, though it has been suggested that the aging cartilage may be more susceptible to fatigue fractures (78). Increased subchondral stiffness or neuromuscular changes associated with aging may also play a role (78, 79).

1.6.2 Gender

It is well known that the prevalence, incidence and severity of OA differ between men and women (80, 81). Knee, hip and hand OA are more common in women than men, and further increases around the time of menopause (81, 82). This prompted many to consider the role of hormones in the progression and development of OA. It was found that 87% of women aged between 55 and 64 years had radiographic OA, compared to only 83% of men (83). Furthermore, OA is reportedly more widespread in women, affecting more than 4 joints in 47% of women compared to only 27% of men (83).

1.6.3 Physical Activity

One of the non-pharmacologic treatment methods recommended for OA is physical activity (84), which is aimed at improving pain and disability associated with the disease. Although physical activity has been shown to produce symptomatic benefits in OA patients (85), the evidence on its association with structural benefits is rather conflicting. Earlier radiographic studies have found adverse (86, 87) or no effect (88, 89) of physical activity on risk of OA. Notably these studies often did not exclude those with previous knee injury (86, 87), a known risk factor for OA (70), and despite adjusting for knee injury in the statistical analyses, residual confounding may have remained as those who exercise more vigorously are at greater risk of injury.

Moreover, radiography is a less sensitive measure which may have missed the potential benefits of physical activity on joint structure that have subsequently been demonstrated by MRI studies: increased cartilage volume and reduced

prevalence of cartilage defects with vigorous exercise (90), reduced prevalence of BMLs in those who walk regularly (90), and reduced cartilage loss associated with greater muscle strength and fitness endurance (90, 91). This is further supported by a recent systematic review of 22 studies which concluded that current evidence suggests that physical activity may be beneficial rather than detrimental to joint health (92).

1.6.4 Biomechanical Factors

1.6.4.1 Tibiofemoral Alignment

The medial compartment of the knee generally bears 60-80% of the compressive load that passes through the joint (93). However, tibiofemoral malalignment can affect this load distribution such that a 4-6% increase in tibiofemoral angle in the varus direction may increase the loading in the medial compartment by up to 20% (94). A varus-load bearing axis passes though the medial compartment while a valgus-load bearing axis passes through the lateral compartment (94).

Radiographic studies have shown a relationship between tibiofemoral alignment and JSN and JSW (95-97). MRI studies have further demonstrated a relationship between tibiofemoral alignment and cartilage defects (98), subarticular bone oedema, meniscal tear and subluxation, bone attrition, and cartilage morphology (99), as well as cartilage loss in the femoral and tibial compartments (100, 101). With the majority of studies examining the prevalence or progression of OA, the association between tibiofemoral alignment and the development of OA has received less attention. To our best knowledge, only one study has examined this

relationship, reporting an increased risk of incident OA over ~6.6 years in subjects with varus or valgus knees (95).

Tibiofemoral alignment has also been shown to influence joint forces within the patellofemoral compartment (59, 60). A radiographic study of subjects with patellofemoral OA reported that 57% of subjects with lateral patellofemoral OA had valgus malalignment compared to only 24% of subjects with medial patellofemoral OA (60). Varus malalignment was associated with increased odds of medial patellofemoral OA progression whilst valgus malalignment was associated with increased odds for lateral patellofemoral OA progression (60).

Whether malalignment of the knee predicts disease or is simply a marker of disease is still unclear. It is possible that malalignment as a result of genetic, environmental and/or traumatic factors predispose the knee to degenerative changes. Nevertheless the effect of malalignment appears most significant once OA is present.

1.6.4.2 Patellofemoral Geometry

Patella malalignment is a translational or rotational deviation of the patella relative to any axis, which can cause an aberrant dispersion of patellofemoral joint reaction force, subsequently resulting in pain and/or structural progression (102-104). For example, patella alta or patella baja are conditions where the patella lies too far proximally or distally relative to the trochlea, respectively. Patella alta is often associated with patellofemoral instability and pain, which is thought to be due to the reduced osseous stability provided by the femur (105-

107) given that a high-riding patella articulates with the shallower portions of the proximal trochlear groove (106-108). Patella baja may occur after trauma or surgery to the knee, particularly after the harvesting of a patellar tendon autograft, which leads to the progressive shortening of the patellar tendon (109, 110). Patella baja has also been associated with deleterious effects in the knee (110).

The patella may also have an excessive lateral tilt, which can cause maltracking of the patella. Merchant and Mercer in California (111) and Ficat and colleagues in France (112) were among the first to propose that a patella that is tilted with the lateral side down would lead to excessive pressures in the lateral patellofemoral compartment. This was subsequently supported by CT scan evidence demonstrating hyper-pressure on the subchondral bone of the lateral patella in subjects who had a lateral patella tilt (113). Another condition affecting patellofemoral geometry is where the femoral sulcus in which the patella sits is too shallow, which is commonly associated with patellofemoral instability and thus thought to predispose to patellofemoral subluxation (114, 115). Nevertheless, although these parameters of patellofemoral geometry have been associated with aberrant biomechanics in the knee, how they may relate to knee pain and structure is not well understood.

1.6.5 Obesity

Obesity has long been recognised as a risk factor for OA, with the one of the first studies to show an association dating back to 1945 (116). Now obesity is considered one of the most important risk factors for OA, with its epidemic

contributing to the rising numbers of OA cases. In 2008, 24.5% of OA in Australia was attributable to obesity, compared to 14% in 2006 (117).

Evidence from the first National Health and Nutrition Examination Survey (NHANES) showed that in subjects with a BMI >27 kg/m^2, for each subsequent unit increase in BMI the risk for knee OA is increased by approximately 15% (69). The Framingham Study found that for every 5 kg/m^2 increase in BMI at baseline, the risk for incident knee OA is increased by 60% over 7-10 years (118), while a decrease in BMI of 2 kg/m^2 or more over 10 years decreased the odds for the development of knee OA by over 50% in women (119). A recent systematic review, which identified 36 studies that have examined BMI in relation to OA development between 1996 and 2008, reported that overweight and obesity are risk factors for incident OA in older adults (120). Another systematic review that examined BMI in relation to OA progression up to the year 2010 found that BMI was a strong predictor for long term OA progression (>3 years) (121).

Data from 2001 suggests that ~11% of OA cases could potentially be eliminated if all overweight and obese individuals reduced their weight by 2 kg or until their BMI is within the recommended normal range (18.5 – 24.9 kg/m^2) (122). Furthermore, almost 24% of OA cases may be eliminated if all overweight and obese individuals reduced their weight by 5 kg or until their BMI is within the normal range, increasing to as much as 57% if all overweight and obese individuals reduce their weight until their BMI is within the normal range (122). Taken together, it is clear that obesity plays a great role in musculoskeletal

disease, and continued research to improve our understanding of how obesity influences the disease and how it can be managed is of great importance.

1.6.5.1 Body Composition

A major disadvantage of using BMI as an indicator for obesity is that BMI measurements do not provide information on the independent contributions of fat and lean mass to the total body mass. Given the evidence that obesity affects non-weight bearing joints such as the hand (123, 124), and that different parameters of body composition have differing effects on the joints (125-129), this indicates that it is important to assess body composition as well as the more traditional measures of obesity such as weight and BMI. For example, a study of 235 Japanese women reported that lower but not upper or total lean body mass was significantly less in people with knee OA compared to normal controls (125), while other studies have demonstrated beneficial effects of increased muscle mass for protection against OA development (126) and loss of tibial cartilage (127, 128). In contrast, fat mass has been shown to adversely affect the risk of OA, whereby higher fat mass increased the risk for tibial cartilage defects (128) and was associated with greater loss of patella cartilage volume (129) in healthy adults.

1.7 Knee Structural Changes Assessed Using MRI

The use of MRI in studies of OA is becoming increasingly common, given its ability to identify structural changes prior to the presence of radiographic disease as well as its sensitivity to change. MRI is able to directly visualise the whole

joint *in vivo,* including articular cartilage, the menisci, the synovium and subchondral bone abnormalities such as BMLs and subchondral bone cysts. The use of MRI in studies has enhanced the understanding of relationships between both traditional and novel risk factors for OA, and how they influence changes in knee structure from early/pre-OA through to established disease.

The use of imaging technologies in knee OA has been presented in detail in the following paper:

***Tanamas SK**, Wluka AE, Jones G, Cicuttini FM. Imaging of knee osteoarthritis. (Report). Therapy. 2010;7(6):635(13).*

This paper has been included in the appendices at the end of this thesis. However the relevant issues are discussed in the following sections.

1.7.1 MRI to Assess Changes in the Tibiofemoral Joint

1.7.1.1 Cartilage Volume

Loss of cartilage volume occurs with natural aging at a rate of ~0.3-0.5% per year (130). In OA, loss of cartilage is accelerated, being a multi-factorial phenomenon which may precede, accompany and/or result from other structural changes. Loss of cartilage in OA results from an imbalance in cartilage turnover in favour of cartilage breakdown. Individuals with knee OA lose up to 5% of cartilage volume annually, and around 60% of cartilage is lost by the time knee joint replacement is indicated (61). Cartilage volume and cartilage loss have

previously been shown to be associated with knee symptoms (pain, stiffness and function) (131, 132). Of note, it is not clear how cartilage loss and knee pain are related, given that articular cartilage is not innervated by nociceptors and therefore cannot be a direct source of pain (133). The loss of cartilage generally follows a normal distribution, with an initial apparent increase in volume caused by cartilage swelling, followed by cartilage loss.

1.7.1.1.1 Factors Associated with Loss of Cartilage Volume

Age

As the body ages, the imbalance between cartilage synthesis and cartilage degradation results in a net loss of cartilage. Cartilage repair is further affected, leading to loss of cartilage elasticity and increased susceptibility to damage (8). The aging process may also allow for the cumulative effect of exposure to environmental factors that may subsequently accelerate the loss of cartilage.

Although it is generally accepted that aging is associated with loss of cartilage, the evidence to support this is rather conflicting. Cross-sectional findings indicate that knee cartilage is generally thinner in older subjects compared to younger subjects (130, 134) though no association with cartilage volume was reported (134). Increased age was also associated with reduced medial and lateral tibial and patella cartilage volume in men without knee OA (135). Longitudinally, in a predominantly non-osteoarthritic population, cartilage volume was lost at a faster rate with increasing age (136), while in a symptomatic population age predicted cartilage loss in the lateral compartment over 2 years (137). Several

other longitudinal studies have examined the relationship but failed to show an association between aging and rate of loss of cartilage (138, 139).

Gender

MRI findings show that men have more articular cartilage than women (140-142) and that women lose cartilage at a higher rate than men (136, 143). A community-based study of asymptomatic adults found that women lost tibial cartilage at a rate 4 times faster than men and patella cartilage at a rate 3 times faster over a period of ~2 years (143). This gender difference may be attributable to several factors, including hormones, differences in body size (144), differences in joint biomechanics (145), and differences in structural and morphometric properties of tendons and ligaments (146-149).

Obesity

BMI is the most commonly used measure to assess obesity (BMI $\geq$30 kg/m^2 defined as obese), and studies have generally found a consistent relationship between BMI and cartilage loss. A study of participants with knee OA noted 3 clear subgroups within their cohort of those with a fast, intermediate and low rate of loss of global cartilage volume, demonstrating a higher baseline BMI for those in the fast subgroup (mean $\pm$ SD 32.6 $\pm$ 2.7 kg/m^2) compared to those in the intermediate (mean $\pm$ SD 31.0 $\pm$ 4.3 kg/m^2) and slow (mean $\pm$ SD 29.6 $\pm$ 4.3 kg/m^2) subgroups (131). Similar findings were reported by other studies which correlated BMI with cartilage loss over 24 months (150) and over 30 months (151).

1.7.1.2 Bone Marrow Lesions

Bone marrow lesions, also known as bone marrow oedema, were first reported in 1988 (152) and are the most common subchondral bone abnormality described in OA. BMLs are visualised on MRI as areas of subchondral bone that appear bright (hypersignals). They are a feature of numerous physiological and disease states, and are heterogeneous in origin. Traumatic BMLs are those that arise from contusions, fractures, spontaneous osteonecrosis of the knee and overuse, and histologically represent trabecular fracture, oedema, osteocyte necrosis and bleeding in the fatty marrow (153, 154). Non-traumatic BMLs are those which occur in a group of disorders, including OA, or following a surgical procedure (155). It is thought that the role played by BMLs in OA may involve the reduction in strength of the bony foundation of articular cartilage or by impairing the supply of nutrients and oxygen to the overlying cartilage plate (156-158).

The relationship between BMLs and knee pain has been well documented (159-161). In subjects with radiographic knee OA, there is evidence for a greater prevalence of BMLs in those with knee pain compared to those without (162). Incident and enlarging BMLs have also been shown to predict the development (161, 163) and progression of knee pain (163). A recent systematic review concluded that there is moderate evidence for an association between BMLs and knee pain in OA (164). The presence and size of BMLs have further been associated with greater cartilage loss (150, 165-167), which may in part be mediated by knee malalignment (165, 166).

1.7.1.2.1 Risk Factors for Bone Marrow Lesions

One of the earliest descriptions of BMLs was in the context of anterior cruciate ligament injury (168, 169) and thus BMLs were often been described following knee trauma (170-173). Tibiofemoral alignment may also influence the risk of BMLs. Amongst elderly participants with knee OA, varus malalignment, particularly marked ones (≥7° varus), was associated with a higher prevalence of BMLs in the medial compartment (74.3%) compared to those with valgus or neutral knee alignments (16.4%) (165). However valgus or neutral alignment was associated with a higher prevalence of BMLs in the lateral compartment (29.5%) when compared to varus alignment (8.6%). Furthermore, there is evidence that increasing body weight was associated with BMLs in clinically healthy asymptomatic middle-aged women (47). Additional factors that are thought to influence BMLs include osteo-protective medications (174) and nutritional factors (49, 175).

1.7.1.3 Subchondral Bone Cysts

Subchondral bone cysts, another bone abnormality associated with OA, are visualised on MRI as well-demarcated hypersignals in contrast to the ill-defined hypersignals that identify BMLs. They are commonly found where the overlying cartilage has been eroded (176) and are present in ~50% of individuals with OA and in 13.6% of asymptomatic individuals (177). Of note, subchondral bone cysts have received less interest than BMLs in OA research, with a recent systematic review concluding that based on only 2 high-quality studies, there is no evidence for an association between subchondral cysts and knee pain in OA

(164). Consequently, the risk factors for subchondral bone cysts are yet to be revealed.

1.7.1.4 Osteophytes

Osteophytes are bony outgrowths that are considered as the earliest radiographic sign of OA. They are often seen prior to JSN (178) and are a primary component of the radiographic grading systems for OA. However, more recently it has been shown that the assessment of osteophytes on MRI may be favourable, given the tomographic viewing perspective of MRI which can delineate osteophytes with greater reproducibility than radiography, and the ability of MRI to detect osteophytes in locations that would otherwise be obscured by projectional superimposition when using radiography (179). Osteophytes are a component of several MRI-based scoring systems for OA, including the Whole-Organ Magnetic Resonance Imaging Score (WORMS) (179), the Boston-Leeds Osteoarthritis Knee Score (BLOKS) (180) and the Knee Osteoarthritis Scoring System (KOSS) (181).

In a small cohort of 19 participants with knee OA, osteophytes were one of the most prevalent structural abnormalities, affecting 92% of the population (179). Osteophytes have also been identified in populations that are asymptomatic (177) or at early stages of disease (182). There is some evidence to suggest that osteophytes may be associated with knee pain (164).

1.7.2 MRI to Assess Changes in the Patellofemoral Joint

1.7.2.1 Patella Cartilage Volume

In middle-aged populations with no clinical knee OA, patella cartilage volume is lost at a rate of 1.6-2.1% per year (183, 184). However in OA, the rate of patella cartilage loss is accelerated to 4.5% per year (185). Interestingly, although tibiofemoral and patellofemoral OA commonly co-exist, the risk factors for cartilage loss in the two compartments are not always the same, and no correlation has been found between patella cartilage loss and tibial cartilage loss (185).

1.7.2.1.1 Risk Factors for Patella Cartilage Loss

Cross-sectionally older age has been associated with reduced patella cartilage volume (186), while longitudinally aging was associated with an increased rate of patella cartilage volume loss (183). Gender has also been shown to have an effect as patellofemoral OA has been shown to be more common and more severe in women than men (187, 188), and women lose patella cartilage at a faster rate than men (189). Furthermore, BMI, weight and fat mass are all positively associated with increased patella cartilage loss, particularly in women (129).

Interestingly, tibiofemoral alignment has been shown to be a risk factor for patella cartilage loss. Varus malalignment at baseline was associated with the radiographic progression of medial patellofemoral OA whilst valgus malalignment was associated with the progression of lateral patellofemoral OA (60). Another study found that change in tibiofemoral alignment was associated

with change in patella cartilage volume in osteoarthritic subjects, where for every 1° change in tibiofemoral alignment in the valgus direction, there was a 23.4 mm^3 annual reduction in patella cartilage volume (190).

Being a former or current smoker was also associated with greater annual loss of medial patella cartilage, with a dose-response relationship between the number of pack-years smoked and medial patella cartilage volume loss (191). In contrast, evidence suggests that physical activity is potentially protective against patella cartilage loss (183, 192).

1.8 Combining Radiographic and MRI-based Studies to Examine Risk Factors

It is important to note that studies examining risk factors for OA that use MRI and radiographic outcomes can provide complementary data. Based on this idea, I performed a systematic review that included both radiography and MRI-based studies to examine the relationship between sex hormones and structural changes of OA at the knee.

The following paper has been included in the appendices at the end of this thesis.

Tanamas SK, *Wijethilake P, Wluka AE, Davies-Tuck ML, Urquhart DM, Wang Y, Cicuttini FM. Sex hormones and structural changes in osteoarthritis: a systematic review. Maturitas. 2011; 69(2):141-56.*

This study highlights the complementary data that can be obtained using the different outcome assessments for OA. It also highlights the strengths of MRI in studies of early OA.

1.9 Knee Joint Replacement

As previously mentioned, surgical treatments for OA are generally considered as a last measure when other treatment options have been unsuccessful. These surgical treatments include arthrodesis, excision, osteotomy and joint replacement. Joint replacement of the hip and knee are considered the gold standard of surgical treatment for OA and their success rates continue to increase. Joint replacements are considered safe and cost-effective for the management of end-stage OA. Nonetheless, up to 20% of patients are unhappy with the outcome (193) and around 5% of patients with 'successful' total knee replacements report worse pain following surgery (194).

1.9.1 Structural Changes on MRI Associated with Joint Replacement

In subjects with symptomatic knee OA, a higher cartilage defect score was associated with a 6-fold increased risk of knee joint replacement over 4 years [28], and for every 1% increase in rate of cartilage loss over 2 years, the risk of knee joint replacement was increased by as much as 20% [91]. Research relating to risk factors for knee joint replacement is scarce. However since rate of cartilage loss is associated with risk of joint replacement (61) and one of the primary indicators for joint replacement surgery is end-stage disease with exposed bone in at least one compartment of the knee, then it could be

hypothesised that risk factors for loss of cartilage may also be risk factors for joint replacement which could therefore represent potential therapeutic targets to prevent or delay the progression of OA to the point of end-stage disease. It is important to note that prosthetic survival is currently around 90% at 15 years (195). Therefore delaying the need for a knee joint replacement will also delay the subsequent need for revision surgery, which is not only costly but also produces poorer outcomes (196).

1.10 Foot Pain and Disability Related to Foot Pain

While the knee is the most commonly affected joint in OA, musculoskeletal disorders also affect other joint in the body. For example, foot pain is a problem which affects up to 42% of adults over the age of 65 (197-199). However despite its prevalence, in the area of musculoskeletal research foot pain and disability related to foot pain has received relatively little attention.

Foot disorders are predominantly diagnosed by physical examination. However the identification of the source of foot pain is often complicated by the vast array of joints, tendons and ligaments in the feet (200). Foot pain may affect the heel, midfoot or forefoot, and may be associated with conditions such as diabetes, OA and rheumatoid arthritis (200). One of the earliest tools for assessing foot pain and function was the Foot Function Index developed in 1991 (201). Subsequently, the American Orthopaedic Foot and Ankle Society developed a foot rating score system in 1994 (202). More recently, several other tools have been developed, including the Manchester Foot Pain and Disability Index (203-205).

1.11 Risk Factors for Foot Pain

It is thought that a significant proportion of foot problems can be attributed to inappropriate foot wear, given that the problem rarely affects populations that do not wear shoes (206, 207). By comparison, 80% of women aged between 20-60 years reported foot pain while wearing shoes, 76% had at least one foot deformity and 88% wore shoes that were too small for their feet (208). The female gender is also associated with greater foot problems, as females are 9 times more likely than males to have various foot problems (209).

Associations between obesity and foot pain have been reported in both adolescents and adults (210-212), with a higher prevalence of foot pain in obese older adults compared to their normal weight and overweight counterparts (212). The feet are involved not only in bearing body weight but also in ambulation. Therefore they have developed unique structures that help to protect against the high ground reaction forces that are generated during ambulation. These include fat pads, which provide cushioning and shock absorption. Obesity may affect these structures, with reports of changes to the plantar fat pad and increased plantar pressure in obese individuals, along with other biomechanical alternations such as changes to gait (213). Nevertheless, biomechanical changes as a result of obesity likely explains only part of the association between obesity and foot pain, with the other part attributable to systemic changes that accompany the increase in adiposity.

1.12 Aims of this Thesis

This thesis aims to fill certain gaps in the literature by examining a range of novel relationships in musculoskeletal disease. There are two main focuses of this thesis:

1. To explore the significance of different structural abnormalities at the tibiofemoral and patellofemoral joint, how they may influence knee pain, cartilage volume, and risk of knee joint replacement
2. To determine the effect of obesity on musculoskeletal disease, particularly in relation to the knee joint, but also to examine the role it plays in the less well-studied joints such as the foot.

Chapter 2: The Role of Bone Abnormalities in Tibiofemoral Osteoarthritis

Traditionally, OA has been considered a disease that revolves predominantly around cartilage loss. However more recent knowledge that other structures in the knee are also affected by the disease has prompted an interest in, amongst others, what could be considered 'bone abnormalities'. This chapter will examine different types of bone abnormalities in relation to tibiofemoral OA.

2.1 Bone Marrow Lesions

Perhaps the most well researched of the bone abnormalities are BMLs, which have been found in both pre-clinical and established OA (46, 162). In established disease, BMLs are associated with knee pain (162, 214), radiographic progression of OA (165) and loss of articular cartilage (166, 167). Nevertheless, whether BMLs also influence knee joint replacement, the clinical end-point of OA, had not been conclusively shown.

Two previous studies had indicated a likelihood that BMLs are related to knee joint replacement. One small cross-sectional study found that 7 out of 9 patients undergoing total knee replacement had subchondral MR signal abnormalities (215) while another study of a highly selected patient population reported an increased risk of knee replacements in those with BMLs (216). Notably these studies were small and no adjustment for potential confounders was made. Thus the first paper in this chapter aimed to determine the effect of BMLs on structural

change as measured by change in cartilage volume and risk of knee joint replacement.

***Tanamas SK**, Wluka AE, Pelletier JP, Pelletier JM, Abram F, Berry PA, Wang Y, Jones G, Cicuttini FM. Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: a longitudinal study. Rheumatology (Oxford). 2010 Dec;49(12):2413-9. (IF 4.17)*

This study found that subjects with knee OA who have more severe BMLs at baseline had less baseline tibial cartilage and greater tibial cartilage loss over 2 years. They also had increased odds for knee joint replacement over 4 years, with an increase of 57% for every unit increase in BML severity. Whilst the majority of the BMLs in the study population remained stable or progressed, there were also a number that regressed. It may be that BMLs represent therapeutic targets to prevent OA progression and the subsequent need for knee joint replacement.

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Original article

Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: a longitudinal study

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Abstract

Objectives. The presence of bone marrow lesions (BMLs) has been linked to pain and progression of knee OA. The aim of this study was to determine the relationship between BMLs and longitudinal change in tibial cartilage volume and risk of knee joint replacement in subjects with knee OA.

Methods. One hundred and nine men and women with symptomatic knee OA were recruited. The same knee was imaged using MRI at baseline and ~2 years later. Tibial cartilage volume and BMLs were measured. Knee joint replacement over 4 years was determined.

Results. The mean age of the subjects at baseline was 63.2 (S.D. 10.3) years. BMLs were present in 66% of the subjects. Cross-sectionally, BMLs were negatively associated with both medial (regression coefficient −121.4; 95% CI −183.8, −859.1; $P < 0.001$) and lateral (regression coefficient −142.1; 95% CI −241.8, −42.4; $P = 0.01$) tibial cartilage volume data. Longitudinally, for every 1-score increase in baseline BML severity (range 0–4), the annual total tibial cartilage loss was increased by 1.14% (95% CI 0.29%, 1.87%; $P = 0.01$). The risk of knee joint replacement over 4 years increased with increasing BML score (odds ratio 1.57; 95% CI 1.04, 2.35; $P = 0.03$).

Conclusion. The prevalence and severity of BMLs are associated with less tibial cartilage volume and greater cartilage loss over 2 years. Moreover, severity of BMLs was positively associated with risk of knee joint replacement over 4 years. This provides further support for the importance of BMLs in identifying those with OA most likely to progress. Identifying factors that prevent or reduce the severity of BMLs may provide an important target in the prevention of disease progression and treatment of OA, and the subsequent need for arthroplasty.

Key words: Bone marrow lesions, Tibial cartilage, Cartilage loss, Knee joint replacement, Osteoarthritis.

Introduction

While cartilage loss is the hallmark of OA, the disease is also known to affect the surrounding tissues and subchondral bone. Areas of subchondral bone that appear bright on MRI are commonly observed in both established OA and pre-clinical OA [1, 2] and have been termed as bone marrow lesions (BMLs). Although it is not possible to histologically investigate BMLs in patients with early OA, studies correlating the MRI findings with histology in severe OA have shown that regions of BMLs exhibit bone marrow necrosis, trabecular abnormalities, bone marrow fibrosis and bone marrow oedema [3]. In a dog model of OA, BMLs were found to undergo histological changes over time [4]. BMLs may originally correspond to an acute inflammatory response, oedema, contusion and/or necrosis, which over time are replaced by more permanent bone marrow remodelling such as fibrosis and myxomatous connective tissue [5].

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There is increasing evidence that BMLs play an important role in the pathogenesis of knee OA. In established OA, BMLs are associated with knee pain [1, 6], radiological progression of knee OA [7] and cartilage loss on MRI [8, 9]. Enlargement of BMLs is strongly associated with increased cartilage loss [8] and reduction of the extent of BMLs is associated with a decrease in cartilage loss [10]. Whether BMLs predict clinically important outcomes such as joint replacement is unknown. In a recent study of 65 subjects with knee OA, those with BMLs were found to have an increased risk of knee replacement [11]. However, in this study, subjects were highly selected as they were drawn from over 4000 clinically indicated MRIs in patients with OA, where only those having two MRIs over 3 years were included. The aim of the current study was to examine the relationship between BMLs and both longitudinal change in tibial cartilage volume as determined by MRI and risk of knee joint replacement in subjects with knee OA.

Patients and methods

Study population

Subjects with knee OA were recruited by advertising through local newspapers and the Victorian branch of the AF of Australia and in collaboration with general practitioners, rheumatologists and orthopaedic surgeons. The study was approved by the ethics committee of the Alfred and Caulfield Hospitals in Melbourne, Australia. All subjects gave informed written consent.

One hundred and thirty-two subjects entered the study. Inclusion criteria were: age over 40 years; knee symptoms (at least one pain dimension of WOMAC [12] score >20% and osteophytes present); and radiographic knee OA (ACR radiographic criteria [13]). Subjects were excluded: if any other form of arthritis was present; contraindication to MRI (e.g. pacemaker, cerebral aneurysm clip, cochlear implant, presence of shrapnel in strategic locations, metal in the eye and claustrophobia); inability to walk 50 feet without the use of assistive devices; hemiparesis of either lower limb; or planned total knee replacement.

Anthropometric and clinical data

Weight was measured to ~0.1 kg (shoes and bulky clothing removed) using a single pair of electronic scales. Height was measured to ~0.1 cm (shoes removed) using a stadiometer. BMI [weight/height^2 (kg/m^2)] was calculated. Pain, function and stiffness were assessed by WOMAC [Visual Analogue Scale (VAS), 10 cm] [12].

Radiograph

Each subject had a weight-bearing antero-posterior tibiofemoral radiograph, taken in full extension, at baseline and follow-up, of the symptomatic knee. Where both knees had OA and were symptomatic, the knee with least severe radiographic OA was used. These were independently scored by two trained observers who used a published atlas to classify disease in the tibiofemoral joint according to the Kellgren and Lawrence (K–L) scale.

Tibiofemoral alignment was measured by a single observer, as previously described [14]. Lines were drawn through the middle of the femoral shaft and through the middle of the tibial shaft. The angle subtended by the lines on the medial side was measured using Osiris software. The intra-observer variability was 0.98 [14].

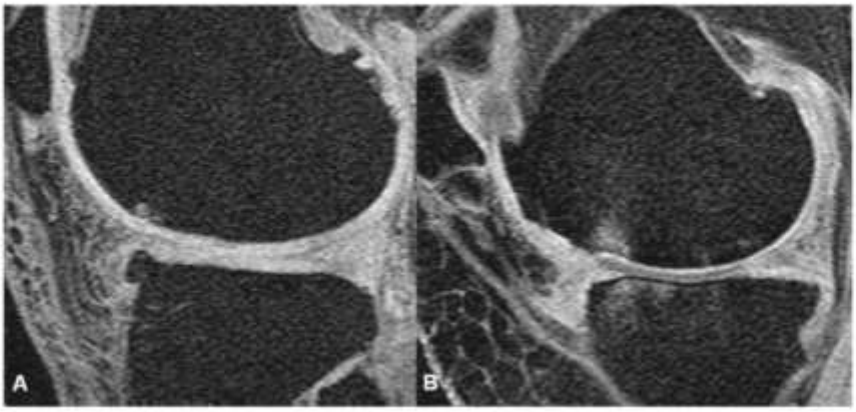
MRI

Each subject had an MRI performed on the symptomatic knee at baseline and ~2 years later [mean (S.D.) 1.95 (0.22)]. Knees were imaged in the sagittal plane on the same 1.5-T whole-body magnetic resonance unit (Signa Advantage HiSpeed GE Medical Systems Milwaukee, WI) using a commercial receive-only extremity coil. The following sequence and parameters were used: a T1-weighted fat-suppressed 3D gradient recall acquisition in the steady state; flip angle 55°; repetition time 58 ms; echo time 12 ms; field of view 16 cm; 60 partitions; 512 × 192 matrix; one acquisition time 11 min 56 s. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 × 0.83 mm (512 × 192 pixels).

Knee cartilage volume was determined by means of image processing on an independent work station using the software program Osiris (University of Geneva, Switzerland) as previously described [15, 16]. Two trained observers read each MRI. Each subject's baseline and follow-up MRI scans were scored unpaired and blinded to subject identification and timing of MRI. Their results were compared. If the results were within ±20%, an average of the results was used. If they were outside this range, the measurements were repeated until the independent measures were within ±20%, and the averages used. Repeat measurements were blinded to the results of the comparison of the previous results. The coefficients of variation for the measurement were 3.4% for the medial, 2.0% for the lateral and 2.6% for the total tibial cartilage volume [16].

A BML was defined as an ill-defined hypersignal (Fig. 1), in contrast to a well-marginated hypersignal that was defined as a cyst. The assessment of BMLs was performed on the MRI slice that yields the greatest BML size. The maximum size was measured in millimetres using software cursors applied to the greatest diameter of each lesion. This was repeated for each lesion throughout all knee subsections. BMLs were assessed in the medial and lateral tibiofemoral compartments and were graded as: 0 = absence of lesion, 1 = mild to moderate lesion and 2 = severe (large) lesion. The intra- and inter-reader correlation coefficient ranged from 0.88 to 0.93 and the κ-statistics from 0.78 to 0.87 [9]. For our analyses, the medial and lateral tibiofemoral BML scores were each calculated as a sum of the scores for the tibial, femoral and femoral posterior sites (scores 0–6). Due to the low number of subjects with scores >4 (3.7% in the medial and 0.9% in the lateral compartment), scores ⩾4 were combined to score 4, to give a final range of 0–4. Similarly, the total tibiofemoral BML score was calculated as a sum of the medial and lateral tibiofemoral scores

FIG. 1 (A) Grade 1 lateral femoral BML; (B) Grade 2 medial tibial and femoral BMLs.



(range 0–12), which was then collapsed into a score of 0–4.

Tibial plateaux area was determined by creating an isotropic volume from the three input images closest to the knee joint which were reformatted in the axial plane. The area was directly measured from these images. The coefficients of variation for the medial and lateral tibial plateau area were 2.3 and 2.4%, respectively [15, 16].

Identification of knee replacement

At Year 4, all subjects were contacted and asked whether they had undergone a knee replacement due to OA of the same knee in which they had baseline MRI. This was confirmed by contacting the treating physician in all cases.

Statistical analysis

Descriptive statistics for characteristics of the subjects were tabulated. Annual percentage change in cartilage volume was calculated by cartilage change (follow-up cartilage volume subtracted from initial cartilage volume) divided by initial cartilage volume and time between MRIs. Outcome variables (baseline tibial cartilage volume and annual percentage change in tibial cartilage volume) were initially assessed for normality, and were found to approximate normal distribution. Linear regression was used to explore the cross-sectional relationship between BMLs and tibial cartilage volume at baseline, and longitudinally, the relationship between baseline BMLs and annual percentage tibial cartilage volume loss. Logistic regression was used to examine the relationship between baseline BMLs and risk of knee joint replacement over 4 years. All analyses were performed using the SPSS statistical package (version 15.0.0; SPSS, Cary, NC) with $P < 0.05$ considered to be statistically significant.

Results

The characteristics of the study population are presented in Table 1. Of the 132 subjects who took part in our study, 23 did not have an MRI from which BMLs could be assessed (MRI not available or image unclear). The 109 subjects analysed had a mean age of 63.2 (S.D. 10.3) years, and a mean BMI of 29.3 (S.D. 5.1) kg/m^2, which was not significantly different from the original population. Seventy-eight (75.0%) subjects had K–L grade $\geqslant 2$ and 72 (66%) had BMLs at baseline. When compared with those without BMLs at baseline, subjects with BMLs were older (P for difference = 0.03), and less likely to be female (P for chi-square = 0.04) (Table 1). Those with BMLs also had higher baseline and follow-up WOMAC scores (Table 1). Eighty-eight (81%) subjects completed the follow-up; 21 (19%) subjects were lost to follow-up for reasons including knee surgery, severe illness, loss of interest, death and unclear MRI images from which BMLs could not be assessed. When compared with those who completed the follow-up, those who did not had a higher mean BMI (P for difference = 0.05).

In cross-sectional analyses examining the association between BMLs and tibial cartilage volume, there was a significant reduction in baseline medial, lateral and total tibial cartilage volume with increasing severity of baseline BMLs after adjusting for age, gender, BMI and bone area. After adjusting for tibiofemoral alignment, significance persisted in the association between BMLs and total and medial tibial cartilage volumes, but not lateral tibial cartilage volume (Table 2). In longitudinal analyses, baseline BMLs were significantly associated with annual percentage loss of total tibial cartilage volume. Significance persisted after adjusting for tibiofemoral alignment (Table 3). When the compartments were analysed separately, there was a significant relationship between increasing severity of BMLs and tibial cartilage loss in the medial compartment but not the lateral compartment.

Increasing severity of BMLs at baseline was associated with a 57% increased risk (95% CI 4, 135; $P = 0.03$) of having a knee joint replacement over 4 years when adjusted for age, gender and K–L grade (Table 4). This association persisted after further adjusting for baseline

Table 1 Characteristics comparison between subjects with and without BMLs

Characteristics	BMLs present ($n = 72$)	No. of BMLs ($n = 37$)	*P* for difference
Age, years	64.8 (10.2)	60.3 (9.8)	0.03*
Female, *n* (%)	32 (44.4)	24 (64.9)	0.04**
Height, cm	168.7 (9.2)	167.6 (8.5)	0.55*
Weight, kg	83.7 (14.9)	81.7 (16.3)	0.53*
BMI, kg/m^2	29.4 (5.0)	29.1 (5.6)	0.77*
Baseline WOMAC score			
Pain	17.3 (8.2)	14.1 (8.6)	0.06*
Stiffness	21.7 (10.8)	17.3 (11.5)	0.05*
Function	19.5 (9.8)	15.5 (10.0)	0.05*
WOMAC score at follow-up			
Pain	14.4 (10.4)	10.0 (9.5)	0.03*
Stiffness	15.9 (11.3)	12.8 (11.4)	0.18*
Function	15.7 (11.1)	11.2 (10.2)	0.04*
K–L grade, *n* (%)			
Grade 1	18 (26.1)	8 (22.9)	0.74**
Grade 2	28 (40.6)	17 (48.6)	
Grade 3	23 (33.3)	10 (28.6)	
Tibiofemoral alignment, degrees	180.3 (6.4)	180.6 (4.3)	0.78*
Baseline medial tibial cartilage volume, mm^3	1795 (496)	1789 (456)	0.95*
Medial tibial cartilage volume at follow-up, mm^3	1396 (646)	1579 (482)	0.13*
Baseline lateral tibial cartilage volume, mm^3	1960 (625)	2114 (499)	0.20*
Lateral tibial cartilage volume at follow-up, mm^3	1697 (548)	1869 (449)	0.11*
Baseline total tibial cartilage volume, mm^3	3755 (929)	3903 (871)	0.42*
Total tibial cartilage volume at follow-up, mm^3	3268 (841)	3492 (797)	0.20*
Knee joint replacement over 4 years, *n* (%)	13 (20.6)	3 (8.8)	0.14**

Values are presented as mean (s.d.) unless otherwise stated. *P* for difference calculated using *independent samples *t*-test or **chi-squared test.

Table 2 Relationship between BMLs and tibial cartilage volume (mm^3) at baseline

Tibial cartilage volume (mm^3)	Univariate regression coefficient (95% CI)	*P*-value	Multivariate regression coefficient (95% CI)[a]	*P*-value	Multivariate regression coefficient (95% CI)[b]	*P*-value
Total cartilage	−63.9 (−186.6, 58.9)	0.31	−175.5 (−280.9, −70.2)	0.001	−156.0 (−262.7, 49.4)	0.01
Medial cartilage	−32.2 (−100.1, 35.7)	0.35[c]	−121.4 (−183.8, −59.1)	<0.001[c]	−81.0 (−148.4, −13.7)	0.02[c]
Lateral cartilage	−206.0 (−313.1, −99.0)	<0.001[d]	−142.1 (−241.8, −42.4)	0.01[d]	−75.0 (−183.6, 33.7)	0.17[d]

[a]Adjusted for age, gender, BMI and tibial plateau bone area. [b]Adjusted for age, gender, BMI, tibial plateau bone area and tibiofemoral alignment. [c]Association with BMLs in medial compartment. [d]Association with BMLs in lateral compartment.

tibial cartilage volume ($P = 0.04$) and a trend towards a positive association when adjusted for annual percentage tibial cartilage loss ($P = 0.06$).

There was no association between severity of BMLs at baseline and annual change in the WOMAC score (data not shown). While the majority of the BMLs in this study remained stable over 2 years (69.3%), 18 (20.5%) lesions progressed and 9 (10.2%) lesions regressed, with 1 completely resolved.

Discussion

In this population of subjects with symptomatic knee OA, the severity of BMLs at baseline was associated with reduced baseline tibial cartilage volume, increased tibial cartilage loss over 2 years and an increased risk of knee joint replacement over 4 years. This provides support for the importance of BMLs in identifying those at higher risk of disease progression in OA.

The association we found between BMLs and cartilage is consistent with previous work showing that BMLs in knee OA were associated with an increase in joint space loss and a surrogate measure for knee cartilage [7]. These results are similar to another study in OA patients in which a higher baseline BML score was predictive of increased tibiofemoral cartilage loss in the corresponding knee compartment [8]. Increased joint cartilage degradation, as indicated by a positive relationship between urinary C-terminal crosslinking telopeptide of type II collagen (CTX-II) levels and BMLs has also been shown to be associated with an increased BML score [17]. A previous study of subjects with symptomatic knee OA reported that subjects with BMLs had a >6-fold increased risk of joint space loss, which was attenuated by 53% and

TABLE 3 Relationship between BMLs at baseline and annual percentage cartilage volume loss over 2 years

Annual tibial cartilage loss	Univariate regression coefficient (95% CI)	*P*-value	Multivariate regression coefficient (95% CI)[a]	*P*-value	Multivariate regression coefficient (95% CI)[b]	*P*-value
Total cartilage loss, %	0.61 (−0.11, 1.33)	0.10	1.14 (0.29, 1.98)	0.01	1.09 (0.24, 1.93)	0.01
Medial cartilage loss, %	0.95 (−0.01, 1.91)	0.05[c]	2.11 (0.96, 3.25)	<0.001[c]	1.98 (0.74, 3.22)	0.002[c]
Lateral cartilage loss, %	−1.27 (−2.81, 0.27)	0.11[d]	−0.53 (−2.15, 1.09)	0.52[d]	0.02 (−1.76, 1.80)	0.98[d]

[a]Adjusted for age, gender, BMI, baseline tibial cartilage volume and tibial plateau bone area. [b]Adjusted for age, gender, BMI, baseline tibial cartilage volume, tibial plateau bone area and tibiofemoral alignment. [c]Association with BMLs in medial compartment. [d]Association with BMLs in lateral compartment.

TABLE 4 Relationship between BMLs at baseline and knee joint replacement over 4 years ($n = 16$)

Tibiofemoral BMLs	Univariate odds ratio (95% CI)	*P*-value	Multivariate odds ratio (95% CI)[a]	*P*-value
Total tibiofemoral BMLs	1.55 (1.04, 2.29)	0.03	1.57 (1.04, 2.35)	0.03
Medial tibiofemoral BMLs	1.65 (1.12, 2.42)	0.01	1.78 (1.16, 2.74)	0.01
Lateral tibiofemoral BMLs	0.84 (0.45, 1.58)	0.59	0.82 (0.43, 1.54)	0.54

[a]Adjusted for age, gender and K–L grade.

was no longer significant after adjusting for mechanical tibiofemoral alignment [7]. This was supported by an MRI study that reported a dilution in the relationship between BMLs and cartilage loss when adjusted for mechanical alignment [8]. This suggested that mechanical factors may mediate the relationship between BML and cartilage loss. However, our study, which examined the relationship between BMLs and percentage change in cartilage, found that this was independent of tibiofemoral alignment. In our population, we used the anatomical angle to measure alignment. The mean tibiofemoral alignment in our population was 180.4° (S.D. 5.8°), with 180° considered normal. Thus, our community-based OA population did not have significant malalignment. Moreover, the method for assessing progression of OA may also be more sensitive in our study as we used change in cartilage volume, whereas previous studies used joint space narrowing as a surrogate for cartilage [7] and the whole-organ MRI score (WORMS) semi-quantitative method [8]. Therefore, in the previous studies, they may have only had power to show change in the more biomechanically unstable group.

Few studies have examined the relationship between BMLs and the risk of knee replacement. Our findings that increasing severity of BMLs is positively associated with risk of knee joint replacement over 4 years, adjusted for potential confounders, is novel. In one small cross-sectional study of patients undergoing total knee replacement, subchondral MR signal abnormalities were observed in seven out of nine patients [18]. A more recent study observed 65 highly selected subjects with knee OA, who were drawn from a series of over 4000 patients with clinically indicated MRIs who had two MRIs over a 3-year period [11]. Among these 65 patients, an increased risk of knee replacements was found in those with BML at the time of first MRI. This was a population with a very high rate of knee replacement, 31.1% in those with BMLs. Furthermore, there was no adjustment for potential confounders. In the current study of subjects with knee OA, we found that the presence of BMLs was associated with knee joint replacement, independent of age, gender and K–L grade. Our results remained significant when adjusted for baseline tibial cartilage volume ($P = 0.04$), and when adjusted for percentage annual cartilage loss ($P = 0.06$). Taken together, the results of this study have shown that BMLs are associated with reduced tibial cartilage cross-sectionally, increased cartilage loss over 2 years and increased risk of joint replacement over 4 years.

BMLs may originally correspond to an acute inflammatory response, oedema, contusion and/or necrosis, which over time are replaced by more permanent bone marrow remodelling such as fibrosis and myxomatous connective tissue [5]. It may be that factors contributing to the development of a BML also result in impairment of the supply of nutrients and oxygen to the overlying cartilage plate that may also reduce the strength of the bony support of articular cartilage [19, 20]. It is possible that this is more pronounced in the medial compartment as this is the compartment that is most exposed to increased forces through the knee during weight-bearing activities [21]. The resultant bone changes may in turn result in increasing cartilage loss. This is supported by the results of this study where we found that BMLs were associated with not only reduced tibial cartilage volume cross-sectionally, but also an increased rate of loss over 2 years and the subsequent increased risk of knee replacement. However, we acknowledge that the low prevalence of BMLs in the lateral compartment (24.8%) compared with the medial compartment (51.4%) may also have affected the power to detect similar relationships in the lateral compartment.

Given that BMLs, even in symptomatic knee OA, have the potential to regress [9], they may represent a therapeutic target to delay disease progression.

While a limitation of our study was the lack of information regarding treatments for OA the participants may have received, such as physiotherapy, ChSu and hyaluronate, that may have affected BML, cartilage and/or delay progression to knee joint replacement, there is little to support that these treatments affect these outcomes or the time to joint replacement surgery. Although some evidence suggests a potential benefit of some of these treatments in delaying or preventing structural progression, results of studies have been inconsistent and as such it is difficult to draw a definite conclusion regarding their efficacy [22–24]. Our study was limited by the absence of T2-imaging sequencing; however, our use of T1 images to measure BMLs instead of T2 is likely to result in a more conservative analysis. For BMLs to be identified on T1 images, BMLs must be larger and more active with surrounding oedema [25]. Any BML identified on T1 images are likely to be definite and larger BML, than were T2 images used: small lesions that may be borderline will not be identified. The low number of subjects with knee joint replacement is another limitation of our study. However, the associations we observed in the total and medial compartments were consistent since BMLs were found to affect cartilage cross-sectionally as well as longitudinally, through to joint replacement [26]. It may be that the location of BML (anterior and/or posterior femoral and/or tibial) adds further risk. We were unable to examine this due to the low number of BMLs for each site in those with joint replacements. This warrants further investigation. The results of this study which are in a population with symptomatic knee OA may not be applicable to the general healthy population without knee OA.

Conclusion

In this study, we have shown that subjects with more severe BMLs at baseline had less tibial cartilage at baseline and greater cartilage loss over 2 years, as well as increased risk of knee joint replacement over 4 years. Identifying factors that prevent or reduce the severity of BMLs may provide an important target in the prevention of disease progression and treatment of OA and the subsequent need for arthroplasty.

Rheumatology key messages

- Severity of baseline BMLs is associated with worse cartilage outcomes.
- Those with more severe BMLs at baseline are at higher risk of knee replacement.

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2.2 Subchondral Bone Cysts

Another less well-researched bone abnormality of OA is subchondral bone cysts. What limited evidence there is on subchondral bone cysts suggests a relationship between subchondral bone cysts and knee pain (217) and femoral cartilage loss (167) in subjects with knee OA.

At present, the origins of subchondral bone cysts remains uncertain. Previously, two theories have dominated the literature: the synovial breach theory (218, 219) and the bony contusion theory (220). The synovial breach theory proposes that cartilage degeneration creates a channel which allows breach of synovial fluid into the marrow space. On the other hand, the bony contusion theory suggests that subchondral bone cysts arise from violent impact between two opposing surfaces which causes areas of bone necrosis.

More recently, there was some suggestion that BMLs and subchondral bone cysts may be more closely related than previously thought. Findings that 92% of cysts developed within BMLs (221) and that BMLs were co-existent in 91% of subregions containing cysts (222) prompted the question of whether BMLs may in fact represent early, pre-cystic lesions. Thus, the relationship between BMLs and subchondral bone cysts presents an interesting research question. In addition, no previous study had examined the effect of the co-existence of BMLs and subchondral bone cysts on knee structure. Therefore the next paper presented in this chapter investigated the effect of BMLs and subchondral bone cysts on cartilage loss and knee joint replacement.

***Tanamas SK**, Wluka AE, Pelletier JP, Martel-Pelletier J, Abram F, Wang Y, Cicuttini FM. 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. Mar 31; 12(2):R58. (IF 4.36)*

The findings of this study demonstrated that subjects with knee OA who had both BMLs and subchondral bone cysts had greater cartilage loss and increased risk of joint replacement, such that those with both BMLs and cysts had a 2-fold increased odds for knee replacement compared to those with BMLs only or those with no BMLs or cysts. Subchondral bone cysts were also shown to have the potential to regress, and even resolve, and that regression was associated with reduced tibial cartilage loss. These findings suggest that subchondral bone cysts identify those with worse structural outcomes who should be targeted for prevention of disease progression.

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RESEARCH ARTICLE Open Access

The association between subchondral bone cysts and tibial cartilage volume and risk of joint replacement in people with knee osteoarthritis: a longitudinal study

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Abstract

Introduction: To examine the natural history of subchondral bone cysts and to determine whether knee cartilage loss and risk of joint replacement is higher in knees with cysts, compared with those with bone marrow lesions (BMLs) only or those with neither BMLs nor cysts.

Methods: The symptomatic knee in 132 subjects with knee osteoarthritis (OA) was imaged by using magnetic resonance imaging at baseline and 2 years later. Tibial cartilage volume, subchondral bone cysts, and BMLs were measured by using validated methods. Knee arthroplasty over a 4-year period was ascertained.

Results: Bone cysts were present in 47.7% of subjects, 98.1% of whom also had BMLs. Over a 2-year period, 23.9% of subjects had cysts progress, 13.0% developed new cysts, and 11.4% had cysts regress. Bone cysts at baseline were associated with lower medial and lateral tibial cartilage volume compared with those with BMLs only or those with neither (*P* for trend 0.004 and <0.001, respectively). Annual medial cartilage volume loss was greatest in those with bone cysts compared with those with BMLs only or those with neither (9.3%, 6.3%, and 2.6%, respectively; *P* for trend, <0.001). As the severity of bone abnormality in the medial compartment increased from no BMLs or cysts present, to BMLs only, to subchondral bone cysts present, the risk of knee replacement was increased (odds ratio, 1.99; 95% confidence interval (CI), 1.01 to 3.90; $P = 0.05$).

Conclusions: When cysts are present, cartilage loss and risk of knee replacement are higher than if only BMLs are present, suggesting that cysts identify those most likely to benefit from prevention of disease progression. As cysts can regress, they may also provide therapeutic targets in knee OA.

Introduction

Subchondral bone cyst formation is often encountered in osteoarthritis (OA) of the knee, particularly in advanced OA [1]. Visualised by using magnetic resonance imaging (MRI), subchondral bone cysts occur where the overlying cartilage has largely been eroded [2]. Two main theories are proposed about cyst formation: the synovial breach theory [3,4] and the bony contusion theory [1,5].

Subchondral bone cysts are present in ~50% of subjects with knee OA [6,7] and in 13.6% of healthy volunteers [8]. Studies of subchondral bone cysts have predominantly been descriptive, relating to the prevalence of subchondral bone cysts in OA [2,7,9,10]. Two recent studies that examined the relationship between subchondral bone cysts and knee pain found conflicting evidence [11,12]. A cross-sectional study of 143 subjects with knee OA reported no association between cysts and knee pain [12]. In contrast, a prospective study, which is part of an ongoing Genetics, Osteoarthritis, and Progression Study, of 205 subjects with knee OA found a trend for an associ-

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ation between subchondral bone cysts and increased risk of knee pain [11]. To our knowledge, the relationship between subchondral bone cysts and change in knee structure has been examined by only one study. This found a correlation between mean cyst size change (mm) and cartilage loss in the medial femoral condyle over a 24-month period [6]. No study has examined the presence of subchondral bone cysts at baseline as a risk factor for structural changes in the knee.

The relationship between bone marrow lesions (BMLs) and subchondral bone cysts is unclear, although it was recently proposed that BMLs may develop into subchondral bone cysts [13-15]. A small retrospective study of 32 patients with knee OA found that 11 (92%) of 12 of cysts developed within BMLs over ~18 months [13]. This is consistent with the findings of a more recent study of 400 patients with or at risk of knee OA, which showed that BMLs were coexistent in 91.2% of the subregions where cysts were found [14]. It may be that subchondral bone cysts indicate those with severe BMLs and more advanced disease.

In a population with symptomatic knee OA, this study aimed to (a) examine the natural history of subchondral bone cysts; and (b) determine whether tibial cartilage volume loss and risk of joint replacement is higher in knees with subchondral bone cysts, compared with those with bone marrow lesions (BMLs) only or those with neither BMLs nor cysts.

Materials and methods

Study population

Subjects with knee OA were recruited by advertising through local newspapers and the Victorian branch of the Arthritis Foundation of Australia and in collaboration with general practitioners, rheumatologists, and orthopedic surgeons. The study was approved by the ethics committee of the Alfred and Caulfield Hospitals in Melbourne, Australia. All subjects gave informed written consent [16].

One hundred thirty-two subjects entered the study. Inclusion criteria were age older than 40 years, knee symptoms (at least one pain dimension of Western Ontario and McMaster University Osteoarthritis Index (WOMAC [17]) score >20% and osteophytes present), and radiographic knee OA (ACR radiographic and clinical criteria [18]). Subjects were excluded if any other form of arthritis was present, MRI was contradicted (for example, pacemaker, cerebral aneurysm clip, cochlear implant, presence of shrapnel in strategic locations, metal in the eye, and claustrophobia), inability to walk 50 feet without the use of assistive devices, hemiparesis of either lower limb, or planned total knee replacement.

Anthropometric and clinical data

Weight was measured to the nearest 0.1 kg (shoes and bulky clothing removed) by using a single pair of electronic scales. Height was measured to the nearest 0.1 cm (shoes removed) by using a stadiometer. Body mass index (BMI; weight/height^2 (kg/m^2)) was calculated. Function and pain were assessed with WOMAC (VAS, 10 cm) [17].

Radiograph

At baseline, each subject had a weight-bearing anteroposterior tibiofemoral radiograph of the symptomatic knee in full extension. Where both knees had OA and were symptomatic, the knee with least severe radiographic OA was used. These were independently scored by two trained observers who used a published atlas to classify disease in the tibiofemoral joint according to the Kellgren and Lawrence (K-L) scale. The radiologic features of tibiofemoral OA were graded in each compartment, on a 4-point scale (0 to 3) for individual features of osteophytes and joint space narrowing [19]. In the case of disagreement between observers, the films were reviewed by a third independent observer, and consensus values were used. Intraobserver reproducibility (κstatistic) for agreement on features of OA was 0.93 for osteophytes (grade 0, 1 versus 2, 3) and 0.93 for joint-space narrowing (grade 0, 1 versus 2, 3). Interobserver reproducibility was 0.86 for osteophytes and 0.85 for joint-space narrowing [20].

Magnetic resonance imaging

Each subject had an MRI performed on the symptomatic knee at baseline and ~2 years later. Knees were imaged in the sagittal plane on the same 1.5-T whole-body magnetic resonance unit (Signa Advantage HiSpeed; GE Medical Systems, Milwaukee, WI) by using a commercial receive-only extremity coil. The following sequence and parameters were used: a T_1-weighted fat-suppressed 3D gradient recall acquisition in the steady state; flip angle, 55 degrees; repetition time, 58 msec; echo time, 12 msec; field of view, 16 cm; 60 partitions; 512 × 192 matrix; one acquisition time, 11 min 56 sec. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 × 0.83 mm (512 × 192 pixels).

Knee cartilage volume was determined by means of image processing on an independent work station by using the software program Osiris, as previously described [16,20]. Two trained observers read each MRI. Each subject's baseline and follow-up MRI scans were scored unpaired and blinded to subject identification and timing of MRI. Their results were compared. If the results were within ± 20%, an average of the results was used. If they were outside this range, the measurements were repeated until the independent measures were within ± 20%, and the averages were used [16,20]. Repeated mea-

surements were made blind to the results of the comparison of the previous results. The coefficients of variation (CVs) for the measurements were 3.4% for the medial, 2.0% for the lateral, and 2.6% for the total tibial cartilage volume [16]. Tibial plateau area was determined by creating an isotropic volume from the three input images closest to the knee joint, which were reformatted in the axial plane. The area was directly measured from these images. The CVs for the medial and lateral tibial plateau area were 2.3% and 2.4%, respectively [16,20].

A subchondral bone cyst was defined as a well-demarcated hypersignal, whereas a BML was an ill-defined hypersignal. The assessments of subchondral bone cysts and BMLs were performed on the MRI slice that yielded the greatest lesion size. The intensity and extent of cysts and BMLs were assessed in the medial and lateral tibiofemoral compartments and were graded as 0, absence of lesion; 1, mild to moderate lesion; and 2, severe (large) lesion. A reliability study done by using a two-reader consensus measure of a specific lesion size twice at a 6-week interval showed an $r = 0.96$, $p < 0.0001$ for subchondral bone cysts and $r = 0.80$, $p < 0.001$ for BMLs (test-retest Spearman correlation) [6]. The medial and lateral cyst and BML scores were each calculated as a sum of the scores for the tibial, femoral, and femoral posterior sites (scores 0 to 6). As a low prevalence of subjects was found with cyst scores >3 for the medial and >1 for the lateral compartment, we collapsed the scores to give a range of 0 to 3 for the medial and 0 to 1 for the lateral compartment.

Identification of knee replacement

At year 4, all subjects were contacted and asked whether they had undergone a knee replacement because of OA of the same knee in which they had a baseline MRI. This was confirmed by contacting the treating physician in all cases.

Statistical analysis

Descriptive statistics for characteristics of the subjects were tabulated. Annual percentage change in cartilage volume was calculated by cartilage change (follow-up cartilage volume subtracted from initial cartilage volume) divided by initial cartilage volume and time between MRIs. Outcome variables (baseline tibial cartilage volume and annual percentage change in tibial cartilage volume) were initially assessed for normality and were found to approximate normal distribution. Estimated marginal means was used to explore the cross-sectional relationship between subchondral bone cysts and tibial cartilage volume at baseline, and longitudinally, the relationship between baseline subchondral bone cysts and annual percentage tibial cartilage volume loss. Logistic regression was used to examine the relationship between baseline subchondral bone cysts and risk of knee-joint replacement over a 4-year period. All analyses were performed by using the SPSS statistical package (version 16.0.0; SPSS, Cary, NC), with a P value < 0.05 considered statistically significant.

Results

Of the 132 subjects who took part in our study, 23 did not have an MRI from which subchondral bone cysts could be assessed (MRI not available or image unclear). The 109 subjects analyzed had a mean age of 63.2 (SD ± 10.3) years, and a mean BMI of 29.3 (SD ± 5.1) kg/m^2. Demographics were not different between those who were included in the study and those who were not (data not shown). Eighty-eight (81%) subjects completed the follow-up; 21 were lost to follow-up for reasons including knee surgery, severe illness, loss of interest, death, and unclear MRI images from which cysts could not be assessed. Those who completed the follow-up had a lower mean BMI than did those who did not (mean ± SD, 28.8 ± 5.0 and 31.3 ± 5.4, respectively; $P = 0.05$).

Fifty-two (47.7%) subjects had at least one subchondral bone cyst at baseline. They were more likely to be male subjects, although no significant difference was found in age, weight, height, or BMI. Those with cysts had less lateral tibial cartilage volume and greater tibial plateau bone area compared with those who did not have a cyst (Table 1). Of subjects with a cyst at baseline, 98.0% also had a BML (Table 1). Furthermore, those with subchondral bone cysts were more likely to have large BMLs (grade ≥ 3). In contrast, those with a BML but no cyst at baseline tended to have small BMLs (grade 1).

Twenty-one (23.9%) subjects had a cyst that increased in score over a 2-year period (cyst progression), including 6 (13.0%) in whom one or more subchondral bone cysts developed (Table 2). All had a coexisting BML at baseline. Of those with a cyst at baseline, cyst progression was observed in 15 (35.7%) subjects, whereas a decrease in cyst score (cyst regression) was observed in 10 (23.8%) subjects, with 6 (14.3%) resolving completely (Table 2). No change in cyst (stable) was observed in the remaining 17 (40.5%) subjects.

The mean cartilage volume was lower in both compartments in those with cysts, compared with those with BMLs only or neither cyst nor BML present (Table 3). In the medial compartment, those with cysts present had a mean medial cartilage volume of 1,589 mm^3 compared with a mean of 1,809 mm^3 in those with BMLs only and 1,923 mm^3 in those with neither (P for trend, 0.004). Similarly those with cysts also had the least amount of lateral tibial cartilage volume compared with those with BMLs only or neither (mean, 1,607, 1,962, and 2,131 mm^3, respectively; P for trend, <0.001). In the longitudinal anal-

Table 1: Comparison of characteristics between subjects

	Cyst present (n = 52)	No cyst (n = 57)	P value
Age (years)	64.5 (10.3)	62.1 (10.1)	0.22[a]
Female, number (%)	21 (40.4)	35 (61.4)	0.03[b]
Height (cm)	168.9 (9.6)	167.8 (8.4)	0.55[a]
Weight (kg)	83.1 (15.6)	83.0 (15.2)	0.98[a]
Body mass index (kg/m^2)	29.1 (4.9)	29.5 (5.5)	0.67[a]
Kellgren-Lawrence grade ≥ 2, number (%)	37 (72.5)	41 (77.4	0.57[b]
Medial tibial cartilage volume (mm^3)	1,819 (511)	1,769 (454)	0.58[a]
Lateral tibial cartilage volume (mm^3)	1,855 (619)	2,156 (522)	0.01[a]
Medial tibial bone area (mm^2)	2,246 (405)	1,976 (349)	<0.001[a]
Lateral tibial bone area (mm^2)	1,446 (243)	1,292 (229)	0.001[a]
Tibiofemoral BML present, number (%)	51 (98.1)	21 (36.8)	<0.001[b]
Knee-joint replacement over 4 years, number (%)	9 (19.6)	7 (13.7)	0.44[b]

BML, bone marrow lesion. Presented as mean (SD), unless otherwise stated. *P* value calculated by using independent sample *t* test[a] or χ^2 test[b].

yses (Table 3), those with cysts had the highest rate of cartilage loss (9.3%) compared with the other two groups (6.3% and 2.6%) (*P* for trend, <0.001). Similar results were obtained when the subject with a cyst but no BML was excluded.

We extended our observation by examining the effect of increasing grade of severity of subchondral bone abnormality (grade 1, normal; 2, BMLs only; 3, BML and cyst present) on risk of knee-joint replacement over a 4-year period (Table 4). For every one grade increase in severity of bone abnormality in the medial compartment, the risk of joint replacement was increased (odds ratio, 1.99; 95% CI, 1.01 to 3.90; $P = 0.05$) when adjusted for age, gender, and K-L grade. No significant association was found in the lateral compartment. Again, similar results were obtained when excluding the subject with a cyst but no BML.

When we examined the effect of change in subchondral bone cyst on cartilage, we found that those who had cyst regression in the lateral compartment had significant reduction in lateral tibial cartilage loss (regression coefficient, -11.81; 95% CI, -16.64 to -6.98; $P < 0.001$) compared with those who were stable or progressed. However, those who had cyst progression tended to have greater medial cartilage loss (regression coefficient, 3.51; 95% CI, -0.35 to 7.37; $P = 0.07$) than did those who were stable or regressed, although the results did not reach significance. Sixteen (33.3%) subjects had a knee-joint replacement

Table 2: Natural history of subchondral bone cysts

	Whole population (n = 109)	No BML or cyst at baseline (n = 36)	BML at baseline (n= 21)	Cyst at baseline (n = 52)
	No. (%)a	No. (%)b	No. (%)c	No. (%)d
Develop	6 (6.8)	0	6 (40.0)	N/A
Progress	21 (23.9)	N/A	N/A	15 (35.7)
Regress	10 (11.4)	N/A	N/A	10 (23.8)
Resolve	6 (6.8)	N/A	N/A	6 (14.3)
Stable	17 (19.3)	N/A	N/A	17 (40.5)

BML, bone marrow lesion; N/A, not applicable. [a]88 subjects; [b]31 subjects; [c]15 subjects; and [d]42 subjects of each subgroup participated in the follow-up; thus, the percentages were calculated accordingly.

Table 3: Relation between increasing grade of severity of subchondral bone abnormality and tibial cartilage volume

	No BML or cyst at baseline Mean (95% CI)	With BML at baseline Mean (95% CI)	With cyst at baseline Mean (95% CI)	P for trend
Medial tibial cartilage volume[a]	1,923 (1,808, 2,038)	1,809 (1,640, 1,979)	1,589 (1,442, 1,735)	0.004
Lateral tibial cartilage volume[b]	2,132 (2,028, 2,236)	1,962 (1,616, 2,309)	1,607 (1,399, 1,817)	<0.001
Medial tibial cartilage volume loss[a]	2.62 (0.82, 4.42)	6.30 (3.43, 9.17)	9.26 (6.78, 11.73)	<0.001
Lateral tibial cartilage volume loss[b]	5.88 (4.18, 7.59)	7.19 (1.46, 12.93)	2.42 (-1.00, 5.84)	0.17

Volume expressed as cubic millimeters. Abnormality: 1, normal; 2, BML only; 3, both BML and cyst present. [a]Association with cysts and BMLs in the medial compartment. [b]Association with cysts and BMLs in the lateral compartment. Mean, 95% confidence interval, and *P* value were calculated by using Estimated Marginal Means. CI, confidence interval; BML, bone marrow lesion.

over a 4-year period (Table 1). Because of the low numbers of progression and regression (one and three subjects, respectively) in this group, we could not examine the relationship between cyst change and risk of joint replacement.

Discussion

In a population with symptomatic knee OA, subchondral bone cysts were common and usually coexisted with BMLs. They showed a varied natural history over a 2-year period, including the development of new cysts and the progression of existing cysts, as well as regression in size, including occurrence of complete resolution. Subjects with cysts had lower mean tibial cartilage volume at baseline, and greater loss of medial tibial cartilage volume over a 2-year period in longitudinal analyses, as well as an increased risk of knee-joint replacement over a 4-year period. Our findings suggest that having a subchondral bone cyst is associated with more severe structural changes and worse clinical outcomes compared with knees having BMLs only or having neither.

Subchondral bone cysts were present in 48% of our study population, similar to the prevalence reported in previous studies [6,7]. As observed in other studies, cysts were found to coexist commonly with BMLs [13-15], particularly large BMLs of grade 3 or higher. Few studies have examined the natural history of subchondral bone cysts. In a randomized double-blind placebo controlled trial of risedronate treatment in 107 subjects with knee OA, although no effect of risedronate therapy was observed on bone lesions (BMLs and cysts), the average size of subchondral bone cysts increased over a 24-month period [6]. However, this study [6] looked only at mean cyst-size change over a 24-month period without discrimination between regression and progression. In the present study, we found that although it was most common for cysts to increase in size, a significant proportion regressed (Figure 1), including complete resolution.

When we examined subchondral bone cysts in relation to knee structure, we found that having a cyst was associated with reduced cartilage volume, increased cartilage loss, and increased risk of knee replacement compared with having BMLs only or having neither. No previous study has examined the effect of cysts and BMLs separately. One previous study found that increased size of subchondral bone cysts (both with and without BMLs) was correlated with cartilage loss in the medial femoral condyle [6]; however, the association between the pres-

Table 4: Effect of increasing grade of severity of subchondral bone abnormality on joint replacement

	Univariate analysis OR (95% CI)	P value	Multivariate analysisa OR (95% CI)	P value
Medial TF compartment	1.72 (0.93 to 3.18)	0.08	1.99 (1.01 to 3.90)	0.05
Lateral TF compartment	0.95 (0.48 to 1.88)	0.89	0.96 (0.48 to 1.94)	0.91

Abnormality: 1, normal; 2, BML only; 3, both BML and cyst present. [a]Adjusted for age, gender, and Kellgren-Lawrence grade. OR, odds ratio; CI, confidence interval; TF, tibiofemoral.

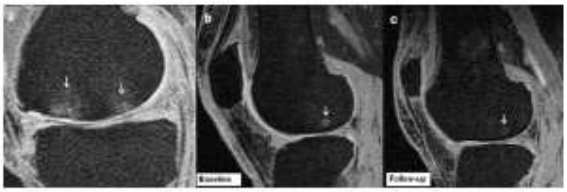

Figure 1 (a) Grade 2 medial femoral bone marrow lesions. (b) Lateral femoral subchondral bone cyst at baseline. **(c)** Regression of lateral femoral subchondral bone cyst at follow-up.

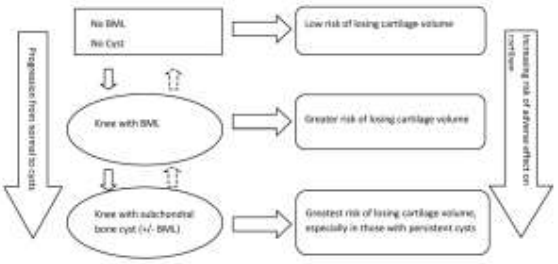

Figure 2 The progression from normal to subchondral bone cysts and its relation with cartilage.

ence of cysts at baseline and cartilage volume was not examined. We also found that those who had an increase in cyst score tended to lose more medial tibial cartilage, whereas regression of cysts was associated with reduced loss of lateral tibial cartilage. It may be that some of the compartment differences observed are due to the modest sample size. However, taken together, these results suggest that subchondral bone cysts identify those likely to have adverse structural outcomes and that regression of cysts is protective against cartilage loss.

Subchondral bone cysts were initially thought to result from degenerative changes to cartilage, creating a communication between subchondral bone and the synovial space, allowing breach of synovial fluid into the marrow space [4,5]. However, subsequent evidence supports the bony contusion theory, in which violent impact between opposing surfaces of the joint results in areas of bone necrosis, particularly when the overlying cartilage has been eroded, and that synovial breach is a secondary event [1,5,14]. Recent studies have shown that cysts may develop in preexisting BMLs, leading to the proposed theory that BMLs may in fact be early "pre-cystic" lesions [13,15]. The results of our study support this notion. However, given that BMLs are the result of a number of different pathogenetic mechanisms, which include both traumatic and nontraumatic mechanisms, it may be that cysts do not develop in all BMLs, but rather in some subgroups, and represent later stages of the pathologic process (Figure 2). Our data suggest that cysts identify those who tend to have worse knee outcomes and who should be particularly targeted for prevention of disease progression.

Several limitations to our study exist. Because of the moderate sample size of the current study, cyst progression was defined simply as an increase in score, and thus included both those who had an increase in score and incident cysts. Similarly, cyst regression was defined as a decrease in score, which did not differentiate those that resolved completely. A larger sample or a longer follow-up period or both will be required to examine further the relationship between subchondral cyst changes and knee structure. Additionally, because T_2-weighted MRI was not available when we started our study, we used T_1-weighted MRI to measure BMLs, which is likely to result in a more-conservative analysis. For BMLs to be identified on T_1 images, BMLs must be larger and more active with surrounding edema [21,22]; thus, any BMLs identified on T_1 images are likely to be definite and larger than were the T_2 images used.

Conclusions

In this study, we found that subchondral bone cysts tend to coexist with BMLs. When cysts are present, they identify patients with worse structural knee outcomes, including increased cartilage loss and increased risk of knee-joint replacement, than patients with BMLs only, and who may most benefit from prevention of disease progression. As we show that not only can cysts regress, but that regression also is associated with reduced cartilage loss, cysts may provide therapeutic targets in the treatment of knee OA.

Abbreviations

BMI: body mass index; BML: bone marrow lesion; CI: confidence interval; CVs: coefficients of variation; MRI: magnetic resonance imaging; OA: osteoarthritis; OR: odds ratio; SD: standard deviation; WOMAC: Western Ontario and McMaster University Osteoarthritis Index.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SKT was involved in data analyses and manuscript preparation. AEW was involved in manuscript preparation. JPP, JMP, and FA were involved in data collection and manuscript revision. YW was involved in data collection and manuscript revision. FMC was involved in manuscript preparation.

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Chapter 3: Bone Geometry and the Patellofemoral Joint

As discussed in the literature review, the knee joint consists of two compartments: the tibiofemoral compartment and the patellofemoral compartment. Medial tibiofemoral disease is most common (223) but patellofemoral OA is also prevalent and may be present either in conjunction with or independent of tibiofemoral disease. This thesis has considered the more novel risk factors for structural changes in the tibiofemoral compartment, yet current evidence indicates that while tibiofemoral and patellofemoral OA may share some common risk factors such as obesity and older age (186), there are others that differ. For example, while baseline tibial cartilage volume is a determinant of change in tibial cartilage volume (138, 224), baseline patella cartilage volume was not a determinant of change in patella cartilage volume (184). That there is poor correlation between patella cartilage and tibial cartilage loss further suggest that the pathogenesis of disease may differ between tibiofemoral and patellofemoral OA (184).

Patellofemoral pain is a common problem that presents to clinics and general practices (225-227) however factors that contribute to its development in the absence of a defined arthropathy, such as OA, remains unclear. Studies have assessed a range of parameters of patellofemoral geometry which relate to patellofemoral maltracking, abnormal patella alignment or abnormal patella congruity (108, 228-232), all of which can contribute to patellofemoral pain. Nonetheless how these parameters may relate to joint symptoms and influence joint structures, such as patella cartilage volume, has not been widely researched.

Thus the aim of this chapter was to examine patella inclination, sulcus angle and patella height, in relation to both knee pain and patella cartilage volume.

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This study demonstrated that increased medial patella inclination was associated with reduced pain score and increased medial patella cartilage volume. In contrast, a higher riding patella was associated with decreased medial patella cartilage volume. These findings provide theoretical support for current interventions for patella malalignment which promote medial patella translation.

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The associations between indices of patellofemoral geometry and knee pain and patella cartilage volume: a cross-sectional study

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Abstract

Background: Whilst patellofemoral pain is one of the most common musculoskeletal disorders presenting to orthopaedic clinics, sports clinics, and general practices, factors contributing to its development in the absence of a defined arthropathy, such as osteoarthritis (OA), are unclear.

The aim of this cross-sectional study was to describe the relationships between parameters of patellofemoral geometry (patella inclination, sulcus angle and patella height) and knee pain and patella cartilage volume.

Methods: 240 community-based adults aged 25-60 years were recruited to take part in a study of obesity and musculoskeletal health. Magnetic resonance imaging (MRI) of the dominant knee was used to determine the lateral condyle-patella angle, sulcus angle, and Insall-Salvati ratio, as well as patella cartilage and bone volumes. Pain was assessed by the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) VA pain subscale.

Results: Increased lateral condyle-patella angle (increased medial patella inclination) was associated with a reduction in WOMAC pain score (Regression coefficient -1.57, 95% CI -3.05, -0.09) and increased medial patella cartilage volume (Regression coefficient 51.38 mm^3, 95% CI 1.68, 101.08 mm^3). Higher riding patella as indicated by increased Insall-Salvati ratio was associated with decreased medial patella cartilage volume (Regression coefficient -3187 mm^3, 95% CI -5510, -864 mm^3). There was a trend for increased lateral patella cartilage volume associated with increased (shallower) sulcus angle (Regression coefficient 43.27 mm^3, 95% CI -2.43, 88.98 mm^3).

Conclusion: These results suggest both symptomatic and structural benefits associated with a more medially inclined patella while a high-riding patella may be detrimental to patella cartilage. This provides additional theoretical support for the current use of corrective strategies for patella malalignment that are aimed at medial patella translation, although longitudinal studies will be needed to further substantiate this.

Background

Patellofemoral pain is one of the most common musculoskeletal disorders presenting to orthopaedic and sports clinics, as well as general practices [1-5]. Factors contributing to the development of patellofemoral pain in the absence of a defined arthropathy, such as osteoarthritis (OA), are unclear and have predominantly been classified as idiopathic [6].

It has been widely hypothesised that patellofemoral pain syndrome is the result of patellofemoral maltracking and abnormal patella alignment and congruity [7,8]. One study hypothesised that the decrease in contact area is a potential source of pain due to the increased cartilage stress [9]. Previous research has predominantly been descriptive, comparing parameters of patellofemoral geometry in those with and without patellofemoral pain [9-11]. In contrast, studies that have examined the relationship between patellofemoral geometry on pain and cartilage are scarce. The small number of studies that have been performed have shown that greater lateral patella inclination, a shallower femoral sulcus and patella

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alta (a high-riding patella) are characteristic of subjects with patellofemoral pain [8,9,11-13]. Similarly, a shallow femoral sulcus is thought to reduce the congruency of the patellofemoral joint, and contribute toward instability, being associated with subluxation/dislocation syndromes [14,15]. Nonetheless, the relationship between these indices of patella alignment and congruity and anterior knee pain has not been widely examined. Moreover, it is unclear how these indices may influence patellofemoral joint structures, such as cartilage. Understanding how patellofemoral geometry may be related to joint structure and symptomatology is important, since conservative treatment options such as patellofemoral taping and bracing may help to reduce symptoms and radiological signs of disease, and may ultimately contribute to a reduced incidence of clinical pathology.

The aim of this study was to determine the relationship between indices of patellofemoral geometry and both knee pain and patella cartilage volume.

Methods

Study population

Men and women aged 25-60 years were recruited to take part in a study of the relationship between obesity and musculoskeletal diseases by advertising in the local press, at the hospitals in the waiting rooms of private weight loss/obesity clinics, and through community weight loss organisations in order to recruit subjects across the spectrum from normal weight to obese. Subjects were excluded if there was a history of any arthropathy diagnosed by a medical practitioner, prior surgical intervention to the knee including arthroscopy, previous significant knee injury requiring non-weight bearing therapy or requiring prescribed analgesia, malignancy or contraindication to MRI. 250 subjects were recruited and had MRI. Ten subjects were excluded from the study as the quality of their MRI was not interpretable. The study was approved by Alfred Hospital Human Research and Ethics committee (HREC) and the Monash standing research ethics committee. All participants gave informed consent.

Data collection

Study participants completed a questionnaire that included information on their demographics. Weight was measured to the nearest 0.1 kg (shoes, socks, and bulky clothing removed) using a single pair of electronic scales. Height was measured to the nearest 0.1 cm (shoes and socks removed) using a stadiometer. From these data, BMI was calculated. Pain was assessed by the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain subscale, analysed using 100 mm visual analogue scales (VAS) [16]. WOMAC pain subscale consists of 5 items (walking on flat surface, going up/down stairs, lying in bed at night, sitting/lying, and standing upright). Patients were required to answer each question using a 100 mm VAS where 0 = no pain and 100 = extreme pain, producing a range of possible scores of 0-500. A decrease in 1 unit WOMAC pain score indicates a decrease of 1 out of 500 units in amount of pain experienced while performing any of the 5 items.

Magnetic Resonance Imaging (MRI)

An MRI of the dominant (defined by the lower-extremity a subject used to step off from when initiating gait) knee of each subject was performed [17]. We did not want to bias our results by using both legs as this would have increased the cost of the study without improving the ability to answer the study question, given that there is a clustering effect where 2 knees are used [18]. Knees were imaged in full extension, with muscles relaxed, in the sagittal plane on a 1.5-T whole body magnetic resonance unit (Philips, Medical Systems, Eindhoven, the Netherlands) using a commercial transmit-receive extremity coil. The following sequence and parameters were used: 1) T1-weighted fat saturation 3D gradient recall acquisition in the steady state (58 ms/12 ms/55°, repetition time/echo time/flip angle) with a 16 cm field of view, 60 partitions, 512 × 512 matrix and acquisition time 11 min 56 sec (one acquisition). Axial images were converted from sagittal images, with a matrix of 0.312 mm*0.312 mm.

Patella cartilage volume was determined by image processing on an independent workstation using the Osiris software (University of Geneva, Switzerland). Patella cartilage volume was isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on each section (Figure 1). Medial and lateral patella facet cartilage volumes were further measured separately on each MRI by manually drawing disarticulation contours around the cartilage boundaries on each section as previously described [19]. The coefficient of variation (CV) for the measure was 2.6% [20]. Patella bone volume was determined by drawing contours around the patella boundaries in images 1.5 mm apart on sagittal views in a similar fashion to that described for cartilage volume. The CV for patella bone volume measures was 2.2% [20].

The lateral condyle-patella angle was measured as the angle between the posterior femoral condyles and the lateral inferior bony margin of the patella (Figure 2). An increase in this angle demonstrated more medial patella inclination, whereas a decrease in this angle demonstrated more lateral patella inclination. The femoral sulcus angle was defined by lines joining the highest points of the medial and lateral femoral condyles and the lowest point of the intercondylar sulcus (Figure 3). An increase in the femoral sulcus angle corresponded to a shallower articular surface whereas a decrease in this angle corre-

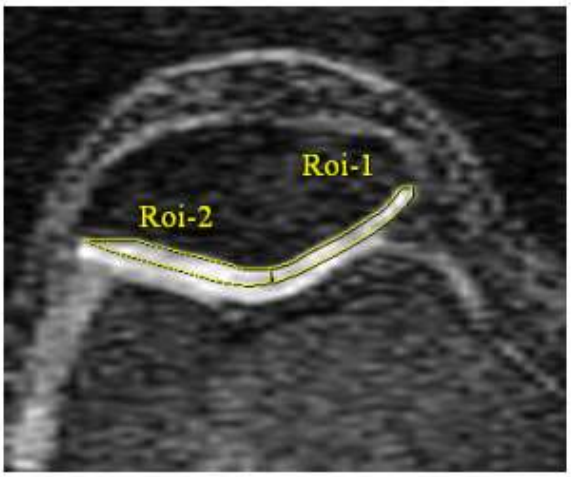

Figure 1 Medial and lateral patella cartilage volumes were determined by the software Osiris (University of Geneva, Switzerland). The patella ridge was used to divide the medial and lateral facets, which were then measured separately on each MRI by manually drawing disarticulation contours around each cartilage boundaries.

sponded to a deeper articular surface. Both the lateral condyle-patella angle and femoral sulcus angle were measured at mid-patella level [21], determined by counting all the slices that go through the patella and using the middle slice. In the case when there is an even number of slices, the two middle slices are measured and averaged. The

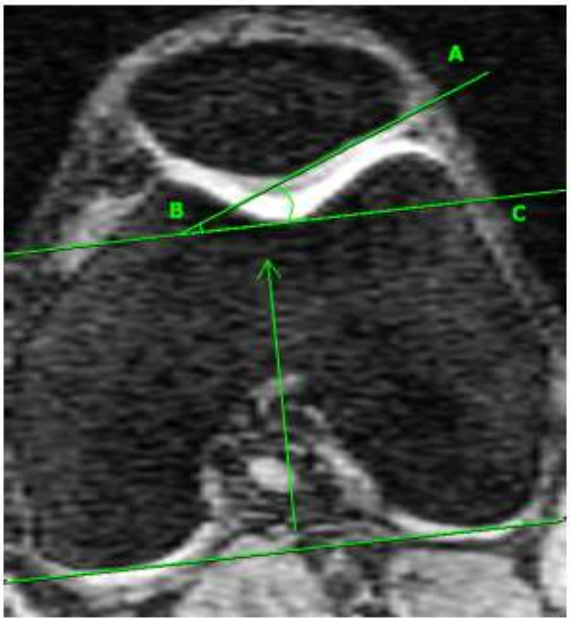

Figure 2 Lateral condyle-patella angle, measured as the angle between the bony posterior femoral condyles (BC) and the bony lateral patella facet (AB).

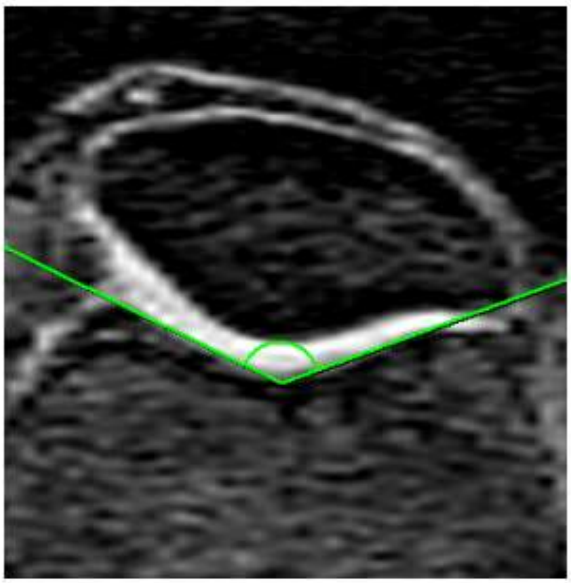

Figure 3 Sulcus angle defined as the angle formed between lines joining the highest points of the bony medial and lateral condyles and the lowest bony point of the intercondylar sulcus.

Intraclass Correlation Coefficient (ICC) was 0.98 for both angles. All angles were measured in degrees.

Patella height was measured using a method previously described by Insall-Salvati [22] which relates to the length of the patella and the patella tendon (Figure 4). A ratio > 1.2 corresponded to a high-riding patella (patella alta) whereas a ratio < 0.8 was low-riding (patella baja). Ratios between these values were defined as normal. Measures were determined from the sagittal plane at the mid-point of the patella [23], determined by counting the number of slices that go through the patella and using the middle slice, as described above. The ICC was 0.86.

Statistical Analysis

All outcome variables were initially assessed for normality. Linear regression was used to explore the relationship between parameters of patellofemoral geometry (patella inclination, sulcus angle and patella height) and WOMAC pain score and patella cartilage volume. The multivariate analyses were adjusted for age, gender, BMI, patella cartilage volume and bone size. Adjusting for patella cartilage volume and bone size allowed us to adjust for the structural state of the patellofemoral joint, since this correlates with the radiological grade of patellofemoral OA [24]. The independent samples z-test was used to compare the relationship between parameters of patellofemoral geometry and WOMAC pain and patella cartilage volume in obese and non-obese subjects. A p-value of less than 0.05 (two-tailed) was regarded as statistically significant. All analyses were performed using the

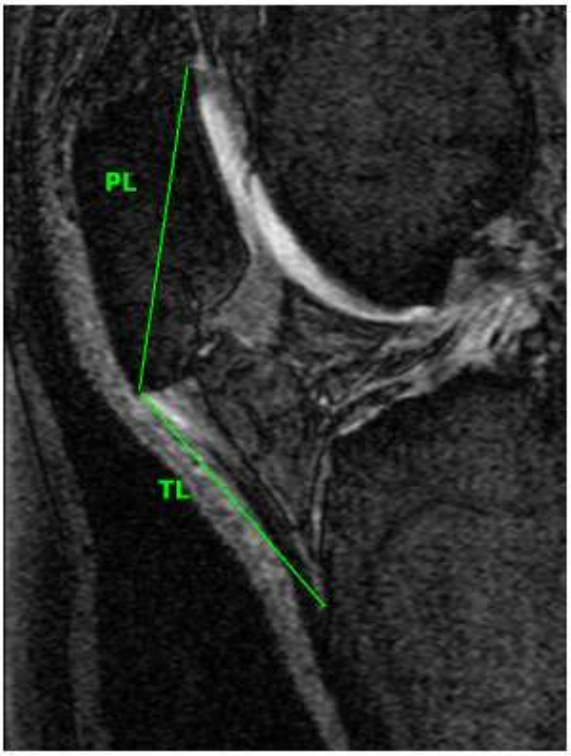

Figure 4 Insall-Salvati ratio calculated as a ratio of tendon length (BC): patella length (AB) [22].

SPSS statistical package (standard version 15.0, SPSS, Chicago, IL, USA).

Results

The demographics of the study cohort are described in Table 1. The mean age of our predominantly female cohort (73.8%) was 45.7 (Standard Deviation (SD) ± 9.4) years, while the mean BMI was of 33.9 kg m^{-2} (SD ± 9.6) (Table 1). Of the 240 subjects in this study, lateral condyle-patella angle, sulcus angle and Insall-Salvati ratio were only able to be measured in 233, 226, and 222 subjects respectively. This was due to poor quality of the MRI images, which did not allow visualisation and accurate assessment of the required measures. When comparing those who did and did not have interpretable MRI, the only significant difference found was a higher BMI in the uninterpretable group (39.1 ± 6.9 versus 33.9 ± 9.6 kg m^{-2}). The study subjects had a mean lateral condyle-patella angle of 19.0 (SD ± 7.0), a mean sulcus angle of 150.8 (SD ± 9.7), and a mean Insall-Salvati Ratio of 1.0 (SD ± 0.1) (Table 1).

Increased lateral condyle-patella angle was negatively associated with WOMAC pain score. In the multivariate analyses, adjusted for age, gender, BMI, patella cartilage volume and bone size as a marker of the state of the joint,

Table 1: Demographic characteristics of the studied population

	N = 240
Age (years)	45.7 (9.4)
Gender: n (% female)	177 (73.8)
Weight (kg)	94.3 (27.1)
Height (m)	1.7 (0.1)
BMI (kg m^{-2})	33.9 (9.6)
WOMAC pain score	53.9 (82.7)
Patella bone volume (mm^3)	10966 (2580)
Patella cartilage volume (mm^3)	2213 (544)
LCPA (degrees) *	19.0 (7.0)
SA (degrees) †	150.8 (9.7)
I-S Ratio‡	1.0 (0.1)

Presented as mean (SD) unless otherwise stated; BMI = Body Mass Index, WOMAC = Western Ontario and McMaster University Osteoarthritis Index, LCPA = lateral condyle-patella angle, SA = sulcus angle, I-S Ratio = Insall-Salvati Ratio
* measured in 233 subjects
† measured in 226 subjects
‡ measured in 222 subjects

for every one degree increase in lateral condyle-patella angle, WOMAC pain score was decreased by 1.57 units (95% CI -3.05, -0.09) (Table 2). We further examined whether this association differed between the obese (BMI ≥ 30) and non-obese (BMI < 30) subjects. There was a dose modification due to obesity in the relationship between lateral condyle-patella angle and WOMAC pain (p = 0.01 for difference between subgroups). For every one degree increase in lateral condyle-patella angle, WOMAC pain was reduced by 3.13 units (95% CI -5.60, -0.67) in the obese, and increased by 0.56 units (95% CI -0.63, 1.75) in the non-obese, although this was not statistically significant (Table 4). There was no significant association between sulcus angle or Insall-Salvati ratio and WOMAC pain score, and no dose modification due to obesity.

In the univariate analysis, there was no significant association between any of the parameters of patellofemoral geometry measured and medial or lateral patella cartilage volume. After adjusting for age, gender, BMI, patella cartilage volume and bone size, there was a positive association between lateral condyle-patella angle and medial cartilage volume, and a negative association between Insall-Salvati ratio and cartilage volume in the medial compartment (Table 3). For every one degree increase in lateral condyle-patella angle, there was an associated 51.38 mm^3 (95% CI 1.68, 101.08 mm^3) increase in medial patella cartilage volume, while for every one unit increase

Table 2: Relationship between patella inclination, sulcus angle and patella height and Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain score

	Univariate Analysis		Multivariate Analysis*	
	Regression coefficient (95% CI)	P value	Regression coefficient (95% CI)	P value
LCPA	-1.74 (-3.27, -0.21)	0.03	-1.57 (-3.05, -0.09)	0.04
SA	0.25 (-0.85, 1.34)	0.66	0.04 (-1.02, 1.09)	0.95
I-S ratio	57.26 (-13.23, 127.74)	0.11	33.01 (-36.83, 102.85)	0.35

LCPA = lateral condyle-patella angle, SA = sulcus angle, I-S Ratio = Insall-Salvati Ratio, CI = Confidence Interval
*adjusted for age, gender, BMI, patella cartilage volume and bone size

in Insall-Salvati ratio, there was a 3187 mm^3 (95% CI -5510, -864 mm^3) reduction in medial patella cartilage volume. No similar results were found in the lateral compartment, although there was a trend for a positive association between sulcus angle and lateral patella cartilage volume. When we examined the obese and non-obese subjects separately, there was no dose modification due to obesity in the relationship between lateral condyle-patella angle and Insall-Salvati ratio and patella cartilage volume. However, when we examined the relationship between sulcus angle and medial patella cartilage, there was a stronger effect in the non-obese (regression coefficient -55.61, 95% CI -104.79, -6.43) compared to the obese population (regression coefficient 12.01, 95% CI -35.76, 59.77) (p = 0.05 for difference between subgroups). There was no significant association between sulcus angle and lateral patella cartilage in either the non-obese (regression coefficient 31.12, 95% CI -44.23, 106.48) or the obese subgroup (regression coefficient 53.63, 95% CI -6.93, 114.19) and no dose modification due to obesity (Table 4).

Discussion

In a community-based population of adults, an increased lateral condyle-patella angle (a more medially inclined patella) was associated with reduced WOMAC pain score and increased medial patella cartilage volume. In contrast, an increased Insall-Salvati ratio (towards patella alta) was associated with reduced medial patella cartilage volume. These results suggest that whereas both symptomatic and structural benefits occur with medial patella inclination, patella alta is associated with aberrations in patella cartilage morphology.

Although the aetiology of patella pain remains unclear, patellofemoral maltracking is thought to play a central role in the genesis of anterior knee pain [7,25]. Previously,

Table 3: Relationship between patella inclination, sulcus angle and patella height and patella cartilage volume

	Univariate Analysis		Multivariate Analysis*	
	Regression coefficient (95% CI)	P value	Regression coefficient (95% CI)	P value
Medial facet				
LCPA	40.34 (-18.30, 98.98)	0.18	67.23 (22.10, 112.36)	0.004
SA	-23.83 (-66.34, 18.68)	0.27	-23.63 (-56.89, 9.63)	0.16
I-S ratio	-3213.15 (-6140.70, 285.60)	0.03	-3186.89 (-5510.01, -863.77)	0.01
Lateral facet				
LCPA	16.90 (-66.20, 100.01)	0.69	48.88 (-12.34, 110.11)	0.12
SA	41.08 (-20.33, 102.49)	0.19	43.27 (-2.43, 88.98)	0.06
I-S ratio	-3390.01 (-7598.65, 818.63)	0.11	-2826.33 (-5985.73, 333.07)	0.08

LCPA = lateral condyle-patella angle, SA = sulcus angle, I-S Ratio = Insall-Salvati Ratio, CI = Confidence Interval
*adjusted for age, gender, BMI, patella cartilage volume and bone size

Table 4: Relationship between parameters of patellofemoral geometry and WOMAC pain and patella cartilage volume: the difference between obese and non-obese subjects

	Obese subgroup		Non-obese subgroup		
	Regression coefficient (95% CI)*	P value	Regression coefficient (95% CI)*	P value	P value for difference†
WOMAC pain score					
LCPA	-3.13 (-5.60, -0.67)	0.01	0.56 (-0.63, 1.75)	0.36	0.01
SA	0.42 (-1.46, 2.29)	0.66	-0.1 (-0.79, 0.77)	0.98	0.68
I-S ratio	87.80 (-30.86, 206.46)	0.15	-37.58 (-101.45, 26.29)	0.25	0.06
Medial patella cartilage volume					
LCPA	86.36 (26.15, 146.58)	0.01	47.81 (-22.37, 117.99)	0.18	0.41
SA	12.01 (-35.76, 59.77)	0.62	-55.61 (-104.79, -6.43)	0.03	0.05
I-S ratio	-3093.84 (-6260.66, 72.98)	0.06	-2943.85 (-6497.61, 603.91)	0.10	0.95
Lateral patella cartilage volume					
LCPA	49.36 (-29.20, 127.93)	0.22	48.77 (-52.06, 149.60)	0.34	0.99
SA	53.63 (-6.93, 114.19)	0.08	31.12 (-44.23, 106.48)	0.41	0.64
I-S ratio	-3594.17 (-75463.31, 357.98)	0.07	-2433.12 (-7752.83, 2886.59)	0.37	0.73

LCPA = lateral condyle-patella angle, SA = sulcus angle, I-S Ratio = Insall-Salvati Ratio, CI = Confidence Interval
*adjusted for age, gender, BMI, patella cartilage volume and bone size
†p value calculated using independent samples z-test for difference between subgroups

it was shown that women with patellofemoral pain had significantly greater lateral patella inclination compared to healthy controls [11]. Similarly, in the current study, we demonstrated that the lateral condyle-patella angle, which assesses the inclination of the patella relative to the orientation of the femur, was associated with knee pain. In particular, a more medially inclined patella (an increased lateral condyle-patella angle) (see figure 2) was associated with reduced WOMAC knee pain scores, and this was more pronounced in the obese subjects. We also demonstrated that a more medially inclined patella was associated with increased medial patella cartilage volume. Consistent with our findings, a recent MRI study examining people with knee OA demonstrated that a medially oriented patella (largest lateral condyle-patella angle) was associated with the least reduction in lateral patella cartilage [26]. In contrast, a recent radiographic study found that a more laterally inclined patella (an increase in the lateral patella tilt angle) was associated with an increase in the medial patellofemoral joint space [12]. This was regarded by the authors as protective of medial joint space narrowing progression, thereby presuming it to be advantageous to the patellofemoral joint. However, when the patella is laterally inclined, the radiographic patellofemoral joint space will intuitively be widened medially, without necessarily being associated with increased cartilage volume.

In patellofemoral subluxation, dislocation, and pain syndromes, the precipitating event is generally considered to be generated by excessive lateral translation of the patella [27,28]. Conservative treatment for these pathologies has therefore been aimed at medial patella translation via strategies including braces, taping and vastus medialis strengthening [27,29-31]. Likewise, surgical approaches such as medial patellofemoral ligament reconstruction [32-34] can be used to optimise patellar tracking, particularly in patellofemoral instability. Although our findings support an advantage imparted by

medial patella inclination, the biomechanical mechanism by which the symptomatic and structural benefits are linked remains unclear. One plausible explanation is that medial inclination of the patella offsets the natural tendency of the patella to track laterally which causes excessive shearing across cartilage. However, since cartilage is not innervated, how pain may arise is even less clear.

We also measured other indices of patellofemoral articulation and alignment. The femoral sulcus angle (see figure 3) measures the depth of the femoral articular surface at the patellofemoral joint, and unlike the lateral condyle-patella angle, is viewed as a measure of joint congruity rather than patella tracking [14,35]. An increased sulcus angle is commonly associated with patella subluxation and dislocation [36,37], and in its most severe form, represents trochlear dysplasia [38]. Nonetheless, our study demonstrated a trend towards a positive association between the femoral sulcus angle and lateral patella cartilage volume. Although it is generally accepted that a shallower sulcus angle is associated with decreased patellofemoral congruency and stability [14,15], and adverse cartilage outcomes [12,26,39], a study in an osteoarthritic population demonstrated a positive association between sulcus angle and patella cartilage volume [19]. Mechanistically, it may be that a shallower sulcus enables a greater articular surface area, which subsequently reduces patellofemoral contact pressures, thus benefiting articular cartilage [19]. However, when analysed separately, there was a negative association between sulcus angle and medial patella cartilage volume in the non-obese population, which was significantly different to the obese population. One hypothesis is that those in the non-obese population are more physically active than those who are obese, therefore it may be that the negative association between sulcus angle and medial patella cartilage in the non-obese subgroup is mediated by physical activity. Those with a shallower sulcus are likely to have greater instability, and may therefore be more prone to cartilage loss during vigorous physical activity. In contrast, we have demonstrated that a high-riding patella is associated with adverse cartilage changes. Previously, patella alta has been shown to lead to higher cartilage loss [26]. The Insall-Salvati ratio is a measure of patella height, calculated as a ratio between the patella tendon and patella length (see figure 4). This ratio helps to identify excessive proximal (patella alta - defined as an Insall-Salvati ratio > 1.2) or distal (patella baja/patella inferra - defined as an Insall-Salvati ratio < 0.8) alignment of the patella relative to the trochlear groove [40]. Both patella alta and baja can alter the biomechanics of the knee joint and have been shown to lead to deleterious structural changes [13,41]. Mechanistically, a higher vertical positioning of the patella (patella alta) corresponds with the largest patellofemoral contact pressures when averaged over the whole range of movement [42], which may structurally manifest as reduced cartilage volume over time.

Our study has several limitations. WOMAC knee pain scores do not differentiate between tibiofemoral or patellofemoral pain. Whilst the Kujala score may be used to assess patellofemoral disorders [43], this data was not available in our study, thus we used the WOMAC knee pain score, which has been widely utilised in previous studies of patellofemoral diseases [44]. Although we did not have radiographic assessment in this study, we adjusted for patella cartilage volume (adjusted for bone size) as we have previously shown that this is strongly related to radiographic grade of OA [24] and is a very sensitive method for detecting early changes of knee OA [45]. Our study was based on MRI which has the benefit of *in vivo* assessment of cartilage and bone. Additionally, our cohort predominantly comprised females, which may have affected our results as patellofemoral joint biomechanics has been shown to differ between males and females [46]. We excluded subjects if there was a history of any arthropathy diagnosed by a medical practitioner, prior surgical intervention, and previous significant knee injury, thus it is possible that some subjects with clinically severe patellofemoral pain syndrome were excluded from our study. Finally, our subjects, who ranged from normal weight to obese, were recruited to take part in a study of the relationship between obesity and musculoskeletal disease. As the BMI of the population was normally distributed, we analysed the population as a whole, however we did perform the independent samples z-test to examine for any difference between the obese and non-obese subjects. Whilst it is possible that those with a high BMI were more likely to have knee pain [47,48], our multivariate analyses were adjusted for BMI. A small number of images were excluded from this study because of their poor quality which tended to occur in those with higher BMI, thus limiting the generalisability of our results to those of vey high BMI. The inability of current imaging equipments to produce the desired image quality in obese subjects is a limitation to today's imaging techniques [49].

Conclusions

In this study, we have demonstrated that an increased lateral condyle-patella angle (a more medially inclined patella) is associated with decreased WOMAC pain score in a community-based population. Moreover, increased lateral condyle-patella angle and increased sulcus angle are associated with increased medial and lateral patella cartilage respectively, whilst patella alta was associated with reduced medial patella cartilage volume. These results support symptomatic and structural benefits being associated with a medially inclined patella and a shallower sulcus angle, and further support a high-riding

patella as a disadvantageous feature of patellofemoral joint biomechanics.

Abbreviations

OA: Osteoarthritis; MRI: Magnetic Resonance Imaging; WOMAC: Western Ontario and McMaster University Osteoarthritis Index; VAS: Visual Analogue Scale; CV: Coefficient of Variation; ICC: Intraclass Correlation Coefficient; SD: Standard Deviation; BMI: Body Mass Index.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SKT was involved in data collection, analyses and manuscript preparation; AJT was involved in manuscript preparation; AEW, DMU and GJ were involved in manuscript revision; YW and MD-T were involved in data collection; FMC was involved in manuscript preparation. All authors read and approved the final manuscript.

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Chapter 4: Obesity and Knee Osteoarthritis

With the first part of this thesis focused on examining OA-related symptoms and structural abnormalities in the tibiofemoral and patellofemoral joints, the next part of the thesis will examine what could be considered one of the most important risk factors in OA: obesity.

4.1 The Relationship between Obesity and Knee Symptoms

The obesity epidemic is of concern worldwide. In Australia, there has been a steady increase in body weight over the past few decades and it still continues to rise (4). Obesity contributes to the metabolic syndrome, which is the collective name for a group of risk factors that are associated with cardiovascular disease and diabetes. Interestingly, OA is fast becoming considered as part of the metabolic syndrome (233). Previously thought of as a degenerative disorder, there is now a growing recognition of OA as a metabolic disorder (234).

Obesity is a well-established, potentially modifiable risk factor for knee OA associated with the incidence and progression of disease (34, 235, 236) as well as knee symptoms. Overweight and obesity provide a substantial contribution to the prevalence of knee pain, with an estimated 21% of all reported knee pain attributable to being overweight or obese, and 36% of knee pain with disability and 37% of intense knee pain with disability attributable to being overweight or obese (237).

While the detrimental effect of obesity on the knee joint is well established, the effect that change in weight may have on knee pain is unclear. Notably, most of the research in the area of weight change and musculoskeletal disorder has been in relation to the benefits of weight loss in those with established knee OA. It is not surprising that the effect of weight gain on knee symptoms has not been properly examined, perhaps with the underlying assumption that weight gain in general is bad. Thus the first paper in this chapter examines the effect of weight gain and weight loss on knee pain, stiffness and function. We also aim to determine whether the effects differ in those who are obese and those with OA.

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This study showed that gaining 5% of body weight or more was associated with significant worsening of knee pain, stiffness and function. Similar results were seen in those who were obese and those with OA, defined as having an osteophyte on MRI. Stratification by the presence or absence of symptoms at baseline indicated that the relationship between weight gain and knee symptoms was particularly in those without symptoms at baseline, suggesting that weight gain is predominantly a risk factor for the development of symptoms. In contrast, weight loss was associated with symptomatic improvement. Given that weight loss can be difficult to achieve and maintain, strategies to promote the prevention of weight gain are important.

Running head: Weight gain and knee symptoms

Weight gain is associated with incident knee pain, stiffness and functional difficulties: a longitudinal study

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Abstract

Objective: To examine the longitudinal association between significant weight change and change in knee symptoms (pain, stiffness, function), and to determine whether the effects differ in those who are obese and those with osteoarthritis (OA).

Methods: 250 subjects from normal weight to obese (range 16.9 to 59.1 kg/m^2) and no significant musculoskeletal disease were recruited from the general community, and weight loss clinics and organisations. Seventy eight percent were followed at ~2 years. Weight, height, and knee symptoms (using Western Ontario and McMaster University Osteoarthritis Index) were assessed at baseline and follow up. Any weight loss methods were recorded.

Results: 30% subjects lost ≥ 5% of baseline weight, 56% subjects' weight remained stable (loss or gain of <5% baseline weight) and 14% subjects gained ≥ 5% of baseline weight. Using estimated marginal means, weight gain was associated with worsening pain (mean 27.1 mm, 95% CI -1.1, 55.2), stiffness (mean 18.4 mm, 95% CI 1.5, 35.3) and function (mean 99.3 mm, 95% CI 4.0, 194.6) compared to stable weight. Weight loss was associated with reduced pain (mean -22.4 mm, 95% CI -44.4, -0.3), stiffness (mean -15.3 mm, 95% CI -28.50, -2.0) and function (mean -73.2 mm, 95% CI -147.9, 1.3) compared to stable weight.

Conclusion: Weight gain was associated with adverse effects on knee symptoms, particularly in those who are obese and who have OA. Although losing weight is potentially beneficial for symptom improvement, the effects were more modest. Avoiding weight gain is important in managing knee symptoms.

Significance and Innovations

- No study has examined the effect of weight gain on knee symptoms
- We demonstrate that further weight gain is associated with the worsening of knee symptoms but weight loss has only modest effects
- Preventing weight gain, particularly in those already obese, may be important in symptom alleviation

Knee pain is common and affects all ages, particularly older adults, and has a major impact on physical and psychological health. A recent survey of the general population in the United Kingdom reported a 46.8% prevalence of knee pain in those aged 50 and over (1). Of these, 25% of subjects reported chronic knee pain, and 6% of the older population having severe knee pain or disability (1). Similarly in a randomly selected cohort of older men and women from Tasmania, the prevalence of knee pain was 48% (2). Notably, incident knee pain has also been identified as a predictor of poor functional prognosis (3), highlighting the importance of its prevention to prevent subsequent functional decline and disability. Predictors of incident knee pain include obesity (4, 5), depression (4), widespread pain (4), smoking (5) and previous knee injury (5).

A cross-sectional survey of over 500 adults aged from 16 to over 75 years in the United Kingdom found a substantial proportion of knee pain to be attributable to overweight and obesity (6). Intense knee pain was reported by 11.7% of this population and intense knee pain with disability was reported by 3.4%. Much of this was related to overweight and obesity, with 21% of all reported knee pain attributable to being overweight or obese, while 36% of knee pain with disability and 37% of intense knee pain with disability attributable to being overweight or obese (6).

Little data is available on the effect of weight change on incident knee pain. One study examined change in BMI in relation to symptomatic OA, reporting a significant association between increased BMI and increased odds for incident symptomatic OA (7). Some recent work suggests that weight loss in older OA populations may improve knee pain and function, particularly in obese subjects (8-11). Less is known about the impact of weight change, or of further weight gain on those who are already obese or those who have evidence of early OA.

The primary aim of this study was to examine the effects of change in weight on change in knee symptoms (pain, stiffness and function) in an adult population. Secondary aims were to determine whether the effects of weight change on symptoms differ between those who are obese and non-obese, or in those with and without early OA, as indicated by the presence/absence of osteophytes, and to determine whether weight change is associated with symptom development, progression, or both.

Materials and Methods

Study population

250 participants (74% women) were recruited by advertising in the local press, at the hospitals in the waiting rooms of private weight loss/obesity clinics, and through community weight loss organisations in Melbourne, Australia. This study aimed to recruit subjects from normal weight to morbidly obese. As the aim of the study was to examine the effect of significant weight loss on change in knee symptoms, we enriched the population for obese participants, and recruited those who were aiming to lose weight, using different methods of weight loss, from surgical to commercial weight loss programmes as well as those who were not planning weight loss. The inclusion criteria was age 25 to 60 years. Subjects were excluded if there was a history of any arthropathy diagnosed by a medical practitioner including OA, prior surgical intervention to the knee including arthroscopy, previous significant knee injury requiring non-weight bearing therapy or requiring prescribed analgesia, malignancy or contraindication to MRI. Recruitment was not dependent on planned weight loss. 196 subjects (78%) completed the follow up (median follow up time 2.3 years, range 1.6 to 3.9). With 196 subjects and the distribution of weight change as observed in this study, there is 80% power to detect a trend of 0.31 standard-deviation units in change in WOMAC scores per increase of one category in weight change. The study was approved

by Alfred Hospital Human Research and Ethics committee (HREC), the Monash University standing research ethics committee and Austin Health Human Research and Ethics Committee. All participants gave informed consent.

Data collection

Magnetic resonance imaging (MRI) of the dominant knee was performed at baseline and follow up (13). Knees were imaged in the sagittal plane on a 1.5-T whole body magnetic resonance unit (Philips, Medical Systems, Eindhoven, the Netherlands) using a commercial transmit-receive extremity coil. The weight limit for the machine is 150 kg. The following sequence and parameters were used: T1-weighted fat saturation 3D gradient recall acquisition in the steady state (58ms/12ms/55°, repetition time/echo time/flip angle) with a 16 cm field of view, 60 partitions, 512 x 512 matrix and acquisition time 11 min 56 sec (one acquisition). A coronal fat-saturated, fast spin echo three dimensional, T2-weighted acquisition (2200ms, 20/80ms/90° repetition time/echo time/flip angle) with a slice thickness of 3mm, a 0.3 interslice gap, 1 excitation, a field of view of 13 cm, and a matrix of 256 × 192 pixels was also obtained (14).

Osteophytes were measured from baseline MR images, which have been shown to be more sensitive than radiographs (15). Osteophytes were measured from coronal images by two independent trained observers. In the event of disagreement between observers, a third independent observer reviewed the MRI. Intra-observer and inter-observer reproducibility for agreement on osteophytes ranged between 0.85 and 0.93 (κ statistic).

Study participants attended the study centre for a baseline and follow up visit. At this time they were asked to complete a questionnaire that included information on their demographic

characteristics and physical activity, and had their weight and height measured. Weight was measured to the nearest 0.1 kg (shoes, socks, and bulky clothing removed) using a single pair of electronic scales. Height was measured to the nearest 0.1 cm (shoes and socks removed) using a stadiometer. From these data, BMI (kg/m^2) was calculated. Pain, stiffness and function were assessed by the Western Ontario and McMaster University Osteoarthritis Index (WOMAC), analysed using 100 mm visual analogue scales (VAS) (12), which was included in the questionnaire. The WOMAC is widely used in community-based studies of adults (16-19). The pain, stiffness and function subscales comprise 5, 2 and 17 questions respectively. Each question is assessed on a 100 mm VAS and summed to give a total score out of 500 mm for pain, 200 mm for stiffness and 1700 mm for function. Increase in score corresponds with worsening of pain, stiffness and functional difficulties.

Statistical analysis

The characteristics of the study population were tabulated. Change in weight was defined as weight loss or weight gain of at least 5% of the initial weight, in accordance with the United States Food and Drug Administration which considers this level as clinically significant (20). Age, weight at baseline, change in weight, WOMAC subscale scores at baseline, and change in WOMAC scores were assessed for normality. Age and change in WOMAC scores were normally distributed, however baseline weight, change in weight and baseline WOMAC scores did not follow a normal distribution, thus non-parametric tests were employed to examine the latter. Difference between subgroups of weight change was assessed using ANOVA, chi-squared test or Kruskal-Wallis test as appropriate. Two subjects were missing height measurements from which BMI would be calculated and 2 subjects did not have baseline MRI from which osteophytes could be assessed. Results are tabulated (mean change (standard error, SE)) and displayed graphically (mean change (95% confidence interval, CI))

using estimated marginal means to indicate the relationship between weight change and change in WOMAC subscale scores, adjusted for age, gender, and baseline weight. Estimated marginal means are the predicted value of the outcome when all covariates adjusted for are set at their average value. Stratification was made by obesity status (BMI <30 kg/m^2 and BMI ≥30 kg/m^2), OA status (osteophytes absent or present), and symptoms at baseline (pain/stiffness/function absent or present). Change in weight was examined as a continuous variable using multivariate regression, adjusted for age, gender and baseline weight. A p-value of less than 0.05 (two-tailed) was regarded as statistically significant. All analyses were performed using the SPSS statistical package (standard version 18.0, SPSS, Chicago, IL, USA).

Results

Two hundred and fifty subjects were recruited and 196 subjects (78%) completed the follow up (mean follow up time ± SD 2.4 ± 0.4 years). The 250 subjects recruited at baseline had a mean age ± SD of 45.7 ± 9.3 years and comprised 185 (74%) females. The median (range) BMI was 33.2 (16.9-59.1) kg/m^2 with 148 subjects (60%) with a BMI ≥30 kg/m^2. Those who did not complete the follow up were younger (mean age ± SD 41.7 ± 9.8 years) compared to those who were followed-up (mean age ± SD 46.7 ± 8.9 years) and had higher WOMAC pain and stiffness scores (median WOMAC pain (range) 40.5 (0-500.0) mm; median WOMAC stiffness (range) 16.0 (0-200.0) mm) compared to those who completed the follow up (median WOMAC pain (range) 20.0 (0-480.0) mm; median WOMAC stiffness (range) 9.0 (0-195.0) mm), but did not differ significantly in terms of gender and BMI.

The characteristics of those who completed follow up are presented in Table 1. Of these, 58 subjects (30%) lost 5% of their baseline weight or more, 110 subjects (56%) remained stable

in weight (loss or gain of <5% baseline weight) and 28 subjects (14%) gained 5% of their baseline weight or more. The median weight loss was 11.1 kg (range 3.0-49.1) and the median weight gain was 6.7 kg (range 2.2-28.1). Methods for weight loss reported by the subjects include laparoscopic adjustable gastric banding (LAGB) and calorie-restriction diets such as Jenny Craig and Weight Watchers. 21 subjects (36.2%) who lost 5% of their body weight or more had undergone LAGB surgery, compared to only 6 (5.5%) subjects and 2 (7.1%) subjects in the stable weight and weight gain subgroups respectively. Baseline WOMAC pain, but not stiffness and function, was highest in those who lost 5% of their baseline weight or more

The difference in mean change of WOMAC pain, stiffness and function scores by subgroups of weight change is presented in Table 2. Those who lost 5% of their baseline weight or more had reduced (improved) WOMAC scores whilst those who gained 5% of their baseline weight or more had increased WOMAC scores across all parameters. When we examine those obese and non-obese and those with OA and without OA separately, similar results are seen in those obese and those with OA. Table 3 and figures 1, 2 and 3 illustrate the increasing WOMAC scores across the categories of weight change, from weight loss to stable weight and weight gain, adjusted for age, gender and baseline weight. Similar results were found when we examined change in weight as a continuous variable. For every 1 kg increase in weight, there was a 1.9 mm increase in WOMAC pain score (95% CI 0.9, 2.8 mm, $p<0.001$), 1.4 mm increase in stiffness score (95% CI 0.9, 2.0 mm, $p<0.001$), and 6.1 mm increase in function score (95% CI 2.8, 9.3 mm, $p<0.001$), adjusted for age, gender and baseline weight.

The relationship between weight gain and change in WOMAC scores

When the relationship between weight gain and change in WOMAC scores was explored in comparison to those whose weight remained stable, those who gained weight displayed increased pain score by an average of 27.1 mm (95% CI -1.1, 55.2 mm, p=0.06), increased stiffness score by 18.4 mm (95% CI 1.5, 35.3 mm, p=0.03) and function score by 99.3 mm (95% CI 4.0, 194.6 mm, p=0.02), adjusted for age, gender and baseline weight. Further adjustment for smoking and physical activity did not alter the results. Weight gain remained associated with increased stiffness score (mean difference 17.3 mm, 95% CI 0.7, 33.9, p=0.04) and function scores (mean difference 98.7 mm, 95% CI 5.4, 191.9, p=0.04), and a trend for an association with increased pain (mean difference 24.7 mm, 95% CI -2.9, 52.2, p=0.08), when adjusted for physical activity. Similar results were seen in those who were obese and those with OA, defined as having an osteophyte on MRI (Figures 2 and 3).

Furthermore, we examined those with and without symptoms at baseline separately, to determine whether weight gain is associated with the development or progression of symptoms, in comparison to remaining stable weight. The association between weight gain and increased pain was predominantly in those without pain at baseline (mean difference 44.2 mm, 95% CI 20.7, 67.6, p<0.001), adjusted for age, gender and baseline weight. Similarly, the association between weight gain and increased stiffness was predominantly in those without stiffness at baseline (mean difference 23.0, 95% CI 6.3, 39.7, p=0.01), and the association between weight gain and worse function was predominantly in those without functional difficulties at baseline (mean difference 99.3, 95% CI 20.8, 177.8, p=0.01). No associations were found in those with symptoms at baseline.

The relationship between weight loss and change in WOMAC scores

The relationship between weight loss and change in WOMAC scores was also explored in comparison to those whose weight remained stable (Figure 1). Those who lost weight showed improvements in pain (mean difference -22.4 mm, 95% CI -44.4, -0.3, p=0.05), stiffness (mean difference -15.3 mm, 95% CI -28.5, -2.0, p=0.02), and function score (mean difference -73.2 mm, 95% CI -147.9, 1.3, p=0.054) compared to those who remain stable in weight. Weight loss remained associated with reduced pain (mean difference -23.1 mm, 95% CI -45.2, -0.9, p=0.04) and stiffness score (mean difference -15.4 mm, 95% CI -28.7, -2.1, p=0.02), and a trend for an association with reduced function score (mean difference -69.7 mm, 95% CI -144.5, 5.2, p=0.07), when adjusted for physical activity. No similar results were seen for pain and stiffness when those obese and non-obese (Figure 2) and those with OA and without OA (Figure 3) were analysed separately, though a trend for an association remained for improvements in function with weight loss in the non-obese subgroup (p=0.06).

When we examined those who lost weight via LAGB compared to those who lost weight via other non-surgical means (e.g. dietary), those who had LAGB lost more weight (median (range) -16.8 (-49.1 - -7.5) kg) than those who did not (median (range) -9.1 (-36.2 - -3.0) kg). Due to the modest numbers of those who have had LAGB, particularly in the stable weight and weight gain subgroups, we were unable to stratify by LAGB status. However, when we excluded those who have had LAGB, similar results were found with regards to improvements in WOMAC pain (mean difference -28.4 mm, 95% CI -53.8, -3.0, p=0.03) and function score (mean difference -84.5 mm, 95% CI -165.7, -3.2, p=0.04) in those who lost weight compared to stable weight.

Discussion

In this population, who were recruited across a spectrum of weight from normal through to obese, we found that gaining at least 5% of baseline weight or more over 2 years was associated with increases in WOMAC pain, stiffness and function scores, and was predominantly in those with no symptoms at baseline. The relationship between weight gain and the worsening of knee symptoms seemed particularly important in those who were already obese and who had evidence of OA. Although weight loss had a beneficial effect, the magnitude of improvement was less than the increase in symptoms seen in those who gained weight (table 3). This study highlights the importance of obesity and weight gain on knee symptoms.

Previous studies have shown a linear relationship between BMI and incident knee pain (4, 21-23). However there is paucity of data regarding change in weight and knee pain. Previous research relating to change in weight and knee pain, stiffness and function has focused on the potential benefits of weight loss (8, 9, 11), or on the effect of weight gain on risk of OA (24, 25). To our knowledge, there is no study that has examined the effect of weight gain on WOMAC scores, though one study reported a positive association between increased BMI and increased risk of subsequent development of symptomatic knee OA (7), where symptomatic knee OA was indicated by the presence of pain in or around the knee on most days of the month combined with the presence of radiographic OA (at least definite osteophytes and possible joint space narrowing). In this study we found that increased weight over 2 years was associated with an increase in not only knee pain, but also stiffness and function. These results were strengthened when adjustment was made for baseline weight compared to when adjusted for age and gender only (data not shown), indicating that the relationship between weight gain and increase in knee symptoms was influenced by the individual's weight at baseline. The ability to differentiate risk factors for development and

progression of disease can be important given that they may identify different populations at risk. Therefore we stratified our population into those with and without knee symptoms at baseline. We found that weight gain was associated with knee pain, stiffness and function particularly in those without symptoms at baseline, which indicates that weight gain plays a greater role in symptom development and less so in symptom progression. This suggests that preventing weight gain is particularly important in those who do not currently have knee symptoms, to prevent the incidence of knee pain, stiffness, and functional difficulties. Furthermore, the relationship between weight gain and worse symptoms was particularly observed in those who were already obese and in those with OA, which indicates that those who are already at risk of knee symptoms are particularly vulnerable to further adverse effects associated with weight gain.

Weight gain may affect the knee joint via changes to the biomechanical components of gait (26), including the external knee adduction moment (27), which determines the load distribution on the medial compartment of the knee (27). Weight gain may also affect body composition, with increasing obesity largely due to increased fat mass. This increase in adipose tissue may have a metabolic effect on joints via the dysregulation of cytokine production by adipose tissue (28, 29), such that there is an overproduction of pro-inflammatory cytokines in the obese person (29), which has been linked to hyperalgesia and the development and progression of chronic pain (30, 31). Thus it is not surprising that further weight gain in obese individuals or individuals with early OA would be related to worsening of knee WOMAC scores since it is likely that there was already existing damage to the joint.

In this study we also found moderate benefits of weight loss on knee pain, stiffness and function. It is important to note that this population includes participants without existing knee OA. Previous studies that have examined the effects of weight loss on WOMAC scores have predominantly been in older cohorts with symptomatic radiographic osteoarthritis (OA). The Arthritis, Diet, and Activity Promotion Trial (ADAPT) reported improvements in WOMAC pain and function scores with modest weight loss (average of 4.9-5.7% of initial weight over 18 months) and moderate physical exercise in a cohort with a mean age of ~69 years (9). Similarly, in a study of OA patients (mean age 44 years) involved in a gastric surgery programme, participants lost a mean of 20% of their initial body weight over 6 months, which corresponded with significant decreases in WOMAC pain, stiffness and function scores (11). A trial of older osteoarthritic patients (mean age 62.6 years) comparing those on a low-energy diet and controls found a mean difference in weight change of 6.6 kg between the two groups over a period of 8 weeks (8). Those in the intervention group had significantly greater decrease in WOMAC function compared to the controls, though no difference was found for WOMAC pain and stiffness scores. Another trial of obese subjects over the age of 60 with self-reported OA comparing weight loss and weight stable groups reported a mean weight loss of 8.5% in the weight loss group, which corresponded with improvements in pain and physical function as assessed by self-report (WOMAC) and performance tasks (32). Although the general effect of weight loss was similar in our study as in previous studies, there are a number of differences between the studies in terms of intervention examined, study population and the amount of weight loss observed. For example the ADAPT cohort had only modest weight loss and moderate exercise thus separating the effect of weight loss and physical activity is difficult (9). The two other studies were in OA populations, one with very large weight loss of 20% of initial weight with gastric surgery, which showed a reduction in pain, while the other showed a more modest weight

loss though over a short period of only 8 weeks, which was not associated with a reduction in pain, although WOMAC function score was decreased (improved function). Taken together these data would suggest that weight loss is associated with some improvement in symptoms, but that large amounts of weight loss are required to have significant benefits.

Much of the focus in management of obesity-related morbidities has been on the promotion of weight-loss. However, obesity rates remain on the rise which suggests that current programs and initiatives designed to combat obesity have not been successful (33). Losing weight is difficult and once achieved maintaining it long-term is questionable (34, 35). It has previously been reported that a higher percentage of weight loss was significantly associated with a higher percentage of weight regain, with a 2.8-fold greater risk of weight regain in participants who lost >20% of their body weight compared to those who lost 10-15% (35). A systematic review examining the relationship between weight loss during a lifestyle intervention and the maintenance of that weight loss after 1 year of unsupervised follow-up in 12 studies found that the average percentage of weight loss maintained was 54% (34). There has been a growing interest in the role of weight gain prevention as a means to curb the rising obesity rates (36, 37). Lifestyle programs, such as mail and phone interventions, that have performed disappointingly in weight loss trials may perform better in preventing weight gain (38). Evidence suggests that small reductions in conscious energy intake and increases in physical activity can reduce weight gain and would be considered achievable for most people (33). While our results suggest a beneficial effect of weight reduction on knee stiffness and function, this effect was modest. Given that weight gain is associated with adverse effects on all WOMAC parameters, without dismissing the importance of weight loss for overall health, particularly in obese individuals, perhaps at the very least a weight maintenance strategy should be employed which may confer significant benefit with regard to knee symptoms.

A potential limitation of our study is the relatively modest number of males, though when we excluded the males similar effects persisted in the females. We also had small numbers in some of the sub groups that would be interesting to explore further. For example, we were unable to explore whether the relationship between weight gain and knee symptoms would differ by categories of percentage of weight gain. The prevalence of obesity in this population was higher than the general Australian community (39). In this study we enriched recruitment for those who were obese in order to have power to examine the effect of weight change across the spectrum of normal through to obese individuals. In addition to recruiting from weight loss clinics and organisations, we also recruited via advertising in the local press. We excluded those with a history of arthropathy and previous surgery or significant knee injury. Thus it may be that the results in the obese population were underestimated since those taking part are likely to be biased towards being more focused on losing weight. Of note, we did not recruit our subjects based on symptoms and therefore there were a proportion of subjects without symptoms at baseline who would be unable to improve. However, when we excluded those without symptoms at baseline, similar results were found. Nevertheless, our main findings pertained to the relationship between weight gain and the worsening of symptoms, which would not be affected by this. There were other potential confounders, such as depression and social economic status, which we were not able to adjust for, thus the potential role of these factors in the association between weight gain and WOMAC scores warrant further investigation. Nevertheless, our study also has several strengths in that this was a younger population and those with clinically significant knee disease were excluded.

This study demonstrates that gaining 5% of baseline weight or more is associated with adverse effects on knee symptoms (pain, stiffness and function), particularly in those who are

already obese and who have OA. Although losing at least 5% baseline weight is potentially beneficial for improvement in knee symptoms, the effects are more modest. Worsening of knee symptoms due to weight gain may impair physical functioning and further exacerbate weight gain, thus this provides an at risk time when maintaining weight, which is easier to achieve than weight loss, may be important in management of knee pain.

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Competing interests

The authors declare no competing interests.

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Table 1. Characteristics of the study population based on weight change category

	Loss ≥5% baseline weight (n=58)	Stable weight (n=110)	Gain ≥5% baseline weight (n=28)	P for difference
Baseline characteristics				
Age (years), mean (SD)	45.9 (9.1)	47.7 (8.5)	44.5 (9.7)	0.18
Female gender, n (%)	46 (79.3)	75 (68.2)	27 (96.4)	0.01
BMI (kg/m^2)	38.5 (22.5-56.8)	29.3 (17.5-59.1)	29.7 (18.0-58.1)	<0.001
Obese (BMI ≥30), n (%)	43 (75.4)	54 (49.5)	14 (50.0)	0.004
Osteophytes, n (%)	29 (50.0)	39 (35.8)	6 (22.2)	0.04
Weight (kg)				
Baseline	104.6 (54.0-166.0)	85.3 (45.0-160.0)	78.7 (49.0-160.2)	<0.001
Change over 2 years	-11.1 (-49.1 - -3.0)	0.7 (-6.2-6.1)	6.7 (2.2-28.1)	<0.001
LAGB, n (%)	21 (36.2)	6 (5.5)	2 (7.1)	<0.001
WOMAC scores (mm): baseline				
Pain	29.0 (0-480.0)	11.0 (0-370.0)	14.0 (0-208.0)	0.05
Stiffness	11.5 (0-195.0)	6.5 (0-150.0)	4.0 (0-85.0)	0.16
Function	99.5 (0-1120.0)	41.0 (0-1250.0)	46.0 (0-855.0)	0.11

Presented as median (range) unless otherwise stated

LAGB = laparoscopic adjustable gastric banding

P for difference in age and BMI were calculated using ANOVA, for difference in proportions of gender, BMI, obesity, osteophyte and LAGB using chi-squared test, and for difference in baseline weight, change in weight and WOMAC scores using the Kruskal-Wallis test

Stable weight defined as +/- <5% of baseline weight

Table 2. Change in WOMAC scores (mm) over 2 years by subgroups of weight change

	Loss ≥5% baseline weight	Stable weight	Gain ≥5% baseline weight	P for trend
Total population	*(n=58)*	*(n=110)*	*(n=28)*	
Pain	-11.2 (11.1)	4.5 (4.6)	32.7 (14.5)	0.02
Stiffness	-2.3 (6.2)	7.1 (3.2)	24.8 (8.2)	0.01
Function	-16.1 (37.5)	16.6 (17.6)	127.5 (44.1)	0.02
Obese	*(n=43)*	*(n=54)*	*(n=14)*	
Pain	-15.2 (14.6)	10.7 (8.9)	59.0 (24.8)	0.01
Stiffness	-0.5 (8.3)	13.4 (6.2)	48.4 (13.7)	0.01
Function	-9.8 (47.0)	43.5 (30.7)	262.9 (63.2)	0.004
Non-obese	*(n=14)*	*(n=55)*	*(n=14)*	
Pain	-0.02 (10.3)	-1.6 (3.1)	6.4 (12.2)	0.68
Stiffness	-5.1 (4.3)	0.9 (2.0)	1.1 (2.8)	0.36
Function	-73.3 (42.3)	-9.3 (17.7)	-8.0 (35.8)	0.28
Osteoarthritis	*(n=29)*	*(n=39)*	*(n=6)*	
Pain	-23.4 (19.1)	8.9 (9.9)	64.6 (49.9)	0.06
Stiffness	-1.3 (11.8)	17.9 (8.0)	86.4 (21.1)	0.003
Function	-4.1 (65.2)	51.6 (32.9)	392.4 (116.4)	0.01
No osteoarthritis	*(n=29)*	*(n=70)*	*(n=21)*	
Pain	1.1 (11.2)	1.7 (4.8)	24.8 (13.4)	0.15
Stiffness	-3.3 (4.5)	1.0 (2.2)	8.2 (4.5)	0.15
Function	-28.2 (38.2)	0.8 (20.2)	57.9 (35.5)	0.24

Presented as mean (SE)

Table 3. Adjusted change in WOMAC scores (mm) over 2 years by subgroups of weight change

	Loss ≥5% baseline weight	Stable weight	Gain ≥5% baseline weight	P for trend*
Total population	*(n=58)*	*(n=110)*	*(n=28)*	
Pain	-15.7 (8.9)	6.6 (6.4)	33.7 (12.7)	0.01
Stiffness	-6.6 (5.3)	8.7 (3.8)	27.1 (7.6)	0.002
Function	-43.1 (30.1)	30.3 (21.5)	129.6 (42.9)	0.01
Obese	*(n=43)*	*(n=54)*	*(n=14)*	
Pain	-17.7 (12.7)	12.0 (11.2)	61.8 (22.3)	0.01
Stiffness	-2.4 (7.7)	13.9 (6.8)	52.1 (13.6)	0.003
Function	-16.3 (40.5)	46.8 (36.0)	270.2 (71.4)	0.003
Non-obese	*(n=14)*	*(n=55)*	*(n=14)*	
Pain	0.5 (8.3)	-0.7 (4.2)	2.3 (8.5)	0.95
Stiffness	-5.0 (3.9)	1.3 (2.0)	-0.7 (4.0)	0.37
Function	-80.7 (36.7)	0.2 (18.6)	-37.6 (37.7)	0.15
Osteoarthritis	*(n=29)*	*(n=39)*	*(n=6)*	
Pain	-32.2 (16.5)	15.3 (13.9)	65.5 (34.6)	0.02
Stiffness	-8.1 (10.9)	22.3 (9.2)	90.1 (22.9)	0.001
Function	-27.1 (54.9)	69.1 (45.8)	389.9 (113.7)	0.01
No osteoarthritis	*(n=29)*	*(n=70)*	*(n=21)*	
Pain	-0.9 (9.6)	3.0 (6.2)	23.1 (11.4)	0.22
Stiffness	-4.9 (3.9)	1.8 (2.6)	7.8 (4.7)	0.10
Function	-47.8 (34.0)	11.9 (22.0)	48.2 (40.2)	0.15

Presented as mean (SE)

*Adjusted for age, gender and baseline weight

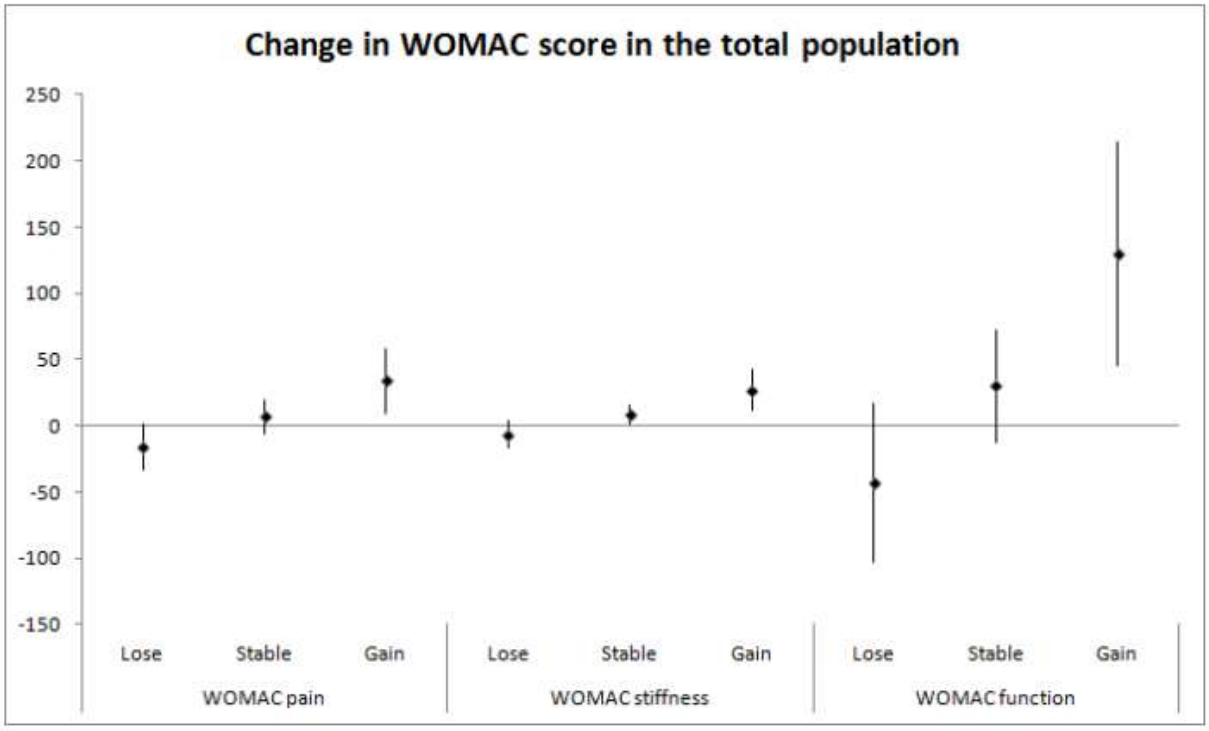

Figure 1. The relationship between change in weight (+/- 5% baseline weight) and change in WOMAC scores (mean change, 95% CI) adjusted for age, gender, and baseline weight in the total population

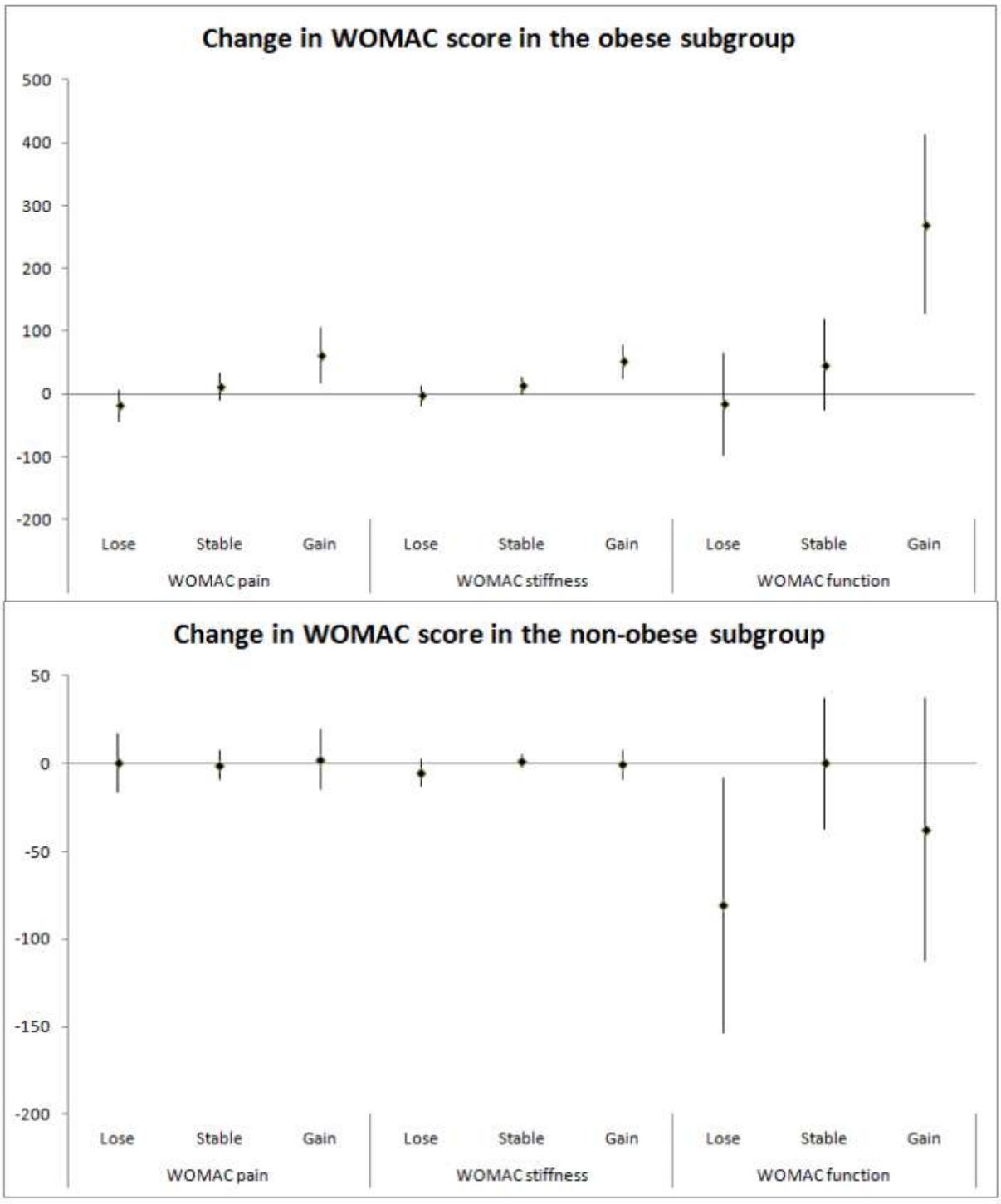

Figure 2. The relationship between change in weight (+/- 5% baseline weight) and change in WOMAC scores (mean change, 95% CI) adjusted for age, gender, and baseline weight in the obese (A) and non-obese (B) subgroups

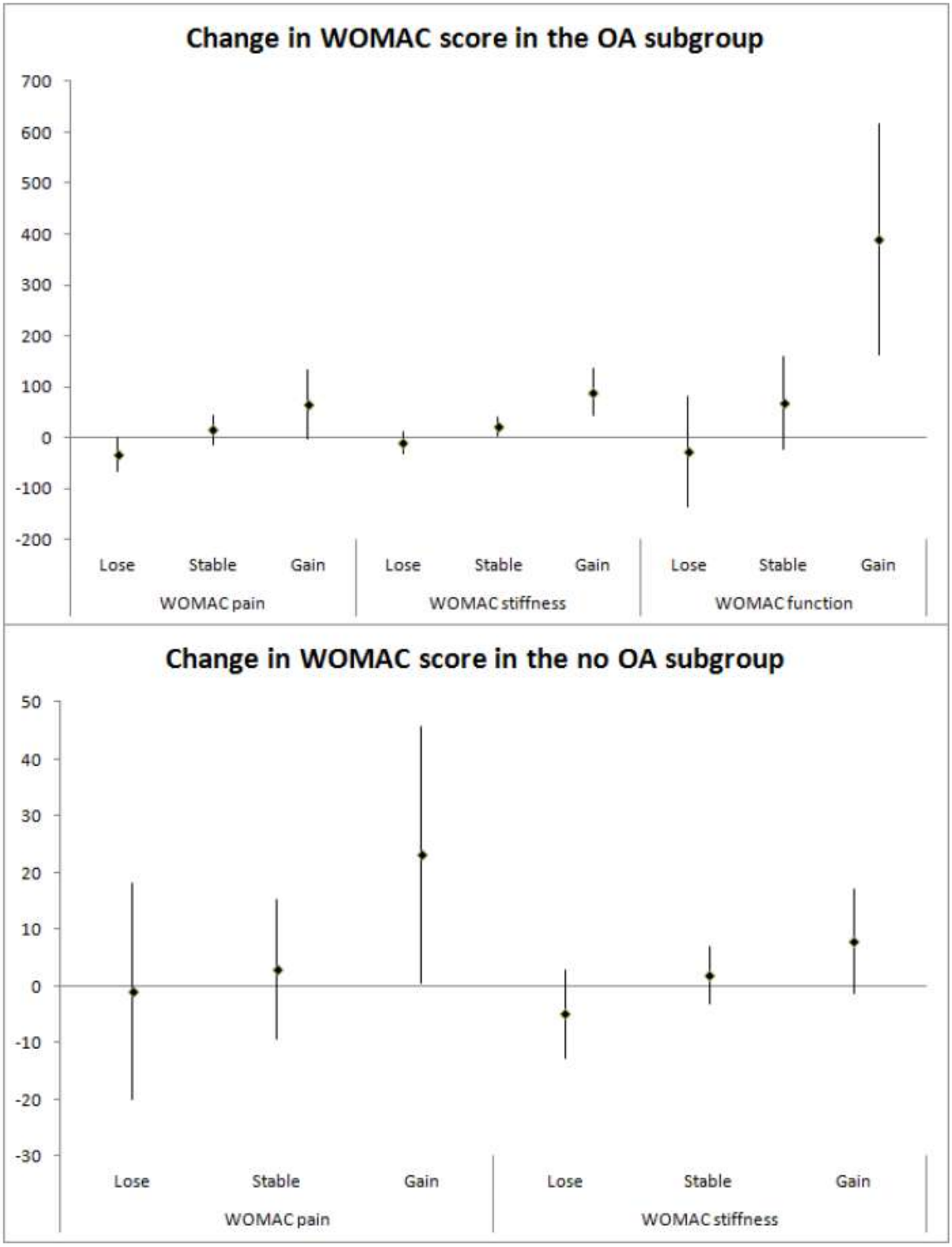

Figure 3. The relationship between change in weight (+/- 5% baseline weight) and change in WOMAC scores (mean change, 95% CI) adjusted for age, gender, and baseline weight in the OA (A) and no OA (B) subgroups

4.2 The Relationship between Obesity and Structural Changes at the Knee

There is surprisingly little information regarding the effect of weight loss on knee structural features. As there is currently no cure for OA, treatments are aimed not only at alleviating symptoms, but also at retarding the progression or development of disease. Given that obesity is one of the chief modifiable risk factors for OA, a better understanding of how it may be used as a therapeutic target is essential.

The potential that weight loss may benefit cartilage could have very important clinical implications. Previous examination of the effect of weight loss on cartilage has only been done using biomarkers as outcome measures (26, 238), suggesting some beneficial effect of weight loss on cartilage turnover. Given the paucity of data, the next manuscript aimed to explore the relationship between changes to body weight over 2 years and cartilage loss as measured on MRI.

Tanamas SK, *Wluka AE, Davies-Tuck M, Wang Y, Strauss BJ, Proietto J, Dixon JB, Jones G, Forbes A, Cicuttini FM. The relationship between change in weight over 2 years and tibial cartilage loss: an MRI study. (In preparation)*

This study demonstrated a linear relationship between increasing weight and greater cartilage loss, whilst losing 5 kg or more was associated with reduced cartilage loss, particularly in the medial tibial compartment. This was

particularly in those who were obese and those with OA, which was defined as having an osteophyte on MRI.

The relationship between change in weight over 2 years and tibial cartilage loss: an MRI study

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Abstract

Objective: To examine the relationship between change in weight and cartilage volume loss as assessed on magnetic resonance imaging (MRI), and to determine whether the relationship differs in those with and without OA

Methods: 250 men and women aged 25-62 years were recruited and 192 (77%) completed the follow up. Weight was measured and MRI of the dominant knee was performed at baseline and ~2 years later.

Results: At ~2 years, 53 subjects (27.6%) lost >= 5 kg, 114 (59.3%) remained stable (lose or gain < 5kg), and 25 (13.0%) gained >= 5 kg. In the multivariate regression, adjusted for age, gender and baseline weight, for every 5 kg increase in weight there was an associated 2.41 mm^3 increase in annual medial cartilage loss (95% CI 0.03, 0.28). When examining those who lost and gained weight separately, compared to those with stable weight, weight loss of >= 5 kg was associated with reduced medial cartilage loss (mean difference -11.80, 95% CI -21.12, -2.47). There was no significant effect of weight gain on cartilage loss over the 2 years.. When stratified by ROA status, losing weight was associated with reduced medial cartilage loss compared to remaining stable weight (mean difference -22.23, 95% CI -36.44, -8.02) in those with ROA. When stratified by obesity status, losing weight was associated with reduced medial cartilage loss compared to remaining stable weight (mean difference -15.62, 95% CI -27.17, -4.08) in the obese subgroup (BMI ≥30).

Conclusion: Weight gain was associated with increased cartilage loss, whereas weight loss associated with reduced rate of cartilage loss. This effect was particularly seen in those with osteophytes and those who were obese. Given that cartilage loss is associated with risk of knee joint replacement, losing weight may help delay or prevent the need for costly joint replacement as well as the potential subsequent need for revision surgery.

Introduction

Osteoarthritis (OA) is the most common musculoskeletal disorder affecting ~30% of adults over the age of 65 (1). It is a disease characterised by a progressive and irreversible loss of articular cartilage (2). Obesity is recognised as one of the most important potentially modifiable risk factors for OA (ref). The Canadian Community Health Survey found that among the 22 health conditions attributable to excess weight, OA was ranked second after coronary heart disease. The burden of OA continues to increase because of the ageing society and the epidemic of obesity. In Australia, it is estimated that there are ~27,000 new cases of radiological OA annually in women, and ~15,500 in men (ref). The rate of knee and hip replacements have increased by almost 30% between 1996-7 and 2000-1, with a further increase by 13.4% by June 2002, representing a significant burden on the healthcare budget (ref). As there is currently no cure for OA, treatments are aimed at slowing disease progression or preventing disease development. Thus the identification and better understanding of risk factors for OA, particularly modifiable ones such as obesity which can be used as therapeutic targets, is of high priority.

Previous examination of the effect of increasing weight on cartilage have explored relationships between baseline weight or BMI and change to cartilage volume, as indicated on MRI (3-5) or using surrogate measures such as joint space narrowing (JSN) (6-8) and total knee replacement (9, 10), as well as the relationship between change in BMI and cartilage volume at follow up (11). Additionally, studies on the effect of weight loss of articular cartilage have not examined cartilage directly on MRI but rather have used change in cartilage biomarkers as outcome measures (12, 13). As such, currently no study has examined the effect of increasing or decreasing weight on articular cartilage loss. Thus the aim of our study is to examine the relationship between changes to body weight over 2 years and

cartilage loss, and to determine whether the relationship differs in those with and without OA and those who are obese and non-obese.

Methods

Study population

250 men and women aged 25-62 years were recruited by advertising in the local press, at the hospitals in the waiting rooms of private weight loss/obesity clinics, and through community weight loss organisations. Subjects were excluded if there was a history of any arthropathy diagnosed by a medical practitioner, prior surgical intervention to the knee including arthroscopy, previous significant knee injury requiring non-weight bearing therapy or requiring prescribed analgesia, malignancy or contraindication to MRI. The study was approved by Alfred Hospital Human Research and Ethics committee (HREC), the Monash University standing research ethics committee and Austin Health Human Research and Ethics Committee. All participants gave informed consent.

Data collection

Study participants completed a questionnaire at baseline and follow-up ~2 years later that included information on their demographics. Weight was measured to the nearest 0.1 kg (shoes, socks, and bulky clothing removed) using a single pair of electronic scales. Height was measured to the nearest 0.1 cm (shoes and socks removed) using a stadiometer. From these data, BMI (kg/m^2) was calculated.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) of the dominant knee was performed (14). Knees were imaged in the sagittal plane on a 1.5-T whole body magnetic resonance unit (Philips, Medical

Systems, Eindhoven, the Netherlands) using a commercial transmit-receive extremity coil. The weight limit for the machine is 150 kg. The following sequence and parameters were used: T1-weighted fat saturation 3D gradient recall acquisition in the steady state (58ms/12ms/55°, repetition time/echo time/flip angle) with a 16 cm field of view, 60 partitions, 512 x 512 matrix and acquisition time 11 min 56 sec (one acquisition). Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 x 0.31 mm (512 x 512 pixels). A coronal fat-saturated, fast spin echo three dimensional, T2-weighted acquisition (2200ms, 20/80ms/90° repetition time/echo time/flip angle) with a slice thickness of 3mm, a 0.3 interslice gap, 1 excitation, a field of view of 13 cm, and a matrix of 256 × 192 pixels was also obtained (15).

Cartilage volume was determined by manually drawing disarticulation contours around the cartilage boundary, using independent workstation software Osiris. Measurement was done by one trained observer with random cross checks blindly performed by an independent trained observer. The coefficient of variation (CV) was 2.1% (16). Annual tibial cartilage loss was calculated as follows: (cartilage volume at baseline – cartilage volume at follow up) / time between baseline and follow up.

Osteophytes were measured from MR images, which have been shown to be more sensitive than X-rays (17). Osteophytes were measured from coronal images by two independent trained observers. In the event of disagreement between observers, a third independent observer reviewed the MRI. Intra-observer and inter-observer reproducibility for agreement on osteophytes ranged between 0.85 and 0.93 (κ statistic). Radiographic OA (ROA) was defined by the presence of osteophytes.

Radiography

At baseline, each subject had a weight-bearing antero-posterior (AP) tibiofemoral radiograph, taken in full extension and a skyline (infero-superior) view, taken in the supine position, with 45º of knee flexion (using a perspex positioning wedge). Radiographs were taken of the dominant knee. Knee angles were measured by a single observer from standing AP radiographs as published (18). Lines were drawn through the middle of the femoral shaft and through the middle of the tibial shaft to obtain the angle subtended at the point at which these two lines met in the centre of the tibial spines based on a modification of the method of Moreland et al (18) described by Felson et al (19). The angle subtended by the lines on the medial side was measured using the Osiris software. The intra-observer variability was 0.98.

Statistical analysis

The characteristics of the study population were tabulated. Difference between subgroups of weight change was assessed using ANOVA, chi-squared test or Kruskal-Wallis test as appropriate. Linear regression was used to examine the relationship between change in weight and annual tibial cartilage loss. Estimated marginal means was used to examine the relationship between weight loss and weight gain and annual tibial cartilage loss. Weight loss was defined as a loss of at least 5 kg and weight gain was defined as a gain of 5 kg or more. A p-value of less than 0.05 (two-tailed) was regarded as statistically significant. All analyses were performed using the SPSS statistical package (standard version 18.0, SPSS, Chicago, IL, USA).

Results

Two hundred and fifty subjects were recruited and 190 subjects (76%) completed the followed up (mean follow up time ± SD 2.4 ± 0.4 years). At baseline, subjects had a mean age ± SD of 46.7 ± 8.8 years and comprised 145 (75.5%) females. The median (range) BMI was 32.7 (17.5-59.1) kg/m^2 with 109 subjects (57.1%) recording a BMI ≥30 kg/m^2. Seventy three subjects (38.0%) had osteophytes. Subjects who did not complete the follow up were significantly younger (mean age ± SD 42.2 ± 9.8 years) and heavier (median weight (range) 101.0 (48.0 – 168.0) kg) at baseline than subjects who did complete the follow up (mean age ± SD 46.9 ± 8.9 years; median weight (range) 86.0 (45.0 – 166.0) kg), however they did not differ with regards to gender and baseline cartilage volume. The characteristics of the subjects who completed the follow up are presented in Table 1. Fifty two subjects (27%) lost >= 5 kg, 114 (60%) remained stable in weight (loss or gain of >= 5 kg), and 24 (13%) gained >= 5 kg. Methods for weight loss reported by the subjects include laparoscopic adjustable gastric banding (LAGB) and calorie-restriction diets such as Jenny Craig and Weight Watchers.

The relationship between change in weight and cartilage loss is presented in Table 2. In the univariate analysis, change in weight was associated with medial cartilage loss (Regression coefficient 2.5, 95% CI 0.8, 4.2), which persisted when adjusted for age, gender and baseline weight (Regression coefficient 2.3, 95% CI 0.4, 4.1) and when further adjusted for knee alignment (Regression coefficient 3.0, 95% CI 0, 5.9). No similar results were found in the lateral compartment or in the patellofemoral compartment.

We were also interested in examining the effect of weight loss and weight gain separately. However, due to the modest number of subjects who gained ≥ 5 kg (n = 24), we were only able to assess the effect of weight loss in comparison to remaining stable weight.

Furthermore, as the effect of change in weight on annual cartilage volume loss was predominantly in the medial compartment (Table 2), we examined the relationship between weight loss and annual cartilage volume loss in the medial compartment only (Table 3).

Discussion

In this cohort of subjects across a spectrum of weight from normal to obese, weight gain over 2 years was associated with increased knee cartilage loss. Furthermore, when compared to those who remained stable weight, those who lost at least 5 kg had reduced cartilage loss. This highlights the role of obesity in structural knee changes.

In this study, weight gain was associated with greater cartilage loss in the medial tibial compartment. Whilst to our knowledge no other study has examined the effect of increasing weight on cartilage, previous studies have explored the relationship between baseline measures of obesity (e.g. weight and BMI) and cartilage, whether measured directly on MRI (3-5) or using surrogate measures such as joint space narrowing (JSN) (6-8) or total knee replacement (9, 10), and the relationship between change in BMI and cartilage volume at follow up (11). However, current evidence is conflicting, with some suggestions of no association between baseline BMI and rate of JSN (6) and structural progression on MRI as indicated by measures of cartilage thickness and cartilage volume (4), but also some reports demonstrating that a high BMI at baseline predicts incidence (7, 8) and progression (8) of ROA, greater loss of articular cartilage (3, 5), and increased risk of total knee replacement (9, 10), which is considered the clinical endpoint of OA. In addition, one MRI study found that those who increase their BMI over 10 years have less cartilage at follow up (11). Thus the findings of this study extend the previous findings by demonstrating that weight gain, independent of weight at baseline, is associated with accelerated articular cartilage loss.

This study also found that subjects who lost >= 5 kg over 2 years had reduced cartilage loss compared to those with stable weight. To our knowledge, no study has examined the effect of weight loss on loss of articular cartilage, though two have examined the effects of weight loss on change in cartilage biomarkers in subjects with knee OA (12, 13). Serum N-terminal propeptide of type IIA collagen (PIIANP) is a marker of type II collagen synthesis (20) and serum cartilage oligomeric matrix protein (COMP) is a biomarker of cartilage degradation (21). In subjects involved in a gastric surgery programme, weight loss (~20% body weight) was associated with increased serum level of PIIANP and decreased serum level of COMP, suggesting a beneficial effect of weight loss on cartilage turnover (12). However results from a randomised clinical trial of the effect of diet and exercise on cartilage biomarkers suggest only weak correlations between change in weight (~5% body weight) and change in COMP levels over 18 months (13).

Obesity may affect the knee joint biomechanically via changes to gait (22), knee adduction moment (23), or knee alignment (24), which may alter the load distribution through the joint. The medial compartment naturally bears a greater proportion of the compressive load transmitted through the knee joint (60-80%) (23) and obesity has been shown to increase loading in the medial compartment (25). However, while biomechanical mechanisms may explain part of the effect of obesity on the knee joint, that obesity is also a risk factor for hand OA (26, 27) suggests a further systemic contribution. One mechanism may be the dysregulation of cytokine production by adipose tissue (28, 29), such that there is an overproduction of pro-inflammatory cytokines in the obese person (29) which potentially contributes to cartilage destruction in OA. Alternatively, leptin, a protein secreted mainly by adipocytes (30), has also been suggested as a systemic link between obesity and knee OA

(31). Its concentration and mRNA expression in cartilage is correlated with BMI (32, 33), and *in vivo* findings show that higher leptin levels have a detrimental effect on chondrocytes as it was associated with reduced cartilage volume (34). From a biomechanical perspective, weight loss decreases the load placed on the joints, such that each pound of weight lost results in a 4-fold reduction in the load exerted on the knee (35). Moreover, weight loss results in reductions in markers of inflammation such as interleukin (IL)-6 (36), tumour necrosis factor (TNF)-α (37) and C-reactive protein (CRP) (38), as well as reduced leptin levels (39). Taken together, these suggest potential mechanisms by which weight loss may benefit the knee joint, though whether they translate into reduced cartilage loss needs further investigation.

This study provides strong support for the role of managing obesity in the prevention of knee OA and in slowing progression of disease in those with OA. In this study, we found that for every 5 kg increase in weight there was an increase in annual cartilage loss by 2.41mm^3, and weight loss of 5 kg or more was associated with an annual reduction in cartilage loss by 11.80 mm^3. Given that on average subjects lost up to 25.9 mm^3 tibial cartilage per annum, this translates to over 50% decrease in annual cartilage loss with at least 5 kg weight loss. By the time ROA is detected, 11-13% of cartilage is already lost (40) and in OA, joint replacement occurs when 60% of cartilage is lost (41). In OA increased cartilage loss is an independent risk factor for knee replacement over the medium term of 4-5 years (41). Weight loss of 5 kg or more has the potential to double the time to development of OA and, in those with OA, the progression to knee joint replacement. In the case of joint replacement, this is important because not only is it desirable to reduce the prevalence of joint replacement, but with the aging of the population the rate of revision surgery is increasing. Although primary joint replacement is cost-effective (42), joints have a limited life span (43). In Australia, revision

surgery now represents 8.4% of knee replacement surgeries being undertaken (44). Revision surgery is more expensive than primary joint replacement surgery with poorer outcomes (45). Thus delaying the time to primary joint replacement also has the potential to reduce the need for revision surgery.

A potential limitation of our study is the relatively modest number of males. Although we showed an effect of weight gain as a continuous variable, we had a small number of subjects who gained >= 5 kg, thus this may have contributed to the lack of significant association between weight gain of this level and cartilage loss. Furthermore, in this study we examined tibial cartilage as the main outcome, rather than femoral cartilage. The respective tibial cartilage plates are well defined anatomical structures, compared to the femoral cartilage that is a continuous structure and the compartment specific portion must be defined based on rules rather than natural anatomical boundaries. Tibial cartilage volume correlates with femoral cartilage in that compartment (46) and longitudinal changes in the tibial and femoral cartilage are strongly correlated (47). Tibial cartilage volume is associated with radiological grade of OA in that compartment (46) and the rate of loss predicts joint replacement (41).

This study demonstrates that weight gain is associated with increased cartilage loss over 2 years, and that those who lose weight lose less cartilage compared to those who remain stable weight. Given that cartilage loss is associated with progression to knee joint replacement, it may be that weight loss can help prevent and delay the need for the costly joint replacement, which subsequently also reduces or eliminates the need for revision surgery.

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Table 1. Characteristics of the study population

	Loss of ≥5 kg (n=52)	Stable weight (n=114)	Gain of ≥5 kg (n=24)	P for difference
Age (years), mean (SD)	45.2 (8.8)	48.3 (8.6)	43.8 (9.2)	0.02*
Female, n (%)	41 (78.8)	79 (69.3)	22 (91.7)	0.052†
BMI (kg/m^2)	40.8 (24.6-59.1)	26.1 (17.5-53.4)	31.3 (18.0-58.1)	<0.001‡
Obese, n (%)	45 (86.5)	46 (40.7)	14 (58.3)	<0.001†
Osteophytes, n (%)	26 (50.0)	39 (34.5)	5 (21.7)	0.04†
Laparascopic Banding, n (%)	21 (40.4)	4 (3.5)	1 (4.2)	<0.001†
Knee alignment, mean (SD)	181.3 (2.4)	179.5 (2.9)	178.9 (3.9)	0.02
Weight (kg)				
Baseline	114.0 (60.9-166.0)	79.9 (45.0-160.0)	83.9 (49.0-160.2)	<0.001‡
Change over 2 years	-11.8 (-49.1- -5.3)	0.5 (-4.9-4.8)	7.0 (5.0-28.1)	<0.001‡
Tibial cartilage volume at baseline, mm^3				
Medial	1416 (812-2593)	1479 (919-3316)	1567 (829-1835)	0.28‡
Lateral	1722 (1054-3310)	1838 (876-4068)	1684 (759-2740)	0.32‡
Patella	2806 (1479-6434)	3290 (1508-7463)	3456 (1824-4953)	0.16‡
Annual tibial cartilage volume loss, mean (SD), mm^3/yr				
Medial	12.4 (23.8)	25.6 (24.9)	22.6 (25.9)	0.01*
Lateral	17.5 (23.7)	18.9 (23.9)	12.5 (27.0)	0.50*
Patella	58.1 (46.0)	69.9 (43.2)	62.2 (56.2)	0.29*

Presented as median (range) unless otherwise stated

P for difference calculated using *ANOVA, †chi-squared test, or ‡Kruskal-Wallis test as appropriate

Stable weight defined as +/- <5 kg, obese defined as BMI ≥30 kg/m^2

1 subject was missing BMI and 2 subjects were missing MRI from which osteophytes could be assessed

Table 2. Relationship between change in weight and annual cartilage volume loss

	Univariate regression coefficient (95% CI)	p-value	Multivariate regression coefficient (95% CI)	p-value	Multivariate regression coefficient (95% CI)	p-value
Total population (n=190)						
Medial tibial	**2.5 (0.8, 4.2)**	**0.004**	**2.3 (0.4, 4.1)**	**0.02**	**3.0 (0.0, 5.9)**	**0.05**
Lateral tibial	0.7 (-1.0, 2.3)	0.44	0.3 (-1.6, 2.1)	0.79	-0.5 (-3.3, 2.3)	0.74
Patella	1.5 (-1.6, 4.7)	0.33	1.2 (-2.2, 4.6)	0.48	1.4 (-3.2, 6.0)	0.55
Obese (n=105)						
Medial tibial	**2.3 (0.3, 4.3)**	**0.02**	**2.9 (0.7, 5.0)**	**0.01**	3.5 (-0.1, 7.2)	0.06
Lateral tibial	0.5 (-1.4, 2.5)	0.59	0.6 (-1.8, 2.5)	0.75	-0.6 (-3.8, 2.7)	0.73
Patella	-0.1 (-3.4, 3.2)	0.95	1.1 (-2.4, 4.7)	0.54	1.4 (-3.2, 6.0)	0.54
Non-obese (n=84)						
Medial tibial	0.2 (-4.9, 5.3)	0.93	-0.6 (-5.6, 4.5)	0.83	1.2 (-6.0, 8.4)	0.74
Lateral tibial	-0.9 (-5.9, 4.0)	0.70	-1.1 (-6.2, 4.0)	0.66	-2.8 (-10.4, 4.7)	0.46
Patella	6.1 (-4.6, 16.9)	0.26	7.7 (-3.4, 18.9)	0.17	8.5 (-6.5, 23.6)	0.26
Osteophytes (n=70)						
Medial tibial	1.7 (-0.6, 3.9)	0.14	1.9 (-0.6, 4.4)	0.13	3.9 (-0.7, 8.5)	0.09
Lateral tibial	1.4 (-1.0, 3.9)	0.25	0.7 (-2.1, 3.5)	0.63	0.3 (-4.8, 5.5)	0.89
Patella	0.3 (-3.9, 4.6)	0.88	1.1 (-3.6, 5.8)	0.65	3.4 (-3.1, 9.9)	0.29
No osteophytes (n=118)						
Medial tibial	3.0 (0.2, 5.9)	0.04	2.7 (-0.3, 5.7)	0.07	2.5 (-1.7, 6.8)	0.24
Lateral tibial	-0.7 (-3.2, 1.9)	0.61	-0.9 (-3.6, 1.8)	0.52	-1.7 (-5.2, 1.8)	0.33
Patella	3.1 (-2.1, 8.2)	0.24	2.5 (-3.0, 8.0)	0.36	-0.5 (-7.5, 6.5)	0.89

Increase in cartilage volume loss for every 5 kg increase in weight over 2 years
Multivariate analysis adjusted for age, gender, and baseline weight
ROA = radiographic osteoarthritis

Table 3. Effect of weight loss on annual medial tibial cartilage loss

	Mean difference between loss of ≥5 kg body weight (LW) and stable weight (SW) (95% CI)	p-value
	(LW: n=52; SW: n=114)	
Total population	-10.9 (-20.3, -1.5)	0.02
	(LW: n=45; SW: n=46)	
Obese	-15.2 (-26.9, -3.4)	0.01
	(LW: n=7; SW: n=67)	
Non-obese	5.5 (-12.3, 23.3)	0.54
	(LW: n=26; SW: n=39)	
Osteophytes	-20.2 (-34.3, -6.1)	0.01
	(LW: n=26; SW: n=74)	
No osteophytes	-7.5 (-20.7, 5.6)	0.26

Adjusted for age, gender, and baseline weight

Chapter 5: Obesity and the Foot

Although the predominant weight-bearing joint affected in OA is the knee, OA is also known to affect other joints (123, 124, 239-241). The feet, in particular, represent a relatively new area of interest. Foot pain and disability related to foot pain affects a significant proportion of the community, particularly the elderly (197-199), and is a significant burden to the community. Therefore, as the previous chapter examined the relationship between obesity and symptoms and structure at the knee joint, this chapter will focus on the relationship between obesity and foot pain.

Obesity may affect the foot biomechanically via changes to foot structure, or it may also have a metabolic effect via correlates of body composition. However, as previous examinations of the relationship between obesity and foot structure have used BMI as an indicator for obesity (242-244), no distinction could be made between the potential biomechanical or metabolic contributions of obesity. If indeed biomechanical changes are the main explanation, it is likely that any increase in body mass, whether fat or lean, would be associated with foot pain. However if metabolic factors play a greater role, it would be expected that different components of body composition would have differing effects on foot pain. To the best of our knowledge, no study had examined the relationship between different components of body composition and foot pain. Thus, the paper presented in this chapter examines the association between parameters of body composition, including fat mass, skeletal muscle mass and fat distribution, and foot pain and disability.

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In this study, the adverse effect of obesity on foot pain was predominantly related to increased adiposity, particularly in the android region. In contrast, a gynoid distribution of fat was beneficial. For every 1% increase in android fat mass the odds for foot pain were increased by almost 50%, and for every 1 unit increase in the android : gynoid fat mass ratio the odds for foot pain was increased 35-fold. In contrast, for every 1% increase in gynoid fat, the odds for foot pain were decreased by 17%. That the relationship between obesity and foot pain was distribution-related supports the theory that obesity affects the feet via metabolic effects, though a biomechanical contribution cannot be ruled out.

Relationship between obesity and foot pain and its association with fat mass, fat distribution and muscle mass

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Abstract

Objective: To examine the relationship between obesity, body composition and foot pain as assessed by the Manchester Foot Pain and Disability Index (MFPDI).

Method: 136 subjects aged 25-62 years were recruited as part of a study examining the relationship between obesity and musculoskeletal health. Foot pain was defined as current foot pain and pain in the last month, and an MFPDI score of ≥ 1. Body composition (tissue mass and fat distribution) was measured using dual energy x-ray absorptiometry.

Results: The body mass index (BMI) in this population was normally distributed around a mean of 32.1 kg/m^2. The prevalence of foot pain was 55.1%. There was a positive association between BMI and foot pain (odds ratio (OR) 1.11, 95% CI 1.06, 1.17). Foot pain was also positively associated with fat mass (OR 1.05, 95% CI 1.02, 1.09) and fat mass index (FMI) (OR 1.16, 95% CI 1.06, 1.28) adjusted for age, gender, and skeletal muscle mass or fat-free mass index (FFMI) respectively. When examining fat distribution, positive associations were observed for android/total body fat ratio (OR 1.42, 95% CI 1.11, 1.83) and android/gynoid fat ratio (OR 35.15, 95% CI 2.60, 475.47), though gynoid/ total body fat ratio was inversely related to foot pain (OR 0.83, 95% CI 0.73, 0.93). Skeletal muscle mass and FFMI were not associated with foot pain when adjusted for fat mass or FMI respectively.

Conclusion: Increasing BMI, specifically android fat mass, is strongly associated with foot pain and disability. This may imply both biomechanical and metabolic mechanisms.

Key words: Obesity; foot pain; Manchester Foot Pain and Disability Index; body composition; fat distribution

Significance and innovations

- The association between obesity and foot pain is well known
- Whether body composition is related to foot pain remains unclear
- We demonstrate a relationship between foot pain and android distribution of fat in particular

Introduction

Foot pain and disability is a problem that affects approximately 14% of adolescents and up to 42% over the age of 65 (1-4). A previous study of obese children and adolescents reported foot pain as the second most common musculoskeletal complaint (5). Similarly in adults, positive associations have been reported with regards to foot pain and obesity (6), noting a higher prevalence of foot pain in obese older adults not only compared to normal-weight older adults, but also compared to those who are overweight (7).

There are a number of mechanisms by which obesity may affect the foot. These include biomechanical changes to foot structure, such as pes planus, and changes to the plantar fat pad; increased plantar pressures; inadequate muscular strength and/or power, particularly in activities requiring movement against gravity; and changes to gait (8). However, recent work in other joints suggest that the metabolic correlates of body composition and its accompanying adipokine profile also affects joint pain as well as structure, such that those with higher adiponectin/leptin ratio (A/L ratio) have lower pain levels (9). This may also relate to a systemic effect on small joints, as exemplified by the recognized association between obesity and hand osteoarthritis (OA), which is a non weight bearing joint (10-11). Taken together, it is clear that in order to understand the relationship between obesity and joint disease it is important to examine body composition as well as other measures of obesity, such as BMI.

A number of methods for examining foot symptoms have been explored. Previously used questionnaires, such as the Stanford Health Assessment Questionnaire and the Functional Limitation Profile questionnaire, while able to give indication of locomotor dysfunction, lacks the capacity to measure disability associated with foot pain (12). More recently, the Manchester Foot Pain and Disability Index (MFPDI) was developed as a self-administrated

questionnaire to assess foot-related problems (12-14). The MFPDI has been validated in rheumatology patients, patients of general health practitioners who have reported foot-related problems and in people from the general community. The aim of this study was to examine the relationship between obesity and body composition and foot pain as assessed by the MFPDI in a population ranging from healthy to obese.

Materials and methods

Study population

Twenty three men (mean age ± SD 47.6 ±8.1 years) and 113 women (mean age ± SD 47.5 ± 9.2 years) who ranged from normal weight to obese were recruited. Recruitment was through the local media and public/private/community weight loss clinics. Subjects were excluded if there was a history of any arthropathy diagnosed by a medical practitioner, prior surgical intervention to the lower limb, previous significant knee injury requiring non-weight bearing therapy or requiring prescribed analgesia, malignancy or contraindication to MRI. The study was approved by the Alfred Hospital Human Research and Ethics committee (HREC) and the Monash standing research ethics committee. Informed consent was obtained from all participants.

Data collection

Study participants completed a questionnaire that included information on their demographics. Weight was measured to the nearest 0.1 kg (shoes, socks, and bulky clothing removed) using a single pair of electronic scales. Height was measured to the nearest 0.1 cm (shoes and socks removed) using a stadiometer. From these data, BMI (kg/m^2) was calculated. Subjects' participation in strenuous physical activity was ascertained by the question "On how many days during the last 14 days did you spend at least 20 minutes doing strenuous exercise? E.g. bicycling, brisk walking, etc that was severe enough to raise your pulse rate, cause you to

breathe faster", as previously described (15). There are no referenced standards for what constitutes significant strenuous activity. We used this definition of strenuous as this is what we have previously found to be associated with other musculoskeletal effects (16).

The Manchester Foot Pain and Disability Index (MFPDI) questionnaire was used to assess foot pain and disability due to foot pain. Foot pain was defined according to the MFPDI case definition for 'disabling foot pain' where a subject is classified as having foot pain if they have current foot pain and pain in the last month, as well as recording an MFPDI score of ≥ 1 (12).

Body composition was measured using dual energy x-ray absorptiometry (DEXA) (GE Medical-Lunar, Madison, WI, using operating system version 9). The machine has a weight limit of approximately 160 kg. Standard regional analyses were used to measure total body, trunk, android and gynoid fat mass. Android fat mass refers to adipose tissue that accumulates in the abdomen region, and gynoid fat mass refers to adipose tissue accumulation around the hips. Total limb lean tissue mass was calculated as the sum of upper-limb lean tissue mass and lower-limb lean tissue mass, which was then converted to total body skeletal muscle mass using a prediction model developed and validated in adults (BMI < 35) (17). Short-term coefficients of variation, assessed in 15 normal young adults, were 1.2% for total body fat mass, 0.4% for total body lean tissue mass (18). Based on the DEXA data, fat mass index (FMI) and fat-free mass index (FFMI) were calculated as follows: FMI = fat mass / height^2, and FFMI = fat-free mass / height^2 where fat-free mass = lean tissue mass + bone mineral content. FMI and FFMI are normalized separately for height, thus allowing height-independent assessment of nutrition status, comparison of results between studies, and the development of body composition percentile tables (19).

The Mental Component Summary (MCS) of the SF-36 was used to examine psychological health and well-being. The SF-36 is a self-report used to assess health-related quality of life (20). Low MCS scores indicate frequent psychological distress, social and role disability due to emotional problems, whereas high MCS scores indicate frequent positive effect, absence of psychological distress and limitations in usual social/role activities due to emotional problems.

Statistical analysis

The difference in body composition between those with and without foot pain was calculated using independent samples t-tests and chi-squared tests. Logistic regression was performed to assess the relationship between measures of body composition and foot pain. The multivariate analyses were adjusted for age, gender, and measures of body composition: fat mass, skeletal muscle mass, FMI or FFMI as appropriate. Logistic regression was also used to assess the relationship between fat distribution and foot pain, adjusted for age and gender in the multivariate regression. Gender was considered a potential confounder as a gender difference has been reported with regards to pain perception (21) as well as obesity, in particular body fat distribution (22). Further adjustment for the MCS of SF-36 was performed since there is increasing interest in the role of psychological well-being in obesity (23-24), and because it has been linked to pain (25-26). Adjustments for measures of body composition were made to establish whether the relationship between obesity and foot pain is chiefly attributable to one measure in particular, or whether they contribute equally. A p-value of less than 0.05 (two-tailed) was regarded as statistically significant. A further Bonferroni correction was used to take into account the potential issue of multiple testing where by a P value of 0.05 divided by the number of analyses was considered as stronger evidence for significance. All analyses were performed using the SPSS statistical package (standard version 18.0, SPSS, Chicago, IL, USA).

Results

The characteristics of the study population are presented in Table 1. Seventy-five subjects (55.1%) reported foot pain. When the subjects with and without foot pain were compared (Table 1), they did not differ significantly in terms of age or gender, however those with foot pain had a higher mean BMI ($p < 0.001$), higher total fat mass ($p<0.001$), and higher FMI ($p<0.001$) and FFMI ($p=0.02$) than those without foot pain. However, the two groups did not significantly differ in skeletal muscle mass. Figure 1 illustrates the difference in mean FMI and FFMI between those with and without foot pain.

We examined the relationship between BMI and body composition and foot pain (Table 2). BMI and foot pain were significantly related in univariate analysis (odds ratio (OR) 1.12, 95% CI 1.06, 1.17). This remained significant when adjusted for age and gender (OR 1.11, 95% CI 1.05, 1.17) (Table 2). Similarly, fat mass was also positively associated with foot pain. In the multivariate analysis, adjusted for age and gender, there was a positive association between foot pain and total body fat mass (OR 1.05, 95% CI 1.03, 1.08). Moreover, when further adjusted for skeletal muscle mass, we found that the association between total body fat and foot pain remained statistically significant (OR 1.05, 95% CI 1.02, 1.09) (Table 2). These remained significant even when using a Bonferroni adjustment for multiple testing which would consider $p<0.01$ as significant in these analyses. Conversely, whilst skeletal muscle mass was positively associated with foot pain, adjusted for age and gender, significance was lost when adjusting for fat mass (Table 2). Furthermore, in the univariate analyses there was a positive association between both FMI and FFMI and foot pain, however, whilst the association between FMI and foot pain was remained significant after adjusting for FFMI, FFMI was not significantly associated with foot pain when adjusted for FMI (Figure 1).

We further analysed the role of fat distribution in foot pain (Table 3). There was a positive association between percent total body fat and foot pain (OR 1.10, 95% CI 1.05, 1.14) adjusted for age and gender. Android/total body fat ratio, which effectively represents percent android fat, was also significantly associated with foot pain, where for every 1% increase in android fat the odds for foot pain were increased by 1.42 (95% CI 1.11, 1.83). Similarly, a positive association was observed between android/gynoid fat ratio and foot pain (OR 35.15, 95% CI 2.60, 475.47). In contrast, increased gynoid/ total body fat ratio, or increased percent gynoid fat, was associated with reduced odds ratio for foot pain, where for every 1% increase in gynoid fat the odds for foot pain were decreased by 0.83 (95% CI 0.73, 0.93). No significant results were found for either trunk/total body fat ratio, trunk/total limb fat ratio, and trunk/lower limb fat ratio. All results remained significant when further adjusted for height (data not shown). The relationships between percent total body fat, android/total body fat ratio, android/gynoid fat ratio and gynoid/total body fat ratio and foot pain remained significant even when using a Bonferroni adjustment for multiple testing which would consider $p<0.007$ as significant in these analyses. Moreover, we investigated whether the associations between obesity and body composition and foot pain were affected by mental status or physical activity. Adjusting for either the MCS of the SF-36 or strenuous physical activity did not affect the results.

Discussion

In this study we have shown that obesity is associated with foot pain and that this relationship was most strongly associated with fat mass, particularly in the android distribution. It did not appear that weight *per se* was the reason for the association, as skeletal muscle mass was not significantly associated with foot pain once adjusted for fat mass. While obesity may affect foot pain biomechanically, for example via increased loading or changes to gait, given that all parameters of fat mass but not muscle mass were associated with foot pain, as well as the

observation that the relationship between an androgenic distribution of fat differed from a gynoid distribution in relation to foot pain, it may also be that systemic processes associated with adipose tissue also plays a role.

To date, studies examining the relationship between obesity and foot structure have used BMI as a surrogate for obesity (27-29), and, as with our study, have predominantly shown a positive relationship between obesity and foot pain, although one study in an older cohort (aged 70 years and over) reported no difference in BMI between those with and without foot pain (14). We have further extended these observations by examining the associations of body composition with foot pain. We demonstrated that those with foot pain have significantly higher fat mass than those without foot pain. However, no difference was detected in skeletal muscle mass between those with and without foot pain. That the association of fat mass and foot pain remained significant after adjusting for skeletal muscle mass suggests that the mechanism of action may not simply be via loading of the joint, but that an increase in adipose mass may also have a systemic effect contributing to foot pain.

Although fat mass and fat free mass are commonly used to assess body composition, expression of absolute fat mass and fat-free mass in kg is more complicated than it may appear, as these are closely related to height and age. For example, lower fat-free mass in the elderly may be either due to changes in body composition or reduction in height associated with aging (19). To overcome these difficulties, FMI and FFMI were developed as a method that allows independent assessment for fat mass and fat-free mass, normalized separately for height (30). Our study demonstrated that in addition to fat mass being positively associated with foot pain, a similar association is also seen between FMI and foot pain but not FFMI, which further supports the notion that obesity impacts foot pain through a more systemic, rather than biomechanical effect, and that this is independent of height.

The importance of fat distribution is widely recognized, particularly in relation to the differing effects of upper body and lower body fat accumulation (31-32). Android fat mass, which refers to adipose tissue that accumulates in the abdomen region, has been linked to an elevated risk of type II diabetes and cardiovascular disease (CVD) (33). Gynoid fat mass refers to adipose tissue accumulation around the hips and, in contrast to android fat, has been linked to a more favourable lipid and glucose profile, as well as reduced risk of CVD and metabolic diseases (32). Our results show that higher percent android fat increased the odds for foot pain while higher percent gynoid fat decreased the odds. We also show that android/gynoid fat ratio is positively associated with foot pain. This suggests a differing mechanism of action of fat on the foot, depending on where it is accumulated, further suggesting a systemic involvement of adipose tissue on foot pain, as we would otherwise expect accumulation of fat in any site of the body to have a similar effect. Nonetheless, we cannot rule out a potential involvement of biomechanical mechanisms since it is possible that carrying excess load in the abdominal region versus the gynoid region may affect a person's stance or gait and thus load the foot differently, producing a detrimental biomechanical environment.

The metabolic effects of adipose tissue are being increasingly recognized: adipose tissue is no longer seen as just a passive energy store, it is highly metabolically active. Adipose tissue produces a number of adipokines (34-35), nearly all of which are dysregulated in obesity such that there is a downregulation of potentially beneficial adipokines and an overproduction of pro-inflammatory cytokines (35). Previous studies have shown the involvement of proinflammatory cytokines in hyperalgesia and the development and progression of chronic pain (36-37). The metabolic correlates of the different patterns of fat distribution may underlie our observations. For example, android and gynoid fats have been shown to produce different

adipokines, and it has been suggested that the protective effects of gynoid fat may be attributable to the secretion of the more beneficial adipokines, leptin and adiponectin (32). In contrast, higher waist-to-hip ratio and central mass accumulation is inversely associated with adiponectin levels (38). Perhaps more important than the individual concentrations of leptin and adiponectin, is the adiponectin/leptin (A/L) ratio. A study of Korean male adults demonstrated significant negative correlations between A/L ratio and measures of obesity and fat distribution, including body weight, BMI, percent body fat and waist circumference (39). In addition, A/L ratio was also inversely correlated with pain in patients with knee OA and this effect was greater than that for the individual adipokines alone (9), though whether the same effect would be seen in non-osteoarthritic patients is unclear.

A potential limitation to our study is multiple testing. However our findings in relation to fat mass remained significant even if a Bonferroni correction, a very conservative method, was used to take this into account. The smaller proportion of males may also be another limitation. There are also several strengths, such as (i) consistency of findings in relation to fat mass and foot pain and disability, (ii) inclusion of participants with a spectrum of weight extending from normal to obese, and (iii) adjustment for confounders including age, gender, and the measure of body composition: fat or muscle mass, and FMI or FFMI. Pain and disability were defined as current foot pain and pain in the last month, and at least one item on the MFPDI recorded on some days, assessed using a self-administered questionnaire, previously validated by Garrow et al (12) for this purpose, in a population of similar age. Although a more conservative definition has been proposed by other investigators (13), such that for foot pain to be present, participants were required to have at least one item on the MFPDI recorded on most/every day, this method was validated for use in an older cohort (14). Thus we felt the definition used by Garrow and colleagues was more appropriate for our study. Lastly, since our study population was initially recruited to examine the relationship between obesity and

musculoskeletal disease, we had a higher prevalence of obese individuals than the general population. We also had a higher prevalence of subjects with foot pain than previously reported by other studies (2-3, 40-41). Nonetheless, when we excluded those who are obese (BMI $\geq$ 30 kg/m^2), we had a similar prevalence of foot pain (34%) as previous studies (prevalence range 18%-42%).

This study demonstrates that the effect of obesity on foot pain is related to an increase in adiposity, particularly in the android distribution of fat. In contrast, we show a beneficial effect of a gynoid distribution of fat. The mechanism for the effect of obesity may be a combination of a mechanical effect via increased loading on the foot as well as a systemic effect. Since obesity is a modifiable risk factor, lifestyle and dietary changes that contribute to weight loss and promote better fat distribution may have an important role in symptomatic relief of foot pain. These data also suggest a role for metabolic factors which may also offer therapeutic targets in the management of foot pain and disability.

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Table 1. Demographics of the studied population

	Total sample (n = 136)	Foot pain (n = 75)	No foot pain (n = 61)	P value
Age (years)	47.5 (9.0)	47.5 (9.2)	47.7 (8.8)	0.90*
Gender (female), number (%)	114 (83.1)	66 (88.0)	48 (77.1)	0.90†
BMI (kg/m^2)	32.1 (8.4)	35.1 (7.8)	28.4 (7.6)	<0.001*
Total fat mass (kg)	36.9 (17.3)	43.1 (15.7)	29.2 (16.1)	<0.001*
Total skeletal muscle mass (kg)	23.4 (5.2)	23.6 (5.3)	23.1 (5.2)	0.60*
Fat mass index	13.7 (6.7)	16.2 (6.2)	10.6 (6.0)	<0.001*
Fat-free mass index	18.4 (2.7)	18.8 (2.6)	17.8 (2.6)	0.02*

Values are reported as mean (SD) unless otherwise stated

P value calculated for difference between subjects with and without foot pain, using

*independent samples t-test or †chi-squared test

Table 2. The relationship between body composition and foot pain

	Univariate odds ratio (95% CI)	P value	Multivariate odds ratio (95% CI)	P value
BMI	1.12 (1.06, 1.17)	<0.001	1.11 (1.06, 1.17)	<0.001*
Total fat mass**	1.05 (1.03, 1.08)	<0.001	1.05 (1.02, 1.09)	0.001*
Total skeletal muscle mass†	1.02 (0.95, 1.09)	0.59	0.99 (0.86, 1.15)	0.91
FMI‡	1.16 (1.09, 1.23)	<0.001	1.16 (1.06, 1.28)	0.002*
FFMI§	1.18 (1.03, 1.35)	0.02	0.99 (0.78, 1.25)	0.91

CI = Confidence interval, BMI = body mass index, FMI = fat mass index, FFMI = fat-free mass index

Multivariate odds ratio adjusted for age, gender, and the measure of body composition: **skeletal muscle mass, †fat mass, ‡FFMI or §FMI; where *p<0.01 is considered significant using Bonferroni correction for multiple testing

Table 3. The relationship between fat distribution and foot pain

	Univariate odds ratio (95% CI)	P value	Multivariate odds ratio (95% CI)	P value
Percent total body fat	1.09 (1.05, 1.13)	<0.001	1.10 (1.05, 1.14)	<0.001*
Android/total body fat ratio	1.22 (0.99, 1.50)	0.07	1.42 (1.11, 1.83)	0.01
Gynoid /total body fat ratio	0.85 (0.76, 0.95)	0.005	0.83 (0.73, 0.93)	0.002*
Android/gynoid fat ratio	9.55 (1.0, 91.51)	0.05	35.15 (2.60, 475.47)	0.01
Trunk/total body fat ratio	1.01 (0.96, 1.06)	0.76	1.05 (0.98, 1.12)	0.17
Trunk/total limb fat ratio	0.78 (0.29, 2.10)	0.63	1.50 (0.40, 5.56)	0.54
Trunk/lower limb fat ratio	0.89 (0.45, 1.78)	0.75	1.40 (0.57, 3.39)	0.48

CI = Confidence interval

Multivariate analysis adjusted for age and gender, where *p<0.007 is considered significant using Bonferroni correction for multiple testing

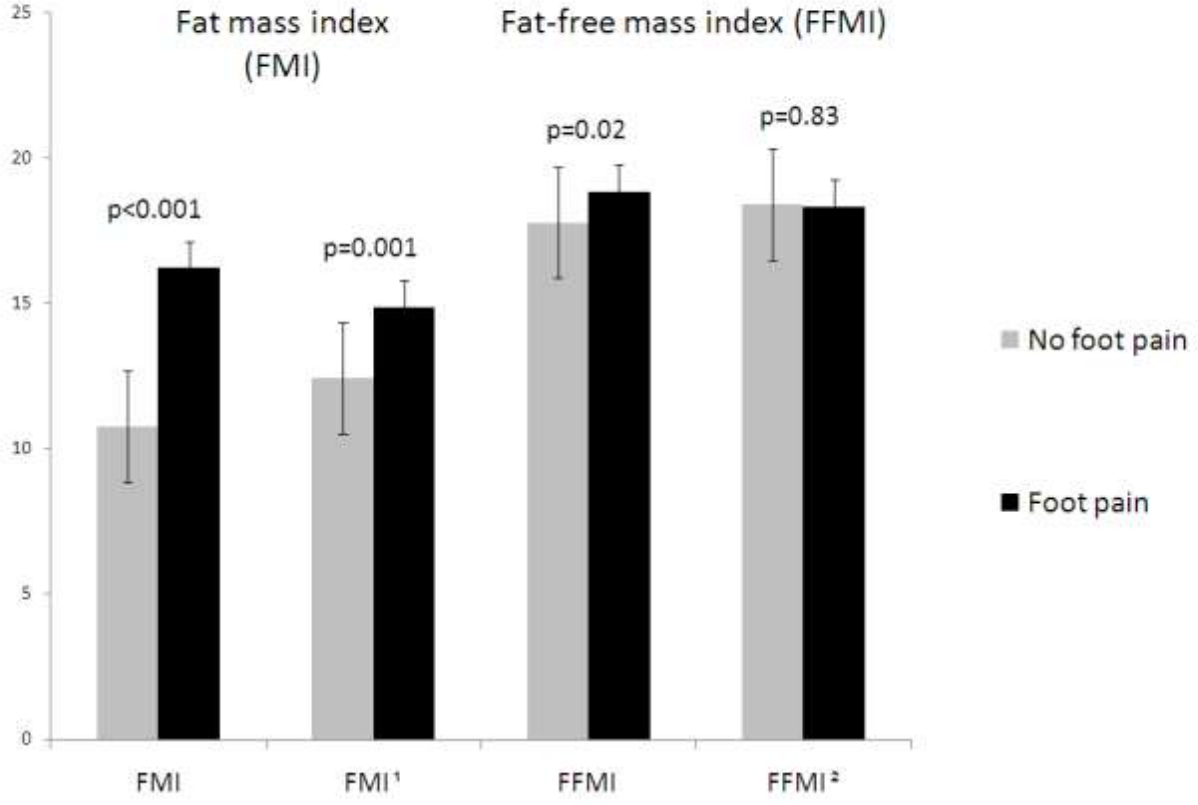

Figure 1. The mean fat mass index (FMI) and fat-free mass index (FFMI) ([1]adjusted for age gender and FFMI; [2]adjusted for age, gender and FMI)

Chapter 6. General Discussion

6.1 Main Findings

This thesis comprises 3 main areas of focus: the significance of different structural abnormalities at the tibiofemoral joint, the association between indices of patellofemoral geometry and knee pain and structure in the patellofemoral joint, and the effect of obesity on musculoskeletal disease. Firstly, this thesis demonstrated an association between bone marrow lesions (BMLs) and subchondral bone cysts and progression of disease. Secondly, at the patellofemoral joint, a medially inclined patella and a shallower sulcus angle were found to be beneficial for knee symptoms and patella cartilage, whilst a high-riding patella was associated with adverse effects on patella cartilage. Finally, an association was observed between obesity and symptomatic and structural outcomes at the knee and the foot.

6.1.1 Bone Marrow Lesions and Subchondral Bone Cysts in Tibiofemoral Osteoarthritis

The first focus of this thesis was to explore the significance of bone abnormalities at the tibiofemoral joint in relation to structural progression of OA. In a population with knee OA, the severity of BMLs at baseline was associated with reduced baseline tibial cartilage volume, increased cartilage loss over 2 years and increased risk of knee joint replacement over 4 years. Importantly, this effect was further compounded by the co-existence of subchondral bone cysts, as we demonstrate that those with both BMLs and cysts had less baseline cartilage,

greater loss of cartilage over 2 years and higher risk of knee joint replacement over 4 years compared to those who have BMLs only or those with no BMLs or cysts. There was also a potential for BMLs and subchondral bone cysts to regress, some to the point of complete resolution.

Our findings that BMLs are associated with cartilage volume is consistent with previous findings from radiographic and MRI studies, indicating a relationship between BMLs and JSN (165) and cartilage loss (166). However, the findings relating to knee joint replacement is novel. The association between BMLs and knee joint replacement was first suggested in 1994, whereby 7 out of 9 cases with knee OA scheduled to undergo prosthetic knee replacement were found to have subchondral MR changes (215). Histologically, these MR changes corresponded to regions where fibrous tissue replaced marrow fat, with some thickening of the trabeculae (215). To our best knowledge, prior to our study, only one other study had reported an association between BMLs and total knee replacement (216). In a highly selected population of 65 patients drawn from a cohort of over 4000, there was an increased risk of knee replacement in those with BMLs at the time of their first MRI (216). Our study was the first to examine and demonstrate a relationship between BMLs and risk of knee joint replacement, independent of potential confounders. Of note, two subsequent studies have corroborated our findings (245, 246). These studies indicated that baseline BML severity was associated with subsequent knee replacement at 5 years (245) and at 8 years (246), though no association was reported between change in BML score over 2 years and risk of knee joint replacement at 8 years (246).

Moreover, our findings strengthen the evidence for a previously suggested relationship between BMLs and subchondral bone cysts (221, 247), not only by demonstrating that 98% of people with cysts had a co-existing BML, which were often large BMLs (grade ≥3), but also by showing that these people are at greater risk of structural progression than those with BMLs only. No other study, previous or subsequent to ours, has examined the concomitant effect of cysts and BMLs. However, one study did indicate increased odds for incident subchondral bone cyst in subregions with prevalent BMLs, particularly larger BMLs (248).

Although we have shown that BMLs and subchondral bone cysts predict loss of cartilage and joint replacement, it is unclear whether they directly facilitate structural progression or are simply markers of those at greater risk of progression. Perhaps more important than our findings that BMLs and subchondral bone cysts predict worse structural outcomes are the findings that even in those with established OA, there is a potential for regression of both BMLs and subchondral bone cysts, with a possibility of complete resolution. This is supported by other studies that have shown a potential for BMLs to regress (166, 249-251), with one particular study showing regression or resolution in as many as 50% of cases (251). However ours was the first study to show a potential for subchondral bone cysts to regress. Of note, we also showed that those who had subchondral bone cyst regression had reduced lateral tibial cartilage loss compared to those who remained stable or progressed. These findings are important given that there is currently no known cure for OA and therefore any means to delay or stop disease progression are worth investigating. A recent review has highlighted the need for further research into

pharmacological or surgical interventions that may facilitate BML regression (252). There is evidence in that anti-tumour necrosis factor (TNF) therapy alone or in combination with methotrexate was able to suppress BMLs in patients with rheumatoid arthritis (RA) (253, 254), and whilst we recognise that BMLs in OA are likely different to those in RA, this encourages the need for similar investigations in OA.

Furthermore, our findings of a relationship between BMLs and subchondral bone cysts potentially contributes to our understanding of how subchondral bone cysts arise. The synovial breach theory of cyst formation hypothesises that subchondral bone cysts arise from the intrusion of synovial fluid into the subchondral bone as a result of elevated intraarticular pressure (218, 219). This theory was proposed as early as 1953 and arose based on observations that there are often patent openings in a number of cysts, that cartilage fragments are found within cysts, and that the cartilage over cysts is never normal (219). Subsequently a second theory was proposed a decade later which hypothesised that subchondral bone cysts are a consequence of violent impact between opposing surfaces which result in areas of bone necrosis, and that synovial breach is a secondary event (220, 255). This theory is known as the bone contusion theory. At present the origins of subchondral bone cysts remain unclear. If the synovial breach theory was valid, one would expect subchondral bone cysts to develop only in areas where the overlying cartilage is fully eroded or fissured, thereby allowing a communication between the synovial cavity and the subchondral bone. Nevertheless, a recent study has shown that in almost 50% of cases, subchondral bone cysts were found in subregions without full-thickness cartilage

loss (247). Another study demonstrated an association between full-thickness cartilage loss and incident subchondral bone cysts, though the effect was significantly attenuated when adjusted for BMLs (248). That several studies have now shown that subchondral bone cysts arise and are present in areas with BMLs supports the bone contusion theory, given that these BMLs often histologically present features of bone trauma, such as necrosis.

6.1.1.1 Limitations

The main limitation to this work was the absence of T2-imaging sequencing. Consequently, T1 images were used to measure BMLs, which is likely to result in a more conservative analysis. For BMLs to be identifiable on T1 images they need to be larger and with more surrounding oedema (256) thus smaller lesions may have been missed. We also had a modest number of subjects who had a knee replacement. Therefore whether the site of BMLs or subchondral bone cysts further influences the risk of knee replacement could not be examined.

6.1.2 Bone Geometry and the Patellofemoral Joint

Although a large body of research has focused on the tibiofemoral joint, it is well known that disorders at the patellofemoral joint are also a significant contributor to knee pain and disability. Thus the second focus of this thesis was to explore the association between indices of patellofemoral geometry and knee pain and patella cartilage volume. It was found that a more medially inclined patella (as indicated by a larger lateral condyle-patella angle) and a shallower (larger) femoral sulcus were associated with reduced pain and increased patella cartilage

volume. On the other hand, a higher riding patella (as indicated by an increased Insall-Salvati ratio) was associated with reduced patella cartilage volume.

Patella inclination (patella tilt) is one of the more commonly assessed parameters of patellofemoral malalignment. Our findings demonstrate that a more medially inclined patella is favourable both with respect to symptoms and structure. Similar findings have been reported by another MRI study which assessed quartiles of lateral patellar tilt angle (257), demonstrating an inverse relationship between lateral patellar tilt angle and lateral patella cartilage volume loss whereby a medial inclination of the patella (as indicated by a larger lateral patellar tilt angle) was associated with less patella cartilage loss in the lateral compartment. These findings are in contrast with radiographic evidence in which a more laterally inclined patella was associated with an increase in medial patellofemoral joint space (231), which the authors attributed to a protective effect against medial cartilage loss. Nevertheless, these are radiographic findings which are limited by the inability to assess cartilage directly. When the patella is laterally inclined, the medial joint space will intuitively be greater without necessarily being a product of greater cartilage volume in that compartment. Of note, studies that have assessed patella inclination have used varying methods both in how the measure of patella inclination was obtained and the images used to measure them (258), thus making it difficult to adequately compare their findings. For example, patella inclination can be measured as the angle formed by the lines joining the maximum width of the patella and the posterior or anterior femoral condylar line, or as the angle formed by the lines joining the lateral patella facet and the posterior or anterior femoral condylar line (258). This

issue of the various methods by which patella inclination can and has been assessed in the literature has previously been highlighted by Alemparte *et al* (259) who proposed a standardisation to the technique. To date, no standardised method to assess patella inclination exists.

The sulcus angle is another index of patellofemoral geometry that is commonly assessed. Our findings indicated a trend for a positive relationship between sulcus angle and patella cartilage volume but no association with knee pain. It is commonly accepted that a shallower sulcus is associated with a decrease in patellofemoral congruency and stability (114, 260), thereby posing the risk of patella subluxation and dislocation (261, 262). Previous studies predominantly reported unfavourable effects associated with a shallower sulcus angle (231, 257, 263). One radiographic study found a positive association between sulcus angle and lateral joint space narrowing (JSN) progression (231). This is consistent with MRI findings whereby a greater sulcus angle was associated with increased medial and lateral patella cartilage loss (257). Since the publication of our findings, a subsequent MRI study has reported a 50% increase in odds for lateral cartilage damage in those in the highest quartile of sulcus angle compared to those in the lowest quartile (264), thus further supporting the hypothesis that greater sulcus angles are associated with adverse knee events. Whilst the reason for the discrepancy in findings between our study and others is unclear, mechanistically it may be that a shallower sulcus provides greater surface for articulation, thereby reducing contact pressures and potentially benefiting articular cartilage. This hypothesis was proposed by the authors of another study

which similarly showed a beneficial relationship between a shallower sulcus and increased patella cartilage in an osteoarthritic population (265).

Lastly, we examined the Insall-Salvati ratio, which is an indicator of patella height. Both a high-riding patella (Insall-Salvati ratio >1.2) and a low riding patella (Insall-Salvati ratio <0.8) can have deleterious effects on structure (108, 110). Previous studies of populations with knee OA have shown an association between high-riding patella and increased cartilage loss (257) and JSN progression (263). Accordingly our results indicate that a greater Insall-Salvati ratio is associated with reduced cartilage volume in a community-based population of adults without history of any arthropathy. These findings are further supported by a subsequent study which demonstrated an association between Insall-Salvati ratio and both baseline and the progression of cartilage damage in the medial and lateral compartments in a population with knee OA (266). It is believed that the detrimental effects of a high-riding patella are related to the decrease in load-bearing surface area (107, 108).

Taken together, it appears that while it is generally accepted that patella alignment and geometry play an important role in patellofemoral pain and OA, the aetiology behind it is somewhat unclear. A recent review of patella alignment and tracking has highlighted inconsistent findings in relation to associations with patellofemoral pain (258). One potential explanation for the conflicting results, particularly in relation to patella inclination and sulcus angle, is likely the various methods by which the measures for these indices of patellofemoral alignment and geometry are obtained. For example, several imaging techniques

are commonly used, including radiography, computerized tomography (CT) and MRI (258). This is further complicated by the varying degrees of knee flexion in which the knee can be imaged (258). A study of *in vivo* patellar tracking has indicated that the patella was in a lateral tilting position between 0º and 75º of knee flexion but then gradually tilted medially beyond 75º (267). Femoral sulcus angle is also affected, with a mean angle of 143.3º at full extension reduced to 139.2º at 30º of knee flexion and 134.8º at 135º of knee flexion (267). We have also discussed previously in this section the varying methods that have been employed to measure patella inclination. As such comparing the results of different studies can be problematic. This highlights the importance of further research to determine a standardised method by which patella alignment and geometry should be assessed.

6.1.2.1 Limitations

A limitation of this work is that the Western Ontario and McMaster Osteoarthritis Index (WOMAC) knee pain score does not differentiate between tibiofemoral and patellofemoral pain. The Kujala score would have been preferable as an indicator of patellofemoral pain, however as this data was not available we used the WOMAC pain score which has previously been utilised in studies of patellofemoral disorders (231, 268-270). In addition, our study cohort was predominantly women, which may have influenced the results since there is evidence for a gender difference in patellofemoral joint biomechanics (271). Our study also excluded those with a history of any arthropathy diagnosed by a medical practitioner, prior surgical intervention and previous significant knee

injury, thus some subjects with clinically severe patellofemoral pain may have been excluded from our study.

6.1.3 Obesity and Knee Osteoarthritis

Finally, the effect of obesity on musculoskeletal disease was explored. At the knee, obesity was associated with adverse outcomes both related to symptoms and structural changes. Weight gain was associated with incident knee pain, stiffness and functional difficulties whilst weight loss was associated with some modest benefits on the alleviation of symptoms, as well as reduced cartilage loss.

The association between obesity and musculoskeletal disorders has long been recognised. Much research has been done to examine the role of obesity in OA. Our findings indicate that gaining 5% of initial body weight or more was associated with the worsening of knee pain, stiffness and function, whilst weight loss was beneficial for improvements in these symptoms. Previous studies have shown a linear relationship between BMI and knee pain (272-274), beneficial effects of weight loss on knee symptoms (25, 26, 275), and detrimental effects of weight gain on risk of OA (62, 276). However, our finding that weight gain is related to worse knee symptoms compared to remaining stable weight is novel. Adipose tissue produces a number of adipocytokines including interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α), leptin and adiponectin (277, 278). In obesity, the downregulation of potentially beneficial adipokines (adiponectin) coupled with the overproduction of pro-inflammatory cytokines (IL-6 and TNF-α) creates a chronic state of mild inflammation (278, 279) which may contribute

to the development of pain (280, 281). However it is important to also note that obesity has been shown to affect joint biomechanics via increased joint loading (282), and increased knee loading frequency and magnitude has subsequently been shown to be associated with increased knee pain (283). Thus, it is likely that obesity affects joint pain in a multi-faceted way via changes in joint biomechanics as well as via systemic factors associated with greater adiposity.

The relationship between weight loss and knee structural changes is an area of great interest, albeit one that has not been greatly researched. Despite the abundant evidence that weight loss is beneficial for alleviation of symptoms, studies that have examined the impact of weight loss on structural progression, particularly cartilage loss, is scarce. To our best knowledge, no study prior to ours had examined weight loss in relation to cartilage loss as imaged on MRI. Previous evidence of the benefits of weight loss on knee structure was largely from studies of cartilage biomarkers, which reported some correlation between weight loss and cartilage turnover (26, 238). In our study, participants who lost 5 kg or more over 2 years had reduced medial tibial cartilage loss when compared to those who remained stable weight. However, another paper which was published subsequent to the writing of our manuscript reported an association between weight loss and improvements in cartilage quality and thickness in the medial femoral, but not tibial, compartment (284). It was found that a higher percentage weight loss was associated with reduced loss of cartilage thickness in the medial femoral compartment, and percentage weight loss was positively correlated with medial dGEMRIC index, which is a measure of cartilage integrity (284).

Recently there has been a push to promote not only weight loss, but also the maintenance of stable weight or the prevention of weight gain. A review of 31 long-term weight loss studies found that dieting is a predictor of future weight gain (285), and analysis of normal weight and overweight women found that only 40% of participants maintained their baseline weight over 3 years and these women were the least likely to have tried dieting (286). Weight loss has long been the goal of obesity management, with guidelines recommending a loss of at least 5-10% of initial body weight (287, 288). Unfortunately, while there is much evidence to show the benefits of weight loss, it is becoming increasingly clear that achieving, and more importantly maintaining, weight loss is difficult. The regulation of body weight is modulated by circulating hormones which influence the desire to eat. These include ghrelin, a hunger stimulator which is produced in the stomach, as well as a number of known hunger inhibitors: cholecystokinin (CKK), oxyntomodulin, glucagon-like peptide-1 and peptide YY3-36 which are produced in the gut; amylin, insulin and pancreatic polypeptide which are produced in the pancreas; and leptin which is produced in adipose tissue (289). These hormones create a physiological defence of body weight and encourage weight regain after weight loss. The level of the hunger-promoting hormone, ghrelin, rises after weight loss (290), whereas the levels of hunger-inhibiting hormones, such as leptin, CKK and insulin, are decreased (291). Thus it is not surprising that weight regain is commonly observed in studies where participants have successfully achieved significant amounts of weight loss. The average weight loss maintained at 4-5 years was reportedly around 2.1% to 6.6% (292).

Taken together, there is a need to encourage at the very least the maintenance of stable weight, which is often viewed as more attainable than weight loss, given that without any action future weight gain is likely. This would also prevent those who have not been able to lose weight or achieve their target weight loss from being discouraged from taking further action. Indeed our findings suggest that weight gain is associated with adverse effects on the knee joint in comparison to remaining stable weight, which indicates that even if a person is unable to lose weight then at least the maintenance of body weight may prevent or delay the onset of knee symptoms and any progression in joint damage associated with further weight gain. Women have been shown to gain up to an average of 830 grams annually (293). It has been hypothesised that since losing 3-5 kg can reduce cardiovascular and diabetes risk (294), then avoiding the predicted weight gain of ~3 kg over 4 years would have similar health benefits (295). Although much of the research in this area was done in relation to cardiovascular health and risk of diabetes, our findings suggest that the benefits of curbing weight gain may also extend to musculoskeletal disease.

6.1.3.1 Limitations

A potential limitation to this work was the modest number of men, which may affect the generalisability of these results across both genders. Nevertheless, when we excluded men from our analysis similar results were found. There are several potential confounders which we were not able to adjust for, such as depression and socioeconomic status, which would be interesting to explore further. We also only assessed tibial and not femoral cartilage. Nevertheless tibial cartilage volume correlates with femoral cartilage in that compartment

(296) and longitudinal changes in the tibial and femoral cartilage are strongly correlated (297).

6.1.4 Obesity and the Foot

At the foot, the effects of obesity were further extended by the findings that the adverse effects of obesity relate to fat mass and that fat distribution is important. In this cohort where foot pain affected 55% of the population, fat mass was associated with increased odds for foot pain, independent of muscle mass. In particular, a gynoid fat distribution was found to be preferable over an android distribution as it was associated with reduced odds for foot pain.

The role of obesity in foot pain is an area that has not received great interest. Although there is evidence to support a relationship between obesity and foot pain (242-244), they are limited by the use of BMI as a measure of obesity, which provides no information about the differential contributions of fat and muscle mass. Our study was the first to show a relationship between fat distribution and foot pain and disability related to foot pain. In this study, we have extended previous observations by demonstrating that fat mass was associated with increased odds for foot pain, independent of muscle mass, and that muscle mass was not associated with odds for foot pain. We further demonstrated that the site of fat storage was also important, as a gynoid fat distribution was related to reduced odds for foot pain while an android distribution was related to increased odds for foot pain.

As previously discussed, adipose tissue is a highly active endocrine organ which produces a number of cytokines known as adipokines (277). There is much evidence to suggest that the metabolic activity of adipose tissue is different at different sites (298). One of the much investigated adipokines, particularly in relation to diabetes and cardiovascular disease, is adiponectin. Adiponectin is an anti-inflammatory adipokine produced exclusively by adipocytes. It is negatively correlated with BMI, waist circumference and estimated visceral fat area (299), and higher adiponectin levels predict beneficial effects such as lower risk of type 2 diabetes (300, 301). Adiponectin has been shown to strongly suppress the production of TNF-α [33] and induce the anti-inflammatory cytokines IL-10 and 1L-1 receptor antagonist [37]. That we found differing effects between android fat and gynoid fat distributions likely reflects the fact that certain adipokines, including adiponectin, are secreted differently by android and gynoid fat tissues such that those with a gynoid fat distribution have a better adipokine profile (302-304).

The implication of the findings that the effect of obesity on foot pain and other disorders is distribution-related remains unclear. Despite identifying android fat as having adverse effects compared to gynoid fat, to what degree a person's fat distribution itself can be influenced by the individual is uncertain. It has been suggested that fibre intake, vigorous activity, weight training, and walking pace are negatively associated with waist gain (defined as an increase in waist circumference) in men over a period of 9 years, whilst smoking cessation and television watching was positively associated with waist gain (305). A separate study found increased consumption of vegetable oil, pasta, 1.5% milk and

reduced consumption of 3% milk is associated with the more favourable gynoid fat distribution (306). Nevertheless, it is likely that for the most part, having an android distribution simply serves as a marker for those at greater risk of certain diseases.

6.1.4.1 Limitations

Multiple testing may be a limitation to this work, though we have attempted to correct for this using the Bonferroni adjustment method. We also had a smaller proportion of men, thus the relationship between body composition and foot pain in men may require further research. Other methods of defining disabling foot pain have been used previously (203, 307, 308), however we chose our definition based on the work by Garrow *et al* (203) as their population was most similar to ours. Lastly, we had a high prevalence of obese individuals in our study which may account for the higher prevalence of subjects with foot pain compared to that reported by other studies (197, 198, 309). Indeed when we excluded those with a BMI $\geq$30 kg/m^2, our prevalence of foot pain was similar to those previously reported.

6.2 Limitations of this Work

The specific limitations pertaining to each section of work has been discussed above. This section will discuss in greater detail the more general limitations of the work in this thesis.

6.2.1 Study Populations

6.2.1.1 Knee Osteoarthritis

The population studied in chapter 2 was one with symptomatic knee OA, therefore the findings could not be generalised to asymptomatic populations. One of our main findings was that BMLs and subchondral bone cysts commonly co-exist. However we were unable to explore whether this also holds true in populations without knee OA. BMLs and cysts have both been shown to be present in asymptomatic populations (46, 177, 310), albeit at a lower prevalence. Thus future studies examining the role and the potential co-existence of BMLs and subchondral bone cysts in individuals without knee OA may help to better understand their relationship.

6.2.1.2 Volunteers

A proportion of the subjects studied were volunteers, which may have biased our sample towards a population that was generally more health conscious than the general population. This is unlikely to affect structural abnormalities such as BMLs and patellofemoral geometry, however it may influence change in weight such that a more health conscious population may be more motivated to lose weight and less likely to gain weight. Of note, planned weight loss was not part of the criteria for recruitment.

6.2.1.3 Gender

Some of our populations were also predominantly comprised of women. This may be important since it may affect some of our findings. For example, there is

evidence that patellofemoral disorders are more common in women, at least in part due to the difference in patellofemoral contact areas and pressures (271). Obesity is also known to affect men and women differently. Whereas men are more likely to have abdominal obesity, women tend to store fat in their hip and thigh (gynoid) area (311). Furthermore, a study of elderly Koreans demonstrated that a gender difference exists in the relationship between obesity and chronic diseases, including arthritis, diabetes and the metabolic syndrome (312). In our study, when we excluded men, the results remained significant in women. Nevertheless, our findings may have limited generalisability and further research is required to confirm these findings in men

6.2.2 Study Designs

6.2.2.1 Cross-sectional Studies

The work presented in chapters 3 (the association between patellofemoral geometry and knee pain and patella cartilage) and 5 (the association between body composition and fat distribution and foot pain) were cross-sectional in nature. Of note, these were areas that to date are still not well researched and our findings highlight potentially interesting relationships to be further explored longitudinally. Nevertheless, one of the greatest limitations of cross-sectional studies is the inability to establish a temporal relationship. Thus it is possible, for example, that in the study presented in chapter 3 that patella cartilage loss resulted in changes to patella inclination due to changes to the joint space, or that the presence of knee pain resulted in changes to gait as a compensation mechanism, which subsequently resulted in alterations to some of the indices of

patellofemoral geometry. Similarly in chapter 5, we cannot exclude the possibility that the presence of foot pain and disability related to foot pain resulted in a more sedentary lifestyle which then contributed to obesity and increased fat mass.

6.2.2.2 Cohort Studies

Other findings in this thesis were longitudinal in nature. Although these had adequate follow-up time to examine outcomes such as joint replacement and cartilage loss, they may benefit from longer observations. For example, whilst we show an association between changes in weight and changes in knee symptoms, we cannot be certain that the change in weight preceded the change in symptoms. It may be that the worsening of knee pain resulted in decreased physical activity, which contributed to weight gain. Notably, adjustment for physical activity did not significantly alter our results. Extending the observation period would enable us to more adequately examine the relationship, as we would be able to assess change in weight between baseline and the first follow-up and correlate it with change in symptoms between the first and second follow-up.

6.2.3 Sample Size

The sample sizes of the populations in this thesis were sufficient to explore a number of relationships between exposures and outcomes. However there were other potentially interesting relationships that were unable to be examined due to a modest sample size in particular subgroups. In chapter 2, we were unable to assess how the location of BMLs and subchondral bone cysts may influence the

relationship with knee joint replacement, given the modest number of subjects who had had a knee replacement. Similarly in chapter 4, it would have been interesting to explore additional categories of weight change, to see how different amounts of weight gain or weight loss relate to changes in knee symptoms and knee structure, and whether weight gain or weight loss that corresponds to a change in BMI class (e.g. increase from normal (BMI 18.5-24.9 kg/m^2) to overweight (BMI 25-29.9 kg/m^2), or decrease from obese class II (BMI 35-39.9 kg/m^2) to obese class I (BMI 30-34.5 kg/m^2)) is different to a similar weight gain/loss that does not correspond to a change in BMI class, in relation to knee symptoms and structure.

6.2.4 Measurement of Bone Marrow Lesions

The absence of T2-imaging sequencing was a potential limitation to our study. A consensus statement published in 2006 by OMERACT (Outcome Measures in Rheumatology Clinical Trials) and OARSI (Osteoarthritis Research Society International) (256) stated that "bone marrow abnormalities associated with OA are most sensitively demonstrated with fat-supressed T2-weighted fast spin-echo (FSE) images and short-tau inversion recovery (STIR) images". Thus it may be that ours was a conservative measure in that smaller lesions would not have been detected. However, any measurement error and misclassification as a result of our method would likely result in an underestimation of the relationship between BMLs and disease progression, but it would not result in spurious associations. Furthermore, our measure had high reliability and reproducibility, and our findings were consistent since BMLs were shown to affect cartilage volume

cross-sectionally and longitudinally through to knee joint replacement. Of note, there is currently no data comparing the reliability and sensitivity of T1- and T2-weighted images in detecting the presence of BMLs.

6.2.5 Measurement of Pain

Another limitation was the use of WOMAC pain score to assess patellofemoral pain, rather than a more specific measure such as the Kujala patellofemoral score. Whilst WOMAC knee pain scores do not differentiate between tibiofemoral and patellofemoral pain, it has been widely used in previous studies of patellofemoral disorders (231, 269, 270). Nevertheless, it may be that there was some overestimation of patellofemoral pain in our study, and that some participants with knee pain in the tibiofemoral but not patellofemoral compartment were misclassified as having patellofemoral pain. Therefore we cannot rule out the possibility that the observed association between a more medial patella inclination and reduced pain score was overestimated or spurious. Nevertheless the main findings of our study were in relation to patella cartilage volume as an outcome measure, which would not have been affected by this.

6.3 Future Directions

This thesis has demonstrated that bone abnormalities are associated with worse structural outcomes in people with knee OA. The implications of these findings warrant further investigation, given that it remains uncertain whether BMLs and subchondral bone cysts themselves provide therapeutic targets or whether they are simply a marker of disease. It has been suggested that the therapeutic

management of BMLs depend on the disease involved, and in the case of BMLs such as those found in OA, it is thought that they represent a concomitant component of the disease without any main influence on the therapeutic management (313). One study had recommended treatment with the prostacyclin analogue iloprost, particularly for ischemic and post-traumatic BMLs (314). A recent pilot study was the first to examine treatment for BMLs specifically in an OA cohort (315). In this study, 70 patients with knee OA were randomly assigned to receive either chondroitin sulphate (CS) or placebo for the first 6 months followed by another 6 months of treatment with CS for both groups. It was found that CS treatment reduced cartilage volume loss at 6 months particularly in the lateral tibiofemoral compartment and tibial plateaus, which persisted through to the end of the 12-month follow-up period. However the decrease in BMLs with CS treatment occurred only after 12 months and not after 6 months. Interestingly, the anatomical regions where a decrease in BML occurred corresponded with the regions where reduced cartilage loss occurred. Whilst these findings highlight the possibility of BMLs as therapeutic targets, there are nevertheless preliminary and warrant further research.

To our best knowledge no study has examined the therapeutic potential of subchondral bone cysts in OA. Given that our findings and others support an association between BMLs and subchondral bone cysts, particularly if BMLs are indeed pre-cystic lesion, then effective therapeutic treatment for BMLs could potentially have subsequent therapeutic benefits for subchondral bone cysts. Moreover, if BMLs are pre-cystic lesions then future research should aim to

identify potential risk factors which are associated with the progression from BML to subchondral bone cyst as this likely indicates progression of disease.

In the patellofemoral compartment, future studies to determine a standardised technique by which patellofemoral alignment and geometry should be assessed may help to clarify current conflicting findings. Current treatment options which are designed to improve patella alignment include quadriceps retraining, stretching lower limb muscles, patella mobilizing, correcting foot biomechanics with orthoses, and patella taping or bracing (316-319). However, these have predominantly been assessed in relation to symptomatic relief in patellofemoral pain syndrome and it is unknown whether there are any corresponding structural benefits. Patellar taping was first used in 1986 with an aim to create a medial realignment of the patella, thus improving patella tracking (320), and although several studies have observed pain reduction with patellar taping (321-323), 2 randomised controlled trials (RCTs) found no benefit when patellar taping was added to physical therapy (324, 325). Similarly, while bracing alone may provide symptomatic relief, 3 RCTs found no benefit when used in addition to physical therapy (326-328). Taken together, it appears that continued research is required to identify effective treatment options for correcting patella alignment. It remains that parameters such as patella inclination and patella height can potentially be corrected and therefore represent potential therapeutic targets. However, it is uncertain whether the sulcus angle can be influenced, thus it is likely that it represents more of a marker of those who are at risk of adverse patellofemoral events.

Finally, obesity is a growing problem worldwide and, as this thesis has demonstrated, affects musculoskeletal disease in the knee and feet. The findings of this thesis highlight two major areas that require much attention: 1) finding effective means for weight loss and, more importantly, weight loss maintenance for those who are already overweight or obese, and 2) promoting the maintenance of a stable weight and the prevention of weight gain in the general population. It was recently shown that controlling the current obesity epidemic in Australia could potentially prevent around 42.5% of symptomatic knee OA (3). In 2006, The National Agenda to Address Overweight and Obesity in Adults and Older Australians was released with goals to prevent weight gain, achieve better management of early risk, and improve weight management, with a particular emphasis on the prevention of weight gain in the first place to avoid subsequent inappropriate dieting (329). In April 2008, obesity was announced as the 8th National Health Priority Area (330). Yet, obesity continues to be a growing problem. Continued research in this area is crucial, in conjunction with efforts not only from the individual, but also with support from the community and government.

Chapter 7. Conclusions

This thesis identified a number of novel relationships between risk factors and musculoskeletal disease. Musculoskeletal disease, particularly OA, is a problem that affects a significant proportion of the population. Many risk factors for musculoskeletal disease have been identified. However, they are not necessarily well understood. In summary:

7.1 Improved Understanding of the Role of Structural Abnormalities in Musculoskeletal Disease

It is well established that bone abnormalities are a feature of OA, though how they develop and what role they play in the aetiology of disease is unclear. This thesis has strengthened previous evidence of a relationship between BMLs and subchondral bone cysts. It further showed that those with co-existing BMLs and subchondral bone cysts have greater severity of disease compared to those with BMLs only or those with no BMLs or cysts, as having both BMLs and subchondral bone cysts was associated with worse structural outcomes in the tibiofemoral compartment. In light of their ability to regress and resolve, BMLs may represent potential therapeutic targets which may delay or prevent subsequent development of subchondral bone cysts and the progression of disease.

This thesis also highlights the need for a standardised method to measure indices of patellofemoral geometry, particularly given the conflicting findings by studies.

It is also clear that further research in this area is required. Patellofemoral disorders are prevalent, yet there is much greater interest in the tibiofemoral compartment. The findings of this thesis support previous hypotheses that a more medial patella inclination is beneficial and that a high-riding patella is associated with adverse effects. Further research is required into treatment options which promote more favourable patellofemoral geometry.

7.2 Novel Findings Relating to Obesity and Musculoskeletal Disease

Obesity has long been associated with musculoskeletal conditions and it continues to be a challenge. This thesis has several novel findings relating to musculoskeletal disease, firstly by demonstrating that weight gain was associated with worse symptomatic outcomes at the knee compared to remaining stable weight. That this had not previously been examined likely reflects the fact that weight gain was intuitively presumed to be associated with adverse outcomes.

This thesis further demonstrated that weight loss was beneficial as it was associated with reduced knee symptoms and less cartilage loss. This highlights the need to find more effective means to combat the growing obesity epidemic. Although there is no shortage of weight loss promotion through diet, pharmacotherapy and lifestyle changes, effective weight loss and maintenance of weight loss continues to be a problem.

Finally, this thesis identified novel relationships between body composition and foot pain and disability related to foot pain. It was found that whilst fat mass was related to foot pain, skeletal muscle mass was not. Furthermore, fat distribution was also of importance as a gynoid fat distribution, which was associated with reduced odds for foot pain, was preferable over an android fat distribution. The use of BMI in studies of obesity is common. However it is important that these studies are also supplemented by the use of other measures of obesity, which allow assessment of the independent contributions of different components of body composition.

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Manuscripts not directly related to this thesis

IMAGING OF KNEE OSTEOARTHRITIS

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SUMMARY

The use of Magnetic Resonance Imaging (MRI) in studies of OA is becoming increasingly common. Its benefit over radiography relate to its enhanced ability to identify structural changes prior to the presence of radiographic disease. Although cartilage loss is the hallmark of OA, it is clear that OA is a disease of the whole joint. MRI is able to directly visualise the whole joint *in vivo,* including articular cartilage, the menisci, the synovium and subchondral bone abnormalities. Using MRI, studies have begun to explain the relationships between traditional and novel risk factors for OA, demonstrating how they influence changes in knee structure from early/pre-OA through to established disease. Other imaging modalities such as ultrasound may provide complementary approaches for the assessment of synovitis. The role of Positron Emission Tomography (PET) scanning is still unclear but as with Computed Tomography (CT), may be used as an alternative when MRI is contraindicated.

INTRODUCTION

Osteoarthritis (OA) affects approximately 6% of adults over the age of 30 and 30% of adults over the age of 65 [1]. Despite being the leading cause of chronic disability in the elderly, there is no cure for OA, and the only established treatment for end-stage OA is the costly joint replacement surgery. Imaging modalities such as radiography and MRI enable the non-invasive assessment of joint structure. Improving this is important in order to better understand the pathogenesis of OA, the relationship between structural changes and both

symptoms and progression of disease, the role of risk factors, and the opportunity to identify novel outcome measures for use in therapeutic and preventive studies of OA.

RADIOGRAPHY

Radiography, currently the gold standard for measuring OA, carries the benefits of simplicity, low cost, and clear visualisation of bony features such as osteophytes and subchondral sclerosis. Radiography has made a major contribution towards our understanding of risk factors for OA. One study found an increased risk of radiographic OA progression in those over 60 [2], whilst rate of incident OA was increased by approximately 2% annually in another study, particularly in women [3]. This is not surprising as female gender is a known risk factor for OA [4]. Moreover, the findings of a recent sibling study confirmed genetics as a risk factor for OA, with the heritability of OA estimated to be 0.62 [5]. Obesity has also been associated with both incidence and progression of radiographic knee OA [2, 6, 7]

Limitations of radiography

A major limitation of radiography is that it does not allow direct visualisation of soft tissues. The assessment of joint space narrowing (JSN) or joint space width (JSW) is used as a surrogate measure of cartilage, however, the presence of structures other than articular cartilage in the joint space may result in apparent increases in JSN which, for example, could be a result of meniscal extrusion rather than loss of cartilage itself [8, 9]. In addition,

radiography is insensitive to structural changes since once radiographic changes are detected, significant disease is usually already present: knees with grade 1 JSN have lost approximately 11-13% of cartilage [10], while bone marrow lesions (BMLs), meniscal extrusion and tibiofemoral cartilage defects were prevalent in 14%, 4% and up to 62% respectively of subjects without radiographic OA [11-14]. Moreover, the radiographic grading systems for OA often require the presence of osteophytes. This may have influenced the interpretation of previous results, since the pathogenesis of osteophytes differs to change in articular cartilage.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging allows *in vivo* visualisation of a joint, providing excellent tissue contrast and anatomical resolution. While it is more expensive, its major advantage over radiography lies in the ability to visualise articular cartilage directly. In particular, MRI has enabled the examination of changes to joint structure from early/pre-OA through to established disease.

The role of MRI in assessment of symptoms and structural changes in OA

Although OA is often characterised by the presence of pain, the source of pain is poorly understood: hyaline articular cartilage, loss of which characterises OA severity, lacks pain fibres [15]. Thus the role of other innervated structures in the knee affected by pathologic processes in OA is being studied as potential sources of pain. Whilst studies have shown an

increased prevalence of pain with increasing radiographic OA severity [16, 17], severity of pain has not been linked to the degree of radiographic OA [18, 19]. However, using MRI, studies have been able to demonstrate significant positive relationships between structural changes and increased pain severity.

Measurement of cartilage using MRI

Cartilage is a three-dimensional structure that can be measured from images obtained by MRI. Different methods have been used in the literature to determine the amount and quality of cartilage. These include semi-quantitative methods such as the WORMS scoring system [20] and quantitative methods such as measurement of cartilage volume and cartilage thickness [21]. These methods have yielded complementary findings.

Cartilage volume

Cartilage volume is naturally lost in normal aging, with an annual reduction of 0.3-0.5% [22]. However, in OA, loss of cartilage volume may be accelerated, being a multi-factorial phenomenon which may precede, accompany and/or result from other structural changes within the joint. Assessment of articular cartilage on MRI (Figure 1) can be performed using several techniques, some of which show the composition of cartilage with more detail (e.g. T2 relaxation, T1 in the rotating frame (T1rho), sodium MRI and the proton-based delayed gadolinium enhanced MRI of cartilage (dGEMRIC)) and others which provide quantitative assessment of cartilage morphology (e.g. water-excitation or fat-supressed T1-weighted

spoiled gradient echo (SPGR)) [23]. For quantifying cartilage morphology, the most commonly used MR sequences have been the fat-suppressed T1-weighted SPGR [21, 23]. Fat suppression is an important component of this sequence, required not only to provide adequate dynamic range to the image contrast to delineate cartilage, but also to eliminate chemical-shift artifacts [21].

Cartilage volume loss has previously been associated with WOMAC pain changes over 24 months in those with knee OA [24]. Similarly another study demonstrated a relationship between baseline cartilage volume and knee symptoms (WOMAC pain, stiffness and function scores), and a correlation between the loss of cartilage volume over 24 months and the worsening of symptoms [25]. Pain in knee OA may arise from a multitude of factors and is likely to be caused by structures other than cartilage that are innervated by nociceptors. These include the subchondral bone, meniscus and synovium.

Cartilage volume derived from MRI has been validated against cadaveric specimen, radiographic measures have not. Thus, whilst JSN and JSW have been related to cartilage volume, longitudinal studies suggest that changes in JSW and JSN are less sensitive in detecting cartilage loss than MRI [10]. This suggests that MRI may provide a more sensitive measure of disease severity and progression.

Cartilage defects

Cartilage defects are identifiable using MRI where the cartilage surface or the cartilage adjacent to bone is irregular, or where there is loss of cartilage thickness [26]. They can be detected with high reproducibility on 3D spoiled gradient echo (SGPR)/fast low-angle shot (FLASH) images [27], a method that has been used in and linked to clinical outcomes [28]. However, while they provide high spatial resolution, they are limited by the high imaging time and sensitivity to motion artifacts [29]. Nevertheless this technique was found to be more accurate than the standard spin-echo MRI for detecting cartilage defects, as compared with arthroscopic findings [30].

The correlation between knee pain and cartilage defects has been reported in particular when the defect is moderate to severe (grade 2-3) [31, 32]. Furthermore, there was an additive association between the number of sites with severe defects (grade ≥3) and the prevalence of knee pain in older adults [31]. These studies graded defects on a 5-point scale as follows: grade 0 = normal cartilage, grade 1 = focal blistering and intracartilaginous low-intensity area with an intact surface, grade 2 = irregular surface or basal layer and loss of thickness <50%, grade 3 = deep ulceration with loss of thickness >50%, and grade 4 = full-thickness chondral wear with exposure of subchondral bone. How cartilage defects are related to pain is unclear, although the relationship may be mediated, at least partially, by BMLs. When the overlying cartilage is damaged, protection to the subchondral bone is reduced and stresses on the bone are increased. This may cause subsequent changes to the cortical bone, including generation of BMLs. Nevertheless, the findings of Zhai and colleagues [31] were independent of BMLs, indicating that it is likely that other factors are also in play. The authors offered substance P, a neuropeptide involved in pain transmission

which is found in abnormal cartilage in osteoarthritic articulations, as a potential alternative explanation.

Cartilage defects, even using earlier less sensitive techniques, are associated with reduced cartilage volume [33] and increased cartilage loss in the tibiofemoral [34, 35] and patellofemoral compartment [28]. They are commonly found to increase in size in both osteoarthritic [8, 36] and non-osteoarthritic [37, 38] subjects, although a number of studies have reported them to largely remain constant [8, 39]. Several studies have also shown a potential for regression [37-39], particularly in those of a younger age, lower BMI and without OA [37], which may be attributable to cartilage's self-repair capacity of small sized defects (3-6 mm in diameter) with hyaline or fibrocartilage [40]. It may be that the improvement in cartilage defects is, at least in part, attributable to measurement issues, however since cartilage defects had to be present on ≥ 2 consecutive slices [36, 41] is seems unlikely that this is due to measurement error alone in multiple independently assessed cohorts.

Bone marrow lesions (BMLs)

BMLs are visualised on MRI as areas of subchondral bone that appear bright (Figure 2). They are best assessed using water sensitive sequences, which include fat suppressed, T2-weighted, proton density-weighted, and short tau inversion recovery sequences [42-44]. Histologically, BMLs may represent bone marrow fibrosis, bone marrow necrosis, trabeculae abnormalities and some edema [42].

Several studies have demonstrated a relationship between BMLs and knee pain [31, 45, 46]. In subjects with radiographic knee OA, the prevalence of BMLs were much greater in those with knee pain [17]. Another study of subjects with, or at high risk of OA, demonstrated a link between enlarging BMLs and incident knee pain in those without baseline pain, and increased pain severity in those with baseline pain [47]. When the natural history of BMLs was examined, there was a positive association between incident BMLs and the development of knee pain over 2 years [46]. The investigation of pain in OA has been complicated by the occurrence of multiple pathologic features. As OA is a disease of the whole joint, it can be difficult to distinguish the contribution of each structure to pain of the joint [47]. However, it has been suggested that impaired venous drainage in OA patients may contribute to pain as the ensuing venous hypertension increases intraosseous pressure in the bone marrow compartments, which potentially leads to the development of BMLs [48].

In knee OA, presence and mean size change of BMLs are associated with greater loss of cartilage [49-52]. Several studies have found that this relationship is in part mediated by limb alignment [51, 52]. Varus knees had a much higher prevalence of medial BMLs compared to neutral or valgus knees, which had a higher prevalence of lateral BMLs [51, 52]. Furthermore, BMLs in the medial compartment were more likely to progress when the knee is varus, whilst BMLs in the lateral compartment were more likely to progress when the knee is valgus [52]. As with cartilage defects, BMLs are also present in subjects without

knee OA [11, 53], although not only are BMLs less common in subjects without clinical knee OA, they are also less likely to develop and more likely to resolve [36]. Nonetheless, when present in non-osteoarthritic subjects, BMLs are associated with increased prevalence of cartilage defects [12] and increased risk of their progression [11, 53] as well as loss of cartilage [53]. Whether limb alignment influences the relationship between BMLs and cartilage in knees without OA has not yet been examined. This is important as malalignment may be the result of the disease process involving cartilage and menisci. It may be that factors that contribute to the development of BMLs also result in impairment of the supply of nutrients and oxygen to the overlying cartilage plate which may reduce the strength of the bony support of articular cartilage [54, 55]. The resultant bone changes may in turn result in increasing cartilage loss.

Subchondral Bone Cysts

Of more recent interest in OA are subchondral bone cysts, identifiable on MRI as well-demarcated hypersignals (Figure 3), usually where the overlying cartilage has largely been eroded [56]. They are found in approximately 50% of OA subjects [50, 57] and 13.6% of asymptomatic controls [58]. Previously, two main theories were proposed about subchondral cyst formation: the synovial breach theory [59, 60] and the bony contusion theory [61]. However, there is recent suggestion that BMLs may in fact be early 'pre-cystic' lesions that may develop into subchondral cysts [62, 63]. One study reported 92% of subchondral cysts developed in BMLs over approximately 18 months [62]. Another study showed that BMLs were co-existent in 91.2% of subregions where subchondral cysts were

found [63]. Further to that, a longitudinal examination of subchondral cysts found that BMLs and cysts co-existent in 98% of subjects, and when present together they identify those with worse structural knee outcomes than those with BMLs only [64]. Whilst the majority of cysts were stable or progressed over the study period, there was also a potential for regression, even complete resolution. Regression of cyst in the lateral compartment was associated with significant reduction in lateral cartilage loss [64].

Trabecular bone changes

Animal studies have shown trabecular bone structure to also be affected by OA pathology. Microscopic computed tomography (micro-CT) evaluation observed initial loss of trabecular bone volume fraction (BV/TV) and thinning of trabeculae, followed by an increase of BV/TV via eventual thickening of trabeculae in a guinea pig model [65]. In a canine model there was an increase in subchondral bone thickness and decreased trabecular thickness (Tb.Th), also assessed on micro-CT [66]. Although MRI is superior in assessment of the whole joint *in vivo*, it is unable to visualise bone directly. As such, the majority of studies of trabecular structure in OA have used CT. Nevertheless, it is still possible to quantify trabecular architecture using MRI techniques [67, 68]. As the spatial resolution of MRI is comparable with trabecular dimensions, there may be some partial volume effects. However, these may be minimised by using lower resolution of the slice, along the direction of primary trabecular orientation [69].

An MRI study comparing normal and osteoarthritic trabecular bone structure in humans found significant differences in the trabecular structure of the femur and tibia [68]. When comparing those without OA to those with mild OA, the apparent BV/TV, apparent trabecular number (Tb.N) and apparent Tb.Th were higher in the femur while the apparent trabecular separation (Tb.Sp) was lower then in the tibia. This may be attributable to the difference in loading function since loading forces are concentrated in the two condyles in the femur, whereas in the tibia, there are more even distribution of forces across the tibial plateau surface. However when the OA is severe, only BV/TV differed significantly between the tibia and the femur, which may indicate a change in loading function with disease progression such that femoral trabecular bone may be lost in the late stage of OA [68].

Synovitis and joint effusion

Synovial thickening and joint effusion have long been recognised as a feature of OA, even in the early stages of disease [70, 71]. One study found synovial thickening in 73% of subjects with idiopathic OA but in none of the controls [72]. A subsequent biopsy study confirmed that synovial thickening within the infrapatellar fat pad corresponds to mild chronic synovitis [70]. Several types of synovitis are found in OA depending on the stimuli: mechanical synovitis (hyperplasia of the villi) and particulate synovitis (hypertrophy of the villi) [73]. Synovial hypertrophy is best visualised on MRI using the contrast agent gadolinium [74], however, as the use of gadolinium impacts scanning duration, sequence selection and may carry serious side effects [75], non-gadolinium sequences optimised to

allow assessment of the synovium have also been used [70, 76]. On the other hand, joint effusions are commonly assessed using non-contrast enhanced MRI (Figure 4) [20].

Previous examinations of the association between synovial pathology and pain in knee OA have not consistently differentiated between synovitis and joint effusion. One study demonstrating an association between synovitis/effusion and knee pain lacked discrimination between synovitis and joint effusion due to the absence of intravenous contrast [45]. Another study showed that a decrease in grade and score of synovitis over 60 days corresponded with significant improvement in WOMAC pain [75], although joint effusion was not adjusted for. An association was previously found between effusion and knee pain, but again no adjustment for synovitis was made [77]. Nonetheless, one recent study did find a modest correlation between changes in synovitis and worsening pain, independent of joint effusion, baseline cartilage score, and BML score [78].

It is thought that synovitis contributes to chondropathy and cartilage degeneration via the release of cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor alpha which act to suppress collagen and proteoglycan synthesis [79, 80]. In a previous arthroscopic study, OA patients with reactive or inflammatory medial synovium had more severe medial chondropathy [81]. Similarly, a more recent MRI study demonstrated a positive correlation between global severity of synovitis at baseline and cartilage volume loss at 60 days in subjects with knee OA [75]. In contrast, no association was found between

synovitis and tibiofemoral and patellofemoral cartilage loss in subjects with symptomatic knee OA from the Boston Osteoarthritis of the Knee study [78].

Meniscal pathology

Meniscal damage associated with OA includes meniscal subluxation or extrusion, and meniscal tear. Whilst several studies have demonstrated a positive association between meniscal tears and subluxation and knee pain [45, 82], the majority have found no significant results [13, 43, 77, 83]. A prospective evaluation of OA patients found no association between knee pain and meniscal tears or subluxation [77]. Similar in a mixed cohort of subjects with and without OA, those with knee symptoms (pain, aching and stiffness) on most days had a higher prevalence of meniscal tears, though this association was attenuated when adjusted for radiographic evidence of OA [83]. Interestingly, the same study noted that 61% of the meniscal tears were in subjects who reported no pain symptoms in the past month. Taken together, current evidence suggests that meniscal pathology is commonly found even in those without OA, thus rather than contributing directly to pain, they may indicate early signs of disease or may be linked with BMLs.

Whilst meniscal extrusion occurs more frequently in those with OA, it is a risk factor for cartilage loss in both individuals without knee OA [13, 84] as well as those with OA [85, 86]. It is likely that with greater meniscal extrusion, there is increased contact stress within the joint which subsequently accelerates cartilage damage [13]. Meniscal tears can be classified into two different morphological patterns: traumatic and degenerative. Traumatic lesions

occur due to trauma to a previously healthy joint, usually in active younger persons, and are associated with increased risk of knee OA [87, 88]. In contrast, degenerative lesions occur in older people, particularly those with pre-existing OA [89, 90].

Structural changes on MRI and risk of knee joint replacement

In symptomatic knee OA, higher cartilage defect score was associated with a 6-fold increased risk of knee joint replacement over 4 years [28]. Similarly, rate of tibial cartilage loss over 2 years was an independent predictor of joint replacement, reporting a 20% increase in risk of joint replacement for every 1% increase in rate of cartilage loss [91]. The same study also reported a 20% increased risk of joint replacement for every 100 mm^2 increase in tibial plateau bone area [91]. Furthermore, BML severity at baseline was associated with risk of knee joint replacement over 4 years, independent of age, gender and Kellgren-Lawrence grade [92]. Subchondral bone cysts were also recently found to influence the risk of knee joint replacement particularly when BMLs were also present [64].

Knee joint replacement is considered the ultimate clinical end point for OA. Structural changes in OA, such as cartilage defects and loss of cartilage, which could be considered surrogate markers for disease severity, predict risk of knee joint replacements. It may be that these structural changes may be used as surrogate markers for disease severity and used as therapeutic targets in studies designed to prevent to delay progression of disease rather than waiting for end-stage disease and joint replacement. As cartilage defects, BMLs and subchondral cysts have the potential to regress or resolve, as previously mentioned, this

makes them attractive therapeutic targets. This warrants further research to investigate factors that may contribute to their regression and resolution.

The role of MRI in understanding risk factors for OA

The increased understanding of the significance of different structural changes in OA has enabled better understanding and novel approaches to determine the effect of risk factors in OA. This has also been made possible by the use of sensitive measures of structural change, enabling the examination of both those with and without radiographic disease.

Malalignment

Tibiofemoral malalignment affects the distribution of load across the articular surfaces of the knee [93], such that a 4-6% increase in knee angle in the varus direction may increase loading in the medial compartment by up to 20% [93]. Using radiography, studies were able to show a relationship between tibiofemoral alignment and risk of OA progression as assessed by JSN or JSW [94-96]. Subsequent MRI studies have found a positive relationship between alignment and cartilage defects [97], subarticular bone edema, meniscal tear and subluxation, bone attrition, and cartilage morphology [98] as well as cartilage loss in the femoral and tibial [99, 100] compartments. Interestingly, in one study the association between alignment and cartilage defects was observed in both healthy and osteoarthritic people [97], though this was not supported by a longitudinal investigation of a healthy population which found no significant association between alignment and changes in

cartilage defects and volume [101]. Only one study has examined malalignment in relation to OA development [94]. In a population based study of a mixed OA cohort, subjects with valgus or varus knees were found to have increased risk of OA development over approximately 6.6 years. It is possible that malalignment resulting from genetic, environmental and/or traumatic factors cause aberrant loading in the knee joint thus predisposing to degenerative changes. However, it may be that the effect of malalignment is most significant once OA is present.

Obesity

Obesity may influence OA via two mechanisms: biomechanically and systemically. Biomechanically, obesity may affect knee OA directly through abnormal loading and/or indirectly via mediators such as tibiofemoral malalignment [102]. In malaligned knees, the effect of excess body weight on the affected compartment is intensified. When the effect of BMI on radiographic severity was examined, there was a positive correlation which was reduced significantly once varus malalignment was added to the model [102]. Another study found increasing risk of radiographic disease progression with increasing weight in knees with moderate malalignment [103]. Whether obesity and malalignment affect cartilage volume as measured on MRI has not been examined. However, obesity has been shown to influence other MRI-assessable features of OA, which may in turn affect the risk of knee OA. Studies in both healthy and osteoarthritic populations have found that cartilage defects scores are positively correlated with BMI [104, 105], and that those with BMLs have higher BMIs than those who do not [12, 50].

Leptin, a protein encoded by the gene obese (ob), is thought to be the systemic mediating factor in the process linking obesity, sex and knee OA [106, 107]. Although *in vitro* studies found increased leptin concentration in cartilage of OA patients [108] the effect of elevated leptin levels on cartilage was unclear. It was suggested that leptin may act in a biphasic manner, in that leptin may be beneficial for cartilage synthesis, but would be detrimental when in excess [109]. This is in line with the findings of a subsequent *in vivo* study where higher leptin levels had a detrimental effect on chondrocytes as it was associated with reduced cartilage volume [107].

Physical activity

Whilst physical activity has been shown to produce symptomatic benefits in OA patients [110], the relationship between physical activity and knee structure is less clear. Previous radiographic studies have suggested adverse [111, 112] or no effect [113, 114] of physical activity on risk of OA, however, many did not exclude those with previous knee injury [111, 112], a known risk factor for OA [115]. As such, whilst knee injury was adjusted for in the statistical analyses, residual confounding may have remained as those who exercise more vigorously are at greater risk of injury. Adding to that, radiography is a less sensitive measure which may have missed potential benefits of exercise in knee OA. Using MRI, recent studies have shown a beneficial effect of physical activity on joint structure: increased cartilage volume and reduced prevalence of cartilage defects with vigorous

exercise [116], reduced prevalence of BMLs in those who walk regularly [116], and reduced cartilage loss associated with greater muscle strength and fitness endurance [117].

Smoking

More recently, smoking has been shown to be a risk factor for structural progression in OA [118-120], with increased cartilage loss and cartilage defects in knee OA, particularly in current smokers [118, 120]. Smoking (current and former) also predicted increased cartilage loss over 2 years in a population without knee OA [119]. The mechanism by which smoking affects structures in knee OA is unclear, although components of tobacco smoke affect chondrocyte function by inhibiting cell proliferation and extracellular matrix synthesis in the spine[121, 122]. Similar mechanisms may operate in the knee. The role of smoking in OA pathogenesis is complicated by interactions with other factors including genetics [120] and BMLs [119]. A gene-environment interaction was observed in one study where smoking influenced cartilage loss and defects primarily in the adult offspring of parents who had knee replacements for primary knee OA [120]. Moreover, BMLs in non-osteoarthritic smokers were more likely to persist over 2 years and this persistence of BMLs is likely to contribute to the association between smoking and cartilage loss [119]. Nevertheless, the mechanism by which smoking affects OA pathology warrants further investigation.

Antioxidants

Vitamins A, C and E are antioxidants which protect against oxidative damage. The Framingham Osteoarthritis Cohort Study found reduced risk of radiographic OA progression with higher intake of vitamins A and C [123], whilst in a similar study serum levels of lutein and ß-cryptoxanthin were inversely associated with radiographic knee OA [124]. However, MRI studies in subjects with and without OA found no evidence for a chondroprotective effect of either vitamin C or E [26, 125]. Yet higher vitamin C intake was associated with reduced risk of BMLs in a healthy population, suggesting a positive effect on bone [26]. At present, the role of vitamin A in OA has not been examined using MRI.

Vitamin D

Vitamin D affects cartilage by stimulating proteoglycan synthesis and has been shown to be beneficial in decreasing the risk of progression [126] and development of radiographic OA [126]. In the Framingham Study, those in the middle tertile of dietary vitamin D intake had increased risk of incident knee OA compared to those in the upper tertile [126]. Additionally, those in the lower and middle tertiles of both serum and dietary vitamin D intake had greater risk of OA progression compared to those in the upper tertile. This is supported by the findings of an MRI study of older adults whereby baseline levels and change in serum levels of vitamin D were both positively associated with tibial cartilage volume [127]. The same study further showed that vitamin D insufficiency predicted cartilage loss over 2.9 years [127].

Fatty Acids

A study of subjects without knee OA found a positive relationship between total, mono- and n-6 polyunsaturated fatty acid intakes and prevalence of BMLs [14] and between saturated fatty acid intake and development of BMLs over 2 years [128]. How this subsequently affects risk of OA is unclear. It is thought that saturated fatty acids and n-6 polyunsaturated fatty acids affect risk of OA via their atherogenic properties [129, 130] since evidence suggests that atheromatous vascular disease is important in OA progression [131]. In contrast, n-3 polyunsaturated fatty acid intake may be beneficial for cartilage via effects on cartilage metabolism [132].

Potential impact of MRI on treatment in OA

The use of MRI has the potential to optimize surgical management of knee pathology. A recent study of knees with ACL injuries found significant differences in BML size and cartilage morphology in surgically treated knees compared to those without surgery [133]. Surgically treated knees had significantly higher joint fluid volumes as well as larger BML volumes after up to 6 months, although the difference was no longer significant after one year. This has raised the interesting prospect that the timing of surgery may be important in minimising adverse structural changes post-surgery. The study also suggests a possibility that surgically treated patients may require longer recovery period prior to rehabilitation since there is ongoing structural remodelling in the traumatic knee.

Recently it has been shown that MRI can be used as an outcome measure in intervention studies in OA. A clinical trial comparing the effects of licofelone and naproxen on the

progression of OA found that although cartilage loss was increased in both groups over time, the loss was significantly smaller in the group receiving licofelone [134]. Importantly, there was no significant change in joint space narrowing over that time. This study demonstrated that outcomes could be established earlier using MRI cartilage measures compared to radiology and that it was feasible to perform a multi-centred study.

OTHER IMAGING MODALITIES IN OA

Ultrasound

The advantage of ultrasonography (US) over MRI predominantly lies in its availability, lower cost and real-time imaging ability [135]. US is the most sensitive tool to evaluate presence of synovitis and joint effusion. Limitations to US include its limited use in cartilage assessment, particularly in weight-bearing joints, since it allows assessment of femoral cartilage with relative ease but almost none of the corresponding tibial cartilage [136]. It is also not possible to visualise several other joint structures such as subchondral bone lesions [137].

Positron Emission Tomography

Positron emission tomography (PET) requires the administration of radiopharmaceuticals to demonstrate changes in target tissues. At present, there are no radiopharmaceuticals to image articular cartilage, although agents have been developed to image bone and soft tissues [138, 139]. Bone turnover changes are imaged using agents with a high affinity to bone such as Tc-99 methylene diphosphonate and 18-Flouride [139]. The positron-emitting

2-^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) is able to detect glucose metabolism and, in knees with medial OA, its increased uptake was found in periarticular regions and intercondylar notch (thought to reflect synovitis) as well as in regions of MRI-detected BMLs [138]. Although PET offers insight into bone turnover and metabolism changes, it lacks spatial resolution, which is key for cartilage studies. Thus the benefit of PET over MRI in studies of OA is questionable.

Computed Tomography

Computed tomography (CT) is a cross-sectional digital imaging technique that is superior to MRI for assessment of cortical bone and soft tissue calcification [23], but without the use of contrast agent, conventional CT has limited ability to delineate cartilage. In contrast, CT arthrography is able to depict surface lesions of all cartilage areas better than MRI. Although evidence suggests that the use of CT arthrography in assessment of knee cartilage is comparable to MRI [140], CT has low soft tissue contrast and involves exposure to ionizing radiation. Thus it is predominantly used as an alternative to MRI in the event of contraindication or unavailability.

FUTURE PERSPECTIVE

To date radiography remains the gold standard for OA assessment, however, MRI has contributed greatly to OA research and may eventually replace radiography even in the clinical setting. As there is currently no cure for OA, it is important to be able to detect early

disease prior to the presence of symptoms and radiographic changes as enabled by MRI. This would potentially reduce subsequent burden on the health system as early treatment of disease may prevent or delay the need for ongoing physical therapy and/or progression to the costly joint replacement. The role of other imaging modalities that may offer complementary information on the state of the joint is currently underway.

EXCUTIVE SUMMARY

Radiography

- Remains the gold standard for defining OA
- Advantages: simplicity, lower costs, clear visualisation of bony features
- Disadvantages: does not allow direct visualisation of soft tissues, once radiographic change detected significant disease is already present

Magnetic resonance imaging

- Provides excellent tissue contrast and anatomical resolution
- Enables identification of early structural changes prior to symptomatic and/or radiographic disease
- MRI-assessed structures, such as subchondral bone lesions, cartilage defects and synovial pathology have been linked to pain in OA

- Cartilage defects, bone lesions and loss of cartilage have been associated with increased risk of joint replacement

- MRI evidence enhances our understanding of known risk factors for OA, including the traditional risk factors: malalignment, obesity and physical activity; and novel risk factors: smoking and diet

- With the aid of MRI, there is potential to improve the management of OA and to provide an effective biomarker for studies of OA

Other imaging modalities

- Ultrasound is the most sensitive tool to evaluate synovitis and joint effusion

- Positron emission tomography had questionable benefits over MRI, particularly as it requires administration of radiopharmaceuticals, however may be used when MRI is contraindicated

- Computed tomography is superior to MRI for assessment of cortical bone and soft tissue calcification, however involves exposure to ionizing radiation. It is also predominantly used as an alternative to MRI

Future perspective

- MRI allows early detection of OA, which is important for our understanding of the early stages of OA in order to optimize preventive and therapeutic strategies

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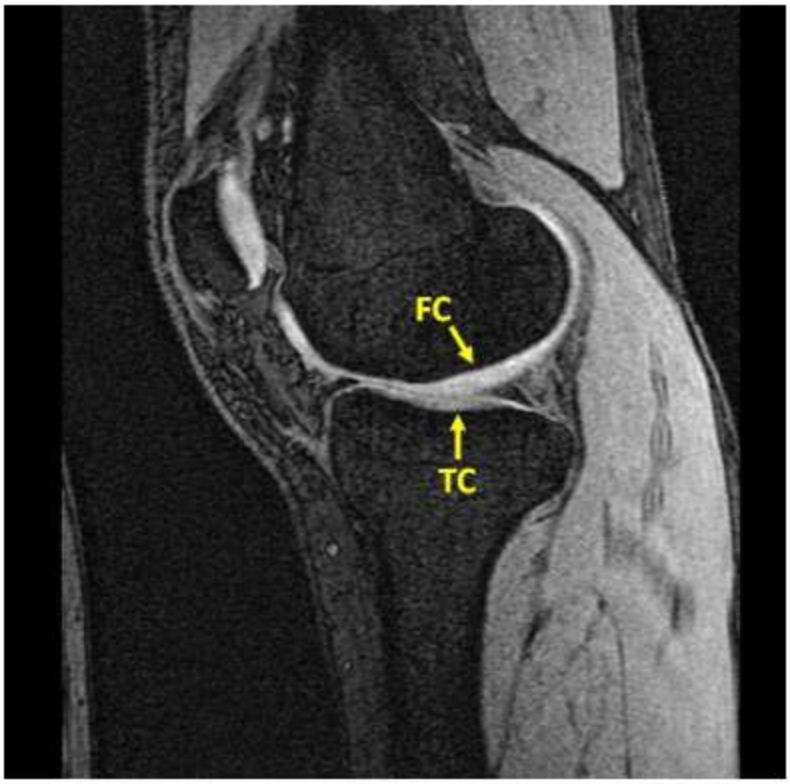

Figure 1. Femoral cartilage (FC) and tibial cartilage (TC) imaged using the T1-weighted fat saturation 3D gradient recall acquisition in the sagittal plane.

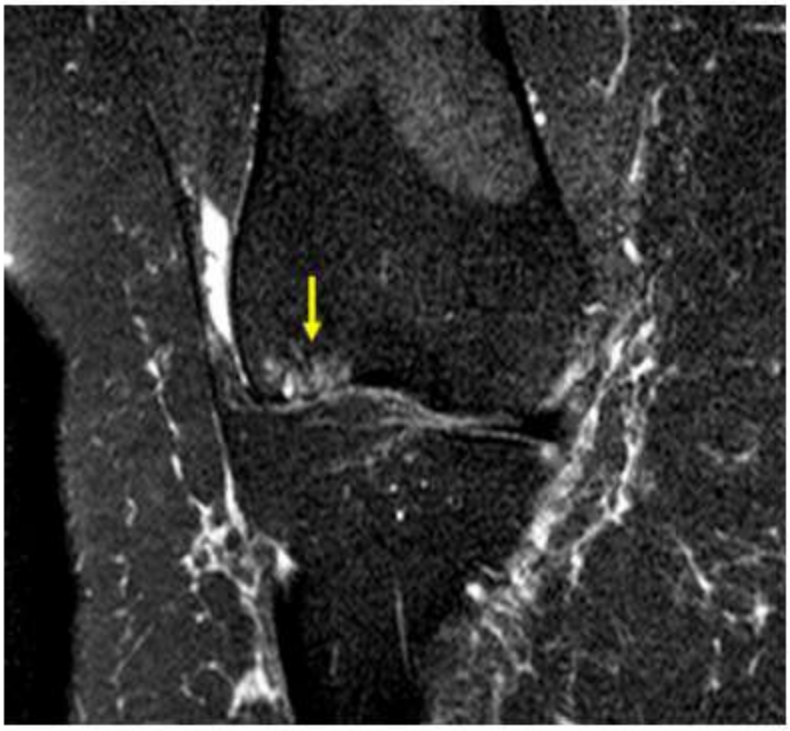

Figure 2. Lateral femoral bone marrow lesion imaged using a coronal T_2 weighted fat-saturated acquisition.

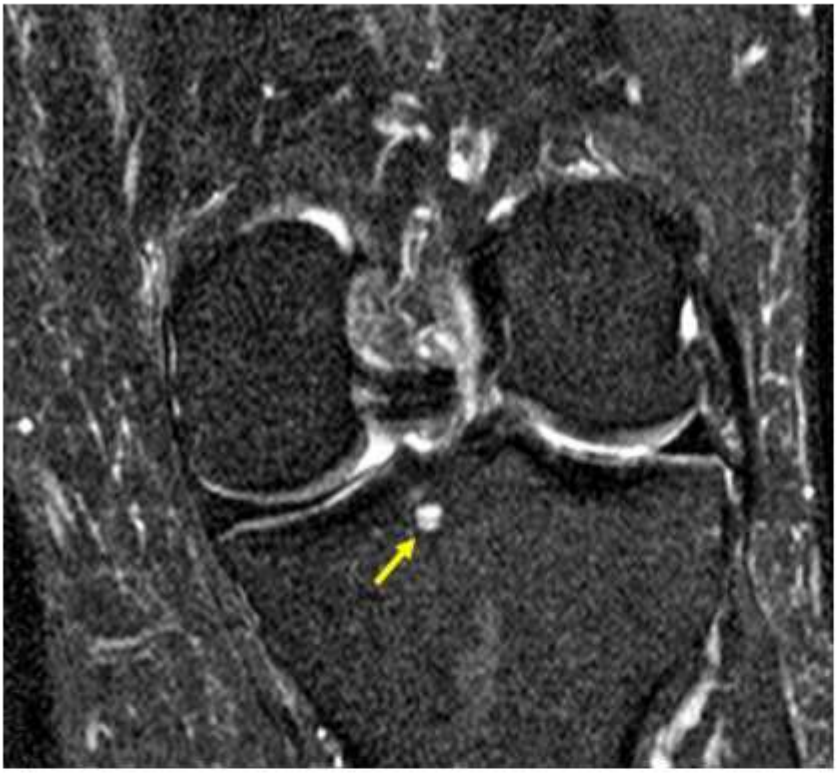

Figure 3. Medial tibial subchondral bone cyst imaged using a coronal T_2 weighted fat-saturated acquisition.

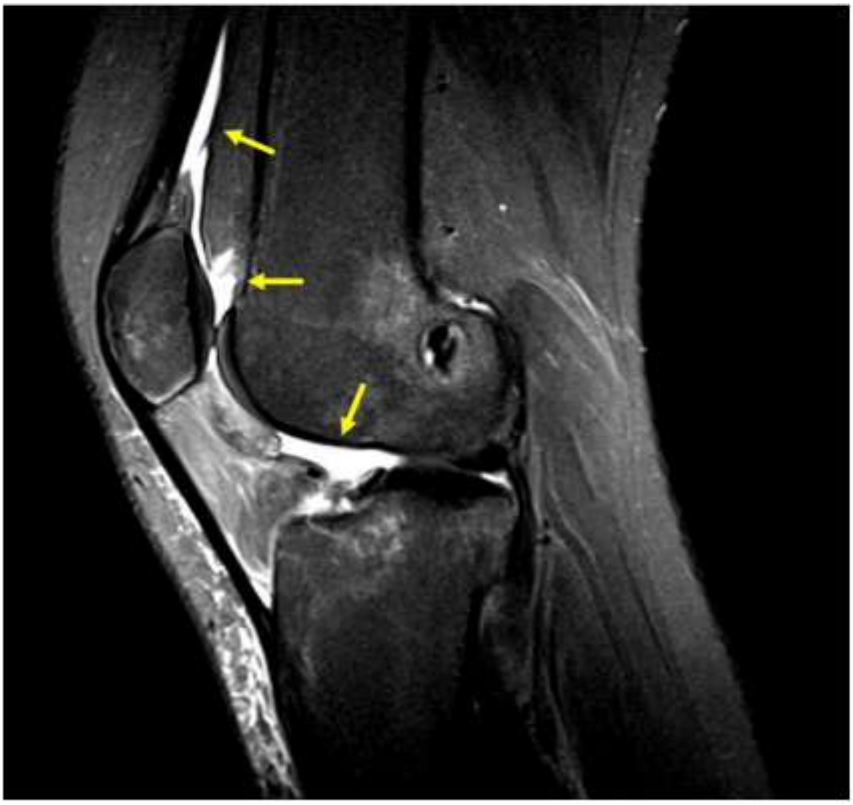

Figure 4. Joint effusions imaged using a coronal T_2 weighted fat-saturated acquisition.

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Review

Sex hormones and structural changes in osteoarthritis: A systematic review

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ABSTRACT

Aim: To systematically review the evidence for a relationship between sex hormones and structural changes in osteoarthritis (OA).
Methods: Electronic searches of MEDLINE were performed in November–December 2010 and in February 2011 for studies of sex hormones and OA that met a predefined set of criteria. Both controlled trials and observational studies were eligible for inclusion. Two independent reviewers extracted the data and assessed the methodological quality of the included studies. Due to the heterogeneity of the studies, we were unable to perform a best evidence synthesis. However we have provided summaries for each section.
Results: Twenty-seven studies were included in this review, of which 11 were considered high quality. The evidence suggests an association between endogenous oestrogen and cartilage turnover and radiographic OA, and between testosterone and cartilage volume. There is also evidence for an association between exogenous oestrogen and cartilage and bone turnover, although its effects on radiographic and MRI structure as well as joint replacement are unclear. The evidence also supports an association between oestrogen receptor α and β gene polymorphisms and OA.
Conclusion: Although the heterogeneity of the studies means that there is insufficient evidence to form strong conclusions, the available evidence supports an effect of endogenous and exogenous oestrogen as well as oestrogen receptor polymorphisms on joint health.

Contents

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1. Introduction

Osteoarthritis (OA) is a disabling, degenerative disease of the joint which affects hyaline articular cartilage as well as surrounding tissues and subchondral bone. Known risk factors for OA include age [1], gender [2], obesity [1] and knee malalignment [3]. The prevalence of OA in men and women are similar up to the age of 50, after which the prevalence in women increases significantly [4,5], suggesting an influence of hormonal factors in the progression and development of the disease. This relationship between hormonal changes due to menopause and OA was first described in 1952, in a group of women with Herberden's nodes characterised by a rapid onset of symptoms and multiple joint involvement, as 'menopausal arthritis', which was later changed to 'primary generalised osteoarthritis' [6].

Previous reviews have generally focused on studies of exogenous oestrogen use and hormone replacement therapy. One systematic review in 2004 concluded that there is weak epidemiological evidence for a role of oestrogen therapy in joint health, particularly in large joint rather than small joint OA [7]. Another more recent review published in 2009 did not observe a relationship between exogenous hormone use and OA, though there was some evidence of a protective effect of unopposed oestrogen use for hip OA [8]. To our knowledge, no systematic review examined the evidence for the relationship between other sex hormone parameters, such as endogenous hormones and oestrogen receptor polymorphisms, and OA. Thus we aim to review the evidence for a relationship between sex hormones, including exogenous, endogenous and polymorphisms and structural changes in OA.

2. Methods

This systematic review was conducted according to the 2009 PRISMA guidelines [9]. Methods of analysis and inclusion criteria have been documented in a protocol.

2.1. Search strategy

Electronic searches of MEDLINE (1948 to present) were performed in November and December 2010 using the following keywords: sex hormones; oestrogen or estrogen; testosterone; aromatase inhibitors; and osteoarthritis. We limited our search to human studies published in English from and including the year 2000. References from studies identified in the search were scrutinized for additional relevant studies. The search was optimized by performing an additional search of MEDLINE in February 2011 using the same keywords and limits.

2.2. Inclusion and exclusion criteria

Both controlled trials and observational studies were eligible for inclusion in this review. A total of 103 references were identified by our search. Nineteen additional studies were identified by screening the reference list of these 103 studies. Of these, 16 were duplicates. A total of 106 studies were screened, of which 27 were included in this review (Fig. 1).

2.2.1. Inclusion criteria for sex hormones

1. Endogenous sex hormones:
   - Androgens (testosterone, dihydrotestosterone, dehydroepiandroterone or androstenedione)
   - Oestrogens (Oestradiol, Oestrol and Oestrone)
   - Progestogens (Progesterone)
2. Exogenous sex hormones:
   - Synthetic anabolic steroids, such as synthetic steroids with androgenic properties
   - Synthetic oestrogens, such as selective oestrogen receptor modulators, antiresorptive medications, synthetic steroids with oestrogenic property, and hormone or oestrogen replacement therapy
   - Synthetic progestogens, such as synthetic steroids with progestogenic properties and hormone replacement therapy
3. Aromatase
4. Oestrogen and androgen receptor polymorphisms

2.2.2. Inclusion criteria for OA and OA-related outcome measures

Joint structural changes in osteoarthritis:

- Biochemical markers for bone and cartilage: collagen type I fragments (CTX I) and collagen type II fragments (CTX II).
- Radiographic measures: joint space width and osteophytes using standard scales (e.g., Kellgren and Lawrence).
- MRI structures: cartilage volume, cartilage defects, subchondral bone marrow lesion or oedema and bone attrition.
- Joint replacement surgery for end stage OA

2.2.3. Exclusion criteria

- In vitro studies
- Examination of outcome variables other than those defined above, for example, general joint symptoms, low bone mineral density, osteoporosis, and craniofacial morphology of temporomandibular joint OA patients.
- Outcome was symptoms of OA, such as knee pain and pain susceptibility
- OA was self-reported or diagnosed clinically
- Outcome was arthritis other than OA, such as rheumatoid arthritis and psoriatic arthritis.
- Review articles

2.3. Data collection

Information was extracted from each study on: (1) characteristics of the study: study design, number of participants (% of females), recruitment method, definition of OA (% with OA) and the joints affected (hip, knee or hand), the mean ± standard deviation (SD) age of the participants, follow up years; (2) assessed exposures; (3) outcome measures; and (4) the study results. One reviewer extracted the data from the included studies, which was cross-checked by a second reviewer (SKT and PW).

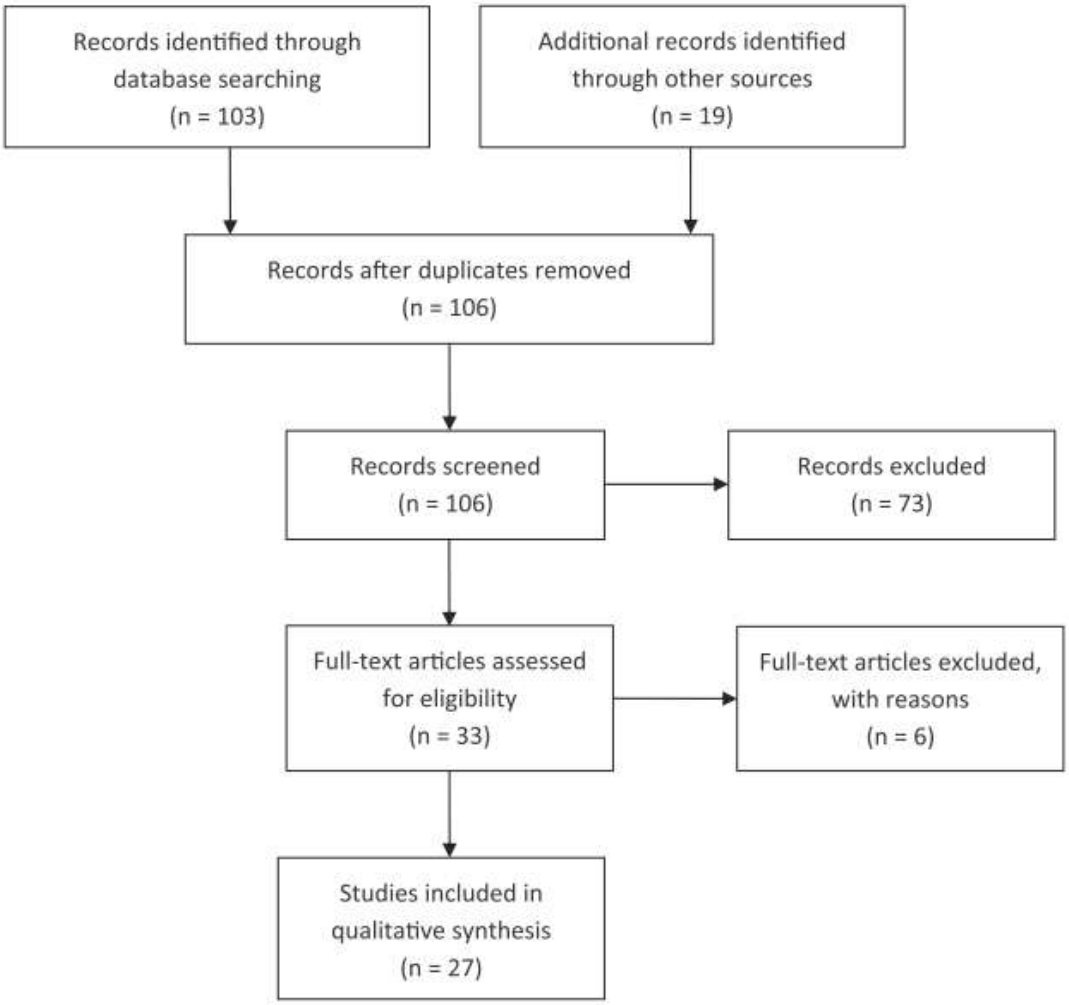

Fig. 1. Flow diagram of included and excluded studies according to the PRISMA statement.

2.4. Methodological quality and risk of bias assessment

Quality scoring of all included studies was performed independently by two reviewers (SKT and MLDT) based on the criteria used by Lievense et al. (Table 1) [10]. These criteria assess the internal validity, risk of bias and informativeness of the study, and have been used in previous reviews of studies in the field of musculoskeletal conditions [10,11]. Not all items were appropriate for all study designs and thus only relevant criteria contributed to the total score for each study. The total score was calculated as a sum of the positive scores. A study was considered to be of high quality if the methodological quality score was greater than 74, which is the mean of all of the quality scores [12].

3. Results

3.1. Characteristics of the included studies

The characteristics of the included studies are presented in Table 2. Two cohort [13,14] and 3 cross-sectional studies [15–17] examined endogenous sex hormones; 2 RCTs [18,19], 1 cohort [20] and 7 cross-sectional studies [21–27] examined exogenous sex hormones; 1 RCT each examined tibolone [28] and levormeloxifene [29]; 2 cohort [30,31], 5 case–controls [32–36] and 2 cross-sectional studies [37,38] examined oestrogen and androgen receptor gene polymorphisms; and 1 cross-sectional

Table 1
Criteria used to assess the methodological quality of selected cohort and cross-sectional studies.

Item	Criterion	CH/CC/CS
Study population		
1	Selection before disease was present or at uniform point	CH/CC/CS
2	Cases and controls were drawn from the same population	CC
3	Participation rate ≥80% for cases/cohort	CH/CC/CS
4	Participation rate ≥80% for controls	CC
Assessment of risk factor		
5	Exposure assessment was blinded	CH/CC/CS
6	Exposure was measured identical for cases and controls	CC
7	Exposure was assessed prior to the outcome	CH/CC/CS
Assessment of OA (knee/hip/hand)		
8	OA was assessed identical in studied population	CH/CC/CS
9	Presence of OA was assessed reproducibly	CH/CC/CS
10	Presence of OA was according to valid definitions	CH/CC/CS
Study design		
11	Prospective design was used	CH/CC/CS
12	Follow-up time ≥2 years	CH
13	Withdrawals ≤20%	CH
Analysis and data presentation		
14	Appropriate analysis techniques were used	CH/CC/CS
15	Adjusted for at least age and gender	CH/CC/CS

CH, cohort study; CC, case–control; CS, cross-sectional study.

Table 2
Characteristics of the included studies.

Author (ref) Country	Study design	No. of subjects (% females)	Recruitment	Definition of OA (% OA)	Age (years) Mean ± SD/(range)	Follow-up (years)	Quality score
Endogenous sex hormones							
Bay-Jensen et al. [15] France	Cross-sectional	100 (100)	From the database of a biobank in Lyon	Asymptomatic	Pre-menopausal: 35 (30–40) Post-menopausal: 59 (48–73)	N/A	60
Sowers et al. [14] United States	Cohort	842 (100)	The South East Michigan arthritis cohort	Radiographic knee OA (11%)	42.0 ± 0.2 (26–54)	10	83
Hanna et al. [17] Australia	Cross-sectional	176 (100)	Community-based	Asymptomatic	52 ± 7 (40–67)	N/A	70
Cicuttini et al. [16] Australia	Cross-sectional	45 (0)	Community-based	Asymptomatic	52.5 ± 13.2	N/A	70
Hanna et al. [13] Australia	Cohort	28 (0)	Community-based	Asymptomatic	51.9 ± 12.8	~2	75
Hernandez et al. [39] Spain	Case–control	104 (62)	Patients undergoing surgery for hip prostheses	Primary hip OA (42%)	76 (49–104)	N/A	62
Exogenous sex hormones							
Ravn et al. [19] Denmark	RCT	240 (100)	Community-based	Asymptomatic	Transdermal placebo: 54.5 ± 2.6 Transdermal 45 μg E_2 + 30 μg levonorgestrel: 54.6 ± 2.7 Transdermal 45 μg E_2 + 40 μg levonorgestrel: 55.6 ± 2.8 Oral placebo: 60.2 ± 3.3 Oral 1 mg E_2 + 1 mg drosperinone: 59.4 ± 4.3 Oral 1 mg E_2 + 2 mg drosperinone: 61.3 ± 3.1 Oral 1 mg E_2 + 3 mg drosperinone: 61.1 ± 3.4	2	83
Karsdal et al. [28] Denmark	RCT	91 (100)	Community-based	Asymptomatic	Tibolone 1.25 mg/day: 66.5 ± 7.0 Tibolone 2.5 mg/day: 64.0 ± 6.7 Placebo: 68.3 ± 6.0	2	67
Christgau et al. [29] Scandinavia	RCT	301 (100)	Community-based	Asymptomatic	Levormeloxifene: 56.9 ± 3.8 Placebo: 57.4 ± 4.1	1	83
Mouritzen et al. [25] Denmark	Cross-sectional	615 (62)	Community-based	Asymptomatic	20–87	N/A	70
Erb et al. [27] Germany	Cross-sectional	809 (62)	The Ulm Osteoarthritis Study	Radiographic hip (41%), knee (59%) and hand OA (35%)	Mean: 66.1	N/A	70
Cooley et al. [23] Australia	Cross-sectional	348 (100)	From a rheumatology practice	Radiographic hand OA (67–79%)	Index cases: 79 ± 5 Non-index cases: 51 ± 11	N/A	60
Carbone et al. [21] United States	Cross-sectional	3075 (50)	The Health ABC Study	Radiographic knee OA (52%)	Antiresorptive users: 74.81 ± 2.90 Non-users: 74.78 ± 2.94	N/A	70
Wluka et al. [26] Australia	Cross-sectional	97 (100)	Community-based	Radiographic OA (8%)	Cases: 58.0 ± 6.1 Controls 56.0 ± 5.4	N/A	80
Cicuttini et al. [22] Australia	Cross-sectional	81 (100)	Community-based	Asymptomatic	ERT users: 58.0 ± 6.1 Controls: 56.0 ± 5.4	N/A	70
Wluka et al. [20] Australia	Cohort	81 (100)	Community-based	Asymptomatic	ERT: 56.0 ± 8.0 Controls: 56.0 ± 5.8	~2.5	92
Karlson et al. [24] United States	Cross-sectional	121,701 (100)	The Nurses' Health Study	Primary hip OA (100%)	42.9 ± 7.2	N/A	80
Cirillo et al. [18] United States	RCT	27,347 (100)	The Women's Health Initiative	Unknown	50–79	Mean range 5.7–7.1	100

Table 2 (*Continued*)

Author (ref) Country	Study design	No. of subjects (% females)	Recruitment	Definition of OA (% OA)	Age (years) Mean ± SD/(range)	Follow-up (years)	Quality score
Oestrogen and androgen receptor gene polymorphisms							
Loughlin et al. [34] United Kingdom	Case–control	740 (49)	Cases: from an orthopaedic centre Controls: spouses	Idiopathic OA (50%)	Cases: 73 (56–90) Controls: 73 (59–89)	N/A	62
Bergink et al. [37] Netherland	Cross-sectional	7983 (N/A*)	The Rotterdam Study	Radiographic knee OA (24%)	68.8 ± 7.5	N/A	80
Valdes et al. [35] United Kingdom	Case–control	1199 (50)	From clinics/centres in Nottingham and Oxford	Clinical and radiographic knee OA (50%)	*Cases* Females: 73.5 ± 7.2, males: 72.1 ± 6.9 *Controls* Females: 72.1 ± 8.5, males: 71.0 ± 7.8	N/A	54
Valdes et al. [31] United Kingdom	Cohort	1003 (100)	The Chingford study	Radiographic knee OA (37%)	43–67	~10 (range 9–11)	92
Wise et al. [38] United States	Cross-sectional	539 (51)	The Framingham Heart Study	Radiographic hand OA (58%)	61 ± 9	N/A	70
Jin et al. [33] Korea	Case–control	548 (56)	Community-based	Clinical and radiographic knee OA (28%)	Cases: 58.8 ± 9.6 Controls: N/A*	N/A	69
Lian et al. [30] United States	Cohort	9704 (100)	The Study of Osteoporotic Fractures	Radiographic hip OA (100%)	Cases: 79.6 ± 5.0 Controls: 78.4 ± 4.6	Mean 8.3	92
Fytili et al. [32] Greece	Case–control	351 (78)	Cases: patients with previous total knee JR Controls: patients with previous treatment for injuries and fractures	Radiographic knee OA (45%)	Cases Females: 68.1 ± 8.2, males: 72.4 ± 5.8 Controls Females: 68 ± 10.9, males: 70.2 ± 9	N/A	69
Riancho et al. [36] Spain and United Kingdom	Case–control	5528 (58)	Cases: patients with severe OA requiring hip or knee JR Controls: volunteers with clinical OA	Radiographic hip OA (39%), radiographic knee OA (18%)	*Recruitment centre: Santander* Hip OA: 71 ± 7, knee OA: 72 ± 7, controls: 71 ± 10 *Recruitment centre: Coruna* Hip OA: 67 ± 14, controls: 65 ± 13 *Recruitment centre: Santiago* Hip OA: 68 ± 5, knee OA: 68 ± 6, controls: 68 ± 9 *Recruitment centre: Oxford* Hip OA: 65 ± 6, knee OA: 64 ± 5, controls: 69 ± 7	N/A	62

SD, standard deviation; OA, osteoarthritis; N/A, not applicable; N/A*, not available; JR, joint replacement.

study examined aromatase [39]. Nine studies recruited participants from existing studies [14,18,21,24,27,30,31,37,38] such as the Women's Health Initiative, the Framingham Heart Study and the Health ABC Study. Others recruited participants from the general community [13,16,17,19,20,22,25,26,28,29,33], clinics or hospitals [23,32,34–36,39], or from a biobank database [15].

The mean age of the study populations of the included studies ranged from 35 to 79.6 years. The number of study participants ranged from 28 to 121,701 and the percentage of women in the studies ranged from 40% to 100%. The follow up time for RCTs ranged from 1 to 7 years whilst the follow up time for the longitudinal studies ranged from 2 to 11 years. Ten studies examined asymptomatic populations with no OA [13,15–17,19,20,22,25,28,29], 13 studies examined populations that were mixed with regards to OA status [14,21,23,26,31–39], 1 study examined a population with hand, knee or hip OA [27], and one study examined a population with hip OA [30]. The OA status of the study population could not be determined in one study [18]. Eleven studies were considered to be of high quality, with a score greater than 74 [13,14,18–20,24,26,29–31,37].

The included studies examined a range of risk factors. Six studies assessed endogenous sex hormones [13–17] including one study which assessed oestrogen deprivation due to menopause [15] and another that examined aromatase [39]. Although aromatase is not a sex hormone, aromatisation of androgenic precursors is the dominant source of oestrogen in men and postmenopausal women [39], thus we have included the study of aromatase in our review. Ten studies examined exogenous sex hormones [18–27], and one study each examined tibolone, a synthetic steroid [28], and levormeloxifene, a selective oestrogen-receptor modulator [29]. For the purpose of our review, we have included both tibolone and levormeloxifene as 'exogenous sex hormones' as tibolone possesses a combination of estrogenic, androgenic and progestogenic properties [28], and levormeloxifene was initially developed as an alternative to oestrogen replacement therapy [40]. Nine studies examined oestrogen receptor and androgen receptor gene polymorphisms [30–38].

Five studies measured cartilage and bone biomarkers as their primary outcome [15,19,25,28,29]. Eleven studies examined OA radiographically [14,23,27,30–33,35–38], 7 studies examined OA-related MRI features [13,16,17,20–22,26], one study examined end-stage idiopathic OA [34], 2 studies examined joint replacement [18,24], and one study assessed aromatase expression in osteoarthritic compared to osteoporotic bone [39].

3.2. Study results

3.2.1. Endogenous sex hormones

A summary of the significant findings of each study are presented in Table 3.

1. Association with cartilage biomarkers
   One cross-sectional study of asymptomatic women found significantly higher levels of urinary CTX-II in postmenopausal women compared to premenopausal women [15]. No association was found for urinary Helix-II.
2. Association with radiographic knee OA
   One study examining the relationship between serum oestradiol and urinary oestrogen metabolites and OA found a significantly higher ratio of 16α-hydroxyestrone: 2-hydroxyestrone in women with prevalent and incident radiographic knee OA compared to those without [14]. However, the mean concentrations of 2-hydroxyestrone and 16α-hydroxyestrone separately were both lower in those with incident OA compared to controls. There was an increased risk of prevalent knee OA in those with low levels of 2-hydroxyestrone. Similarly, risk of incident knee OA was increased in those with low 2-hydroxyestrone and oestradiol levels. Higher 16α-hydroxyestrone:2-hydroxyestrone ratio was associated with increased risk of both prevalent and incident OA.
3. Association with OA-related MRI-assessed structures
   One MRI study of asymptomatic men reported a positive cross-sectional association between testosterone and tibial cartilage volume in the medial compartment [16], however, longitudinal examination found a positive association between testosterone and loss of tibial cartilage volume over 2 years [13]. Conversely, no association was found between testosterone and MRI-assessed knee structure in asymptomatic women [17]. Although there was a positive association between sex hormone-binding globulin (SHBG) and patella bone volume in asymptomatic women [17], it was not associated with any other structures in the patellar or tibial compartment [13,16,17]. No significant relationship was found between knee structure and oestrogen, luteinizing hormone, dehydroepiandrosterone sulphate (DHEAS) [13,16,17], and androstenedione in asymptomatic populations [17].
4. Association between aromatase and hip OA
   In a study examining aromatase expression in osteoarthritic and osteoporotic bone, aromatase RNA levels were significantly lower in bone samples and cell cultures derived from hip OA patients compared to control patients with hip fracture [39].

3.2.2. Exogenous sex hormones

A summary of the significant findings of each study are presented in Table 4.

1. Association with bone and cartilage biomarkers
   One RCT examining the effect of different forms of application of postmenopausal oestrogen therapy on bone and cartilage found decreased urinary CTX-I and II levels after 1 year treatment with either oral or transdermal oestradiol therapy [19]. Similarly, an RCT assessing the effects of levormeloxifene on bone and cartilage turnover reported a decrease in both serum CTX-I and urinary CTX-II levels after 1 year treatment with levormeloxifene [29]. No apparent dose–response relationship for CTX-I was found, and whilst there was a trend for dose-dependent effects for CTX-II, it did not reach statistical significance. This is consistent with the findings of another trial assessing the effects of tibolone, which showed a significant decrease in CTX-I levels after 2 years of treatment with tibolone for both the 1.25 and 2.5 mg/day dose [28], though no significant effect was found on CTX-II levels. Similar results were obtained in an observational study, reporting lower urinary CTX-II levels in those receiving HRT compared to those not on HRT [25]. In particular, urinary CTX-II was lower in those who have received HRT for 4–10 years compared to 0–4 years.
2. Association with radiographic OA
   One study reported no significant association between HRT use and duration and bilateral or generalised hip, knee or hand OA in men and women from the Ulm Osteoarthritis Study [27]. Similarly, in women from Tasmania, no significant association was found between current or ever HRT use and prevalence of distal interphalangeal (DIP) or carpo-metacarpal (CMC) OA [23]. However, current and ever HRT use was associated with prevalence of Heberden's nodes (HNs) and greater severity of HN and DIP OA [23].
3. Association with OA-related MRI-assessed structures
   Oestrogen users had a reduced risk of bone attrition and bone marrow abnormalities [21], as well as greater tibial cartilage [26], than non-users, although no difference in patella cartilage volume [22] or cartilage volume loss [20] was observed.
4. Association with joint replacement
   One cross-sectional study reported an association between hip replacement due to OA and past, but not current, postmenopausal hormone use [24]. Similarly, a longitudinal study found that women receiving oestrogen had lower rates of joint replacement, although receiving both oestrogen and progestin did not affect rates of joint replacement [18].

3.2.3. Oestrogen and androgen receptor gene polymorphisms

A summary of the significant findings of each study are presented in Table 5.

1. Association with radiographic OA
   In a cross-sectional study examining ESR1 polymorphisms, there was an increased risk of osteophytosis in those with 1 copy of the PX allele compared to those with 0 copies, and an increased risk of osteophytosis and K/L score $\geq$2 in those with 2 copies of the PX allele [37]. Another study found an increased risk of radiographic knee OA in women with the CGCA and TAGA haplotype of ESR1, but not in men [35]. Although one study reported change in osteophyte grade over ~10 years was affected by SNPs at ESR1, this was only a trend with a p-value of 0.06 [31]. In one case–control study, there were no differences in allele frequencies and genotype distributions of Pvu II and Xba I between cases with idiopathic OA and healthy controls [34]. In this study idiopathic OA was confirmed, amongst others, radiographically [34]. Other studies also reported no significant associations between ESR1 SNPs and generalised or severe hand OA [38], and no difference in allele frequencies and genotype distributions of Pvu II and Xba I in early onset, late onset, mild and severe radiographic knee OA patients compared to controls [33]. However, the allele frequency of the exon 8 G/A Btg I polymorphisms was higher in late onset OA subjects compared to controls [33]. One longitudinal study found significantly lower odds for prevalent and incident radiographic hip OA in women with the Pvu II C/C genotype compared to the Pvu II T/T genotype [30]. In particular, the relationship between Pvu II genotypes and incident hip OA

Table 3
Results for studies that examined endogenous sex hormones.

Author (year), Ref.	Risk factor	Outcome	Results	Summary of significant findings
Bay-Jensen et al. (2009) [15]	Oestrogen deprivation due to menopause	Urinary Helix-II and urinary CTX-II levels	↑ Urinary Helix-II in post- v. pre-menopausal women; $p = 0.19$ ↑ Urinary CTX-II in post- v. pre-menopausal women; $p < 0.0001$	Urinary CTX-II levels were significantly increased in postmenopausal women compared to pre-menopausal women, but urinary Helix-II levels remained unchanged.
Sowers et al. (2006) [14]	Serum oestradiol Urinary oestrogen metabolites: 2-hydroxyestrone and 16α-hydroxyestrone 16α-hydroxyestrone:2-hydroxyestrone ratio	Prevalent radiographic knee OA	Mean ± SD serum oestradiol concentration: OA 69 ± 48, no OA 62 ± 44; p for difference >0.05 Mean ± SD 2-hydroxyestrone concentration: OA 10.2 ± 8.5, no OA 11.3 ± 8.2; p for difference >0.05 Mean ± SD 16α-hydroxyestrone concentration: OA 7.7 ± 4.7, no OA 7.8 ± 5.5; p for difference >0.05 16α-Hydroxyestrone: 2-hydroxyestrone ratio: OA 0.76 ± 0.47, no OA 0.69 ± 0.27; p for difference <0.05 Odds for prevalent OA: ≤33rd v. 33rd–66th percentile oestradiol: OR 1.20 (0.75, 1.91) ≥66th v. 33rd–66th percentile oestradiol: OR 1.06 (0.66, 1.71) ≤33rd v. 33rd–66th percentile 2-hydroxyestrone: OR 1.62 (1.03, 2.55) ≥66th v. 33rd–66th percentile 2-hydroxyestrone: OR 0.62 (0.37, 1.03) ≤33rd v. 33rd–66th percentile 16α-hydroxyestrone: OR 1.37 (0.86, 2.18) ≥66th v. 33rd–66th percentile 16α-hydroxyestrone: OR 0.85 (0.52, 1.41) ≤33rd v. 33rd–66th percentile 16α-hydroxyestrone: 2-hydroxyestrone ratio: OR 0.73 (0.45, 1.21) ≥66th v. 33rd–66th percentile 16α-hydroxyestrone: 2-hydroxyestrone ratio: OR 1.65 (1.05, 2.61)	The mean ± SD of the 16α-hydroxyestrone:2-hydroxyestrone ratio was significantly higher in those with prevalent OA compared to those without. There was a significant association between low levels of 2-hydroxyestrone and prevalent OA, as well as between a high 16α-hydroxyestrone:2-hydroxyestrone ratio and prevalent OA.
Sowers et al. (2006) [14]	Serum oestradiol Urinary oestrogen metabolites: 2-hydroxyestrone and 16α-hydroxyestrone 16α-hydroxyestrone:2-hydroxyestrone ratio	Incident radiographic knee OA	Mean ± SD serum oestradiol concentration: OA 54 ± 38, no OA 63 ± 43; p for difference >0.05 Mean ± SD 2-hydroxyestrone concentration: OA 8.3 ± 6.7, no OA 11.8 ± 10.2; p for difference <0.05 Mean ± SD 16α-hydroxyestrone concentration: OA 6.8 ± 4.2, no OA 8.0 ± 5.1; p for difference <0.05 16α-hydroxyestrone:2-hydroxyestrone ratio: OA 0.83 ± 0.51, no OA 0.68 ± 0.51; p for difference <0.05 Odds for incident OA: ≤33rd v. 33rd–66th percentile oestradiol: OR 1.88 (1.07, 3.51) ≥66th v. 33rd–66th percentile oestradiol: OR 1.04 (0.52, 2.09) ≤33rd v. 33rd–66th percentile 2-hydroxyestrone: OR 2.91 (1.49, 5.68) ≥66th v. 33rd–66th percentile 2-hydroxyestrone: OR 1.06 (0.49, 2.29) ≤33rd v. 33rd–66th percentile 16α-hydroxyestrone: OR 1.36 (0.74, 2.51) ≥66th v. 33rd–66th percentile 16α-hydroxyestrone: OR 0.87 (0.44, 1.71) ≤33rd v. 33rd–66th percentile 16α-hydroxyestrone:2-hydroxyestrone ratio: OR 0.87 (0.44, 1.73) ≥66th v. 33rd–66th percentile 16α-hydroxyestrone:2-hydroxyestrone ratio: OR 1.86 (1.01, 3.44)	The mean ± SD concentration of 2-hydroxyestrone and 16α-hydroxyestrone was lower in those with incident OA compared to those without, and the mean ± SD ratio of 16α-hydroxyestrone:2-hydroxyestrone was higher in those with incident OA. There was a significant association between low levels of oestradiol and 2-hydroxyestrone and incident OA, and between a high 16α-hydroxyestrone:2-hydroxyestrone ratio and incident OA.

Table 3 (*Continued*)

Author (year), Ref.	Risk factor	Outcome	Results	Summary of significant findings
Hanna et al. (2007) [17]	Dehydroepiandrosterone sulphate (DHEAS) Androstenedione Sex hormone-binding globulin (SHBG) Testosterone	Knee structure	*DHEAS* Tibial cartilage volume: B 72 (−99,243) $p = 0.41$; tibial cartilage defects: OR 0.7 (0.3, 1.5) $p = 0.40$; bone area: B −12 (−91, 66) $p = 0.75$; bone marrow lesions: OR 0.4 (0.1, 1.7) $p = 0.24$ Patella cartilage volume: B 13 (−152, 178) $p = 0.87$; patella cartilage defects: OR 0.5 (0.2, 1.3) $p = 0.16$; patella bone volume: B 372 (−155, 899) $p = 0.17$ *Androstenedione* Tibial cartilage volume: B −24 (−213, 166) $p = 0.80$; tibial cartilage defects: OR 0.8 (0.3, 1.7) $p = 0.51$; bone area: B 34 (−52, 120) $p = 0.44$; bone marrow lesions: OR 0.4 (0.1, 1.8) $p = 0.24$ Patella cartilage volume: B 50 (−130, 230) $p = 0.59$; patella cartilage defects: OR 0.4 (0.1, 1.1) $p = 0.08$; patella bone volume: B 175 (−407, 758) $p = 0.55$ *Total testosterone* Tibial cartilage volume: B −33 (−424, 358) $p = 0.87$; tibial cartilage defects: OR 0.5 (0.1, 26) $p = 0.40$; bone area: B −20 (−198, 158) $p = 0.82$l bone marrow lesions: OR 0.3 (0.0, 7.0) $p = 0.48$ Patella cartilage volume: B 54 (−321, 428) $p = 0.78$; patella cartilage defects: OR 0.2 (0.0, 1.7) $p = 0.14$; patella bone volume: B 797 (−403, 1997) $p = 0.19$ *SHBG* Tibial cartilage volume: B 13 (−47, 74) $p = 0.66$; tibial cartilage defects: OR 0.9 (0.7, 1.2) $p = 0.48$; bone area: B 22 (−5, 49) $p = 0.10$; bone marrow lesions: OR 1.4 (0.9, 2.0) $p = 0.11$ Patella cartilage volume: B −26 (−84, 31) $p = 0.37$; patella cartilage defects: OR 1.0 (0.8, 1.5) $p = 0.78$; patella bone volume: B 218 (39, 396) $p = 0.02$	SHBG was positively associated with patella bone volume but no other structures in the patellar or tibial compartments. No other sex hormones were significantly associated with knee joint structure.
Cicuttini et al. (2003) [16]	Free testosterone SHBG Oestrogen DHEAS Luteinizing hormone	Tibial cartilage volume	*Free testosterone* Total cartilage: B 0.0008 (0.00, 0.002) $p = 0.08$; medial cartilage: B 0.0008 (0.00, 0.02) $p = 0.04$; lateral cartilage: B 0.0008 (0.00, 0.002) $p = 0.19$ *SHBG* Total cartilage: B 0.004 (−0.01, 0.01) $p = 0.51$; medial cartilage: B 0.001 (−0.009, 0.011) $p = 0.84$; lateral cartilage: B 0.009 (−0.006, 0.025) $p = 0.22$ *Oestrogen* Total cartilage: B 0.0008 (−0.003, 0.005) $p = 0.69$; medial cartilage: B 0.0002 (−0.003, 0.002) $p = 0.37$; lateral cartilage: B 0.0002 (−0.006, 0.006) $p = 0.96$ *DHEAS* Total cartilage: B 0.01 (−0.23, 0.25) $p = 0.80$; medial cartilage: B 0.005 (−0.06, 0.07) $p = 0.87$; lateral cartilage: B 0.009 (−0.102, 0.120) $p = 0.87$ *Luteinizing hormone* Total cartilage: B −0.008 (−0.04, 0.06) $p = 0.77$; medial cartilage: B −0.001 (−0.05, 0.05) $p = 0.97$; lateral cartilage: B −0.002 (−0.099, 0.065) $p = 0.68$	There was a positive association between free testosterone and tibial cartilage volume in the medial, but not total or lateral, compartment. No other sex hormones were associated with tibial cartilage.
Hanna et al. (2005) [13]	Free testosterone Oestrogen SHBG DHEAS Luteinizing hormone	Longitudinal change in tibial cartilage volume	Testosterone and Δ cartilage: B 1.16 (0.09, 2.23) $p = 0.036$ Oestrogen and Δ cartilage: B −0.22 (−16.2, 15.7) $p = 0.98$ SHBG and Δ cartilage: B 3.6 (−2.64, 9.79) $p = 0.24$ DHEAS and Δ cartilage: B 29.7 (−79.2, 138.7) $p = 0.57$ Luteinizing hormone and Δ cartilage: B 48.3 (−43.3, 139.8) $p = 0.28$	Testosterone, but no other sex hormone, was associated with loss of tibial cartilage volume.
Hernandez et al. (2008) [39]	Aromatase RNA levels	Hip OA	Lower aromatase RNA levels in bone samples of men with hip OA v. hip fracture; $p = 0.013$ Lower aromatase RNA levels in bone samples of women with hip OA v. hip fracture; $p = 0.001$ Lower aromatase RNA levels in osteoblast cultures of patients with hip OA v. hip fracture; $p = 0.012$	Aromatase RNA levels were significantly higher in both bone samples and cell cultures derived from hip fracture patients compared to OA patients.

OA, osteoarthritis; OR, odds ratio; B, regression coefficient; Δ, change in.

Table 4
Results for studies that examined exogenous sex hormones.

Author (year), ref	Risk factor	Outcome	Results	Summary of significant findings
Ravn et al. (2004) [19]	Oral and transdermal oestradiol therapy	Change in urinary CTX-I and II after 1 year	↓ Urinary CTX-I in oral oestradiol group v. Placebo; $p < 0.001$ ↓ Urinary CTX-I in transdermal oestradiol group v. Placebo; $p < 0.001$ ↓ Urinary CTX-II in oral oestradiol group v. Placebo; $p < 0.01$ ↓ Urinary CTX-II in transdermal oestradiol group v. Placebo; $p < 0.05$	Oral and transdermal oestradiol therapy were significantly associated with reduced urinary CTX-I and II levels.
Karsdal et al. (2008) [28]	Tibolone (1.25, 2.5 mg/day)	Change in urinary CTX-I and II levels over 2 years	↓ Urinary CTX-I after 2 years; $p < 0.001$ ↑ Urinary CTX-II after 2 years; $p > 0.05$	All doses of tibolone were significantly associated with reduced urinary CTX-I levels.
Christgau et al. (2004) [29]	Levormeloxifene (1.25, 5, 10, 20 mg/day)	Change in serum CTX-I and urinary CTX-II over 1 year	↓ Serum CTX-I after 1 year; $p < 0.05$ ↓ Urinary CTX-II after 1 year; $p < 0.05$	All doses of levormeloxifene were significantly associated with decreased CTX-I and II levels.
Mouritzen et al. (2003) [25]	HRT	Urinary CTX-II levels	↓ In HRT users; $p < 0.001$ ↓ In 4–10 years HRT users compared to 0–4 years HRT users; $p < 0.05$	Urinary CTX-II levels were lower in those receiving HRT treatment compared to those not on HRT. It was also lower in those who have received HRT for 4–10 years compared to 0–4 years.
Erb et al. (2000) [27]	HRT (oestrogen + progesterone)	Radiographically defined patterns of OA of the hip, knee and hand	Odds for bilateral OA in: HRT v. Non HRT users: OR 1.21 (0.48, 3.03) <5 years HRT v. Non HRT users: OR 0.91 (0.28, 3.00) ≥5 years HRT v. Non HRT users: OR 1.60 (0.44, 5.83) Odds for generalised OA in: HRT v. Non HRT users: OR 1.21 (0.53, 2.74) <5 years HRT v. Non HRT users: OR 1.13 (0.36, 3.60) ≥5 years HRT v. Non HRT users: OR 1.28 (0.46, 3.66)	HRT use and duration of HRT use were not significantly associated with radiographic patterns of OA.
Cooley et al. (2003) [23]	HRT	Radiographic hand OA	Prevalence of distal interphalangeal (DIP) OA with: Current HRT use: OR 2.21 (0.88, 5.51) Ever HRT use: OR 2.10 (0.94, 4.68) Prevalence of carpo-metacarpal (CMC) OA with: Current HRT use: OR 1.60 (0.76, 3.39) Ever HRT use: OR 1.41 (0.72, 2.79) Prevalence of Heberden's Nodes (HN) with: Current HRT use: OR 3.02 (1.42, 6.44) Ever HRT use: OR 2.46 (1.34, 4.49) Severity of DIP OA with: Current HRT use: B 2.82 (0.13, 5.51) Ever HRT use: B 2.70 (0.32, 5.07) Severity of CMC OA with: Current HRT use: B −0.06 (−0.08, 0.69) Ever HRT use: B 0.65 (−0.01, 1.31) Severity of HN with: Current HRT use: B 1.27 (0.60, 1.93) Ever HRT use: B 1.20 (0.62, 1.78)	Current or ever HRT use was significantly associated with greater severity of HN and DIP, but not CMC, OA. Current or ever HRT use was also positively associated with prevalence of HN. No significant association was found between HRT use and prevalence of DIP or CMC OA.
Carbone et al. (2004) [21]	Oestrogen use	OA-related MRI features	Bone attrition: OR 0.36 (0.17, 0.79) Osteophytes: OR 0.94 (0.33, 2.63) Bone marrow abnormality: OR 0.48 (0.23, 1.00) Cartilage lesions: OR 1.50 (0.48, 4.64)	Oestrogen use significantly reduced the risk of bone attrition and bone marrow abnormalities.
Wluka et al. (2001) [26]	ERT	Tibial cartilage volume	Mean difference in total cartilage 0.30 (0.08, 0.52) Mean difference in medial cartilage 0.073 (−0.01, 0.15) Mean difference in lateral cartilage 0.23 (0.06, 0.40)	Women taking ERT for more than 5 years had more tibial cartilage than those who had never taken ERT.

Table 4 (*Continued*)

Author (year), ref	Risk factor	Outcome	Results	Summary of significant findings
Cicuttini et al. (2003) [22]	ERT	Patella cartilage volume	Difference in mean cartilage volume 0.14 (−0.08, 0.36)	There was no significant difference in patella cartilage volume in women taking ERT for ≥5 years compared to controls.
Wluka et al. (2004) [20]	ERT	Tibial cartilage volume loss	Mean difference in: Total cartilage volume loss 0.006 (−0.05, 0.06) $p = 0.82$ Medial cartilage volume loss 0.013 (−0.02, 0.04) $p = 0.37$ Lateral cartilage volume loss 0.008 (−0.05, 0.03) $p = 0.68$ % Reduction in total cartilage volume 0.3 (−1.4, 2.0) $p = 0.73$ % Reduction in medial cartilage volume1.0 (−0.9, 3.0) $p = 0.29$ % Reduction in lateral cartilage volume 0.4 (−2.7, 1.8) $p = 0.72$	There were no significant differences in mean tibial cartilage volume loss or mean % reduction in tibial cartilage volume between ERT users and controls.
Karlson et al. (2003) [24]	Postmenopausal hormone use	Total hip replacement due to OA	Past hormone use v. Never use: RR 1.2 (1.0, 1.5) Current hormone use v. Never use: RR 1.0 (0.8, 1.2)	There was an association between hip replacement due to OA and past, but not current, postmenopausal hormone use.
Cirillo et al. (2006) [18]	Oestrogen	Incidence of hip and knee replacement	Total joint replacement: HR 0.73 (0.58, 0.93) $p = 0.01$ Hip replacement: HR 0.55 (0.35, 0.88) $p = 0.01$ Knee replacement: HR 0.80 (0.61, 1.05) $p = 0.11$	Women receiving oestrogen had lower rates of joint replacement, although this effect was only borderline for hip and not significant for knee replacement.
Cirillo et al. (2006) [18]	Combined oestrogen + progesterone	Incidence of hip and knee replacement	Total joint replacement: HR 1.02 (0.81, 1.29) $p = 0.77$ Hip replacement: HR 1.08 (0.72, 1.61) $p = 0.71$ Knee replacement: HR 0.95 (0.71, 1.27) $p = 0.72$	Receiving oestrogen and progestin did not significantly affect rates of joint replacement.

OA, osteoarthritis; HRT, hormone replacement therapy; ERT, oestrogen replacement therapy; PME, postmenopausal oestrogen use; AI, aromatase inhibitor; OR, odds ratio.

varied by ERT use. Another study of ESR1 microsatellite repeats polymorphisms found significant difference in the number of TA and CA repeats for ESR1 between OA cases with previous total knee replacement and control patients with previous treatment for injuries and fractures [32]. The same study also found increased odds for OA in those with the SL (one short, one long) or LL genotypes for ESR2 and in women with the LL genotype for the AR gene, though no significant association was found with ESR1 genotypes. One other study examined ESR2 polymorphisms, reporting a significant association between the ESR2 SNPs rs1256034 and rs944460 and severe radiographic hand OA [38].

4. Discussion

Examining the relationship between sex hormones and OA is complex. Sex hormones have been examined in a number of different ways including endogenous hormones, exogenous hormones and receptor polymorphisms. There are also a number of methods by which joint structure can be measured in OA. Structural changes can be measured in several ways, such as radiologically, on MRI, using biomarkers, or using the clinical end-point of OA that is joint replacement. In this review, we have attempted to consider each of these and bring together the relative findings.

4.1. Endogenous sex hormones

1. Association with cartilage biomarkers

   One cross-sectional study examined the association between endogenous sex hormones and cartilage biomarkers [15], showing a significant association between oestrogen deprivation due to menopause and increased urinary CTX-II. Though the evidence suggests increased cartilage breakdown with oestrogen deprivation, this is based on only one low-quality cross-sectional examination with a small sample size. Moreover, studies of collagen turnover largely use only CTX-II as a marker, however this study further analysed urinary levels of Helix-II, another cartilage biomarker, though no significant association was reported. That the level of urinary Helix-II was not affected may be attributable to the favouring of the proteolytic pathway by oestrogen deprivation, which generates CTX-II rather than Helix-II [41]. Notably, whilst this study used menopausal status as a surrogate for oestrogen deprivation, there was no actual measure of circulating levels of oestrogen. Thus further studies are needed to confirm this.

2. Association with radiographic OA

   The relationship between endogenous sex hormones and radiographic OA was examined by only one study [14]. This was a high-quality, 10-year longitudinal study with a large cohort, which examined serum oestradiol as well as the urinary oestrogen metabolites 2-hydroxyestrone and 16α-hydroxyestrone. Those with low oestradiol levels were found to have increased risk of incident knee OA [14]. Similarly those with low levels of 2-hydroxyestrone, a product of oestradiol catabolism with weak oestrogenic activity [42], were also at greater risk of incident, as well as prevalent, knee OA [14]. It was hypothesised that higher 2-hydroxyestrone concentrations could delay the development of knee OA via arachidonic acid metabolism associated with pain and inflammation [14]. The effects of oestrogen on cartilage are complex, in that it may involve the modulation of growth factors, cytokines, adhesion molecules, MMPs and reactive oxygen species [43]. Its effects on a cellular level may also be through the actions of 17β-oestradiol which may decrease collagenolytic activities and increase cartilage matrix synthesis,

Table 5
Results for studies that examined oestrogen and androgen receptor gene polymorphisms.

Author (year), Ref.	Risk factor	Outcome	Results	Summary of significant findings
Loughlin et al. (2000) [34]	Genotype distributions of Pvu II (++), (+−) and (−−) and Xba I (++), (+−) and (−−) Allele frequencies for Pvu II (+) and (−), and Xba (+) and (−)	End-stage idiopathic OA (clinically, radiologically, operatively and histologically confirmed)	Difference in frequency of the Pvu II (+) and (−) alleles between cases and controls; $p = 0.96$ Difference in frequency of the Xba I (+) and (−) alleles between cases and controls; $p = 0.87$ Difference in the distribution of the Pvu II (++), (+−), and (−−) genotypes between cases and controls; $p = 0.94$ Difference in the distribution of the Xba I (++), (+−), and (−−) genotypes between cases and controls; $p = 0.75$	There was no association between ESR1 polymorphisms and end-stage idiopathic OA.
Bergink et al. (2003) [37]	Number of copies of the haplotype allele PX	K/L score, osteophytosis and JSN	Odds for K/L score ≥2 in those with: 1 copy of the haplotype allele PX v. 0 copies: OR 1.3 (0.9, 1.7) 2 copies of the haplotype allele PX v. 0 copies: OR 2.2 (1.5, 3.4) Odds for osteophytosis in those with: 1 copy of the haplotype allele PX v. 0 copies: OR 1.3 (1.0, 1.7) 2 copies of the haplotype allele PX v. 0 copies: OR 2.3 (1.5, 3.4) Odds for JSN in those with: 1 copy of the haplotype allele PX v. 0 copies: OR 1.1 (0.8, 1.4) 2 copies of the haplotype allele PX v. 0 copies: OR 0.9 (0.5, 1.4)	There was a significant association between number of copies of the PX allele and radiographic OA defined by K/L score ≥2 and osteophytosis, but not with JSN.
Valdes et al. (2006) [35]	ESR1 SNPs and haplotypes	Radiographic knee OA	Odds for OA with ESR1 SNP rs1801132: Women OR 0.86 (0.65, 1.15) $p > 0.05$, men OR 0.86 (0.64, 1.15) $p > 0.05$ Odds for OA with ESR1 SNP rs2228480: Women OR 1.34 (1.00, 1.79) $p < 0.052$, men OR 0.86 (0.64, 1.17) $p > 0.05$ Odds for OA with ESR1 SNP rs2234693: Women OR 0.93 (0.73, 1.17) $p > 0.05$, men OR 1.00 (0.80, 1.26) $p > 0.05$ Odds for OA with ESR1 SNP rs827421: Women OR 1.02 (0.80, 1.29) $p > 0.05$, men OR 1.05 (0.83, 1.32) $p > 0.05$ Odds for OA with ESR1 haplotype CGCA: Women OR 1.70 (1.12, 2.58) $p < 0.017$, men OR 1.44 (0.93, 2.25) $p > 0.05$ Odds for OA with ESR1 haplotype CGCG: Women OR 0.85 (0.65, 1.11) $p > 0.05$, men OR 0.89 (0.69, 1.14) $p > 0.05$ Odds for OA with ESR1 haplotype TACG: Women OR 1.20 (0.92, 1.58) $p > 0.05$, men OR 1.27 (0.98, 1.60) $p > 0.05$ Odds for OA with ESR1 haplotype TAGA: Women OR 3.61 (1.18, 10.98) $p < 0.017$, men OR 0.59 (0.14, 1.53) $p > 0.05$ Odds for OA with ESR1 haplotype TAGG: Women OR 0.72 (0.48, 1.06) $p > 0.05$, men OR 0.84 (0.58, 1.22) $p > 0.05$ Odds for OA with ESR1 haplotype TGCA: Women OR 0.04 (0, 1.84) $p > 0.05$, men OR 0.5 (0.15, 3.67) $p > 0.05$	There was a significant association between the ESR1 haplotypes CGCA and TAGA and risk of knee OA in women but not men. No other haplotypes and none of the SNPs were significantly associated with radiographic knee OA.
Valdes et al. (2004) [31]	ESR_int genotypes	Change in osteophyte grade	Mean (SE) Δ osteophyte grade: ESR_int TC + CC genotypes 0.471 (0.053), ESR_int TT genotype 0.353 (0.032); p for difference <0.06	The SNPs at ESR1 affected change in osteophyte grade significantly.

Table 5 (*Continued*)

Author (year), Ref.	Risk factor	Outcome	Results	Summary of significant findings
Wise et al. (2009) [38]	ESR1 and ESR2 SNPs	Radiographic hand OA	Odds for generalised OA for: ESR1 SNP rs2234693: OR 0.88 (0.61, 1.27) ESR1 SNP rs9340799: OR 0.82 (0.56, 1.19) ESR1 SNP rs2077647: OR 0.93 (0.64, 1.35) ESR1 SNP rs1801132: OR 0.91 (0.58, 1.44) ESR2 SNP rs1256031: OR 0.94 (0.67, 1.33) ESR2 SNP rs1256034: OR 1.91 (0.80, 4.56) ESR2 SNP rs1256059: OR 0.88 (0.61, 1.27) ESR2 SNP rs944460: OR 2.25 (0.92, 5.46) Odds for severe OA for: ESR1 SNP rs2234693: OR 1.15 (0.75, 1.76) ESR1 SNP rs9340799: OR 0.92 (0.60, 1.41) ESR1 SNP rs2077647: OR 1.02 (0.66, 1.58) ESR1 SNP rs1801132: OR 0.91 (0.53, 1.56) ESR2 SNP rs1256031: OR 1.00 (0.67, 1.49) ESR2 SNP rs1256034: OR 2.62 (1.01, 6.78) ESR2 SNP rs1256059: OR 0.89 (0.58, 1.36) ESR2 SNP rs944460: OR 2.78 (1.04, 7.48)	There was no significant association between ESR1 or ESR2 SNPs and generalized hand OA. However, the ESR 2 SNPs rs1256034 and rs944460 were significantly positively associated with severe hand OA.
Jin et al. (2004) [33]	Genotype distributions and allele frequencies of intron 1 T/C Pvu II, intron 1 A/G Xba I, and exon 8 G/A Btg I polymorphisms	Clinical and radiographic knee OA	*In early onset OA subjects compared to controls-* Difference in genotype distributions of: Intron 1 T/C Pvu II polymorphisms: $\chi^2 = 0.82$, $p = 0.66$ Intron 1 A/G Xba I polymorphisms: $\chi^2 = 1.00$, $p = 0.60$ Exon 8 G/A Btg I polymorphisms: $\chi^2 = 0.77$, $p = 0.68$ Difference in allele frequency of: Intron 1 T/C Pvu II polymorphisms: $\chi^2 = 0.893$ (0.63, 1.25) $p = 0.50$ Intron 1 A/G Xba I polymorphisms: $\chi^2 = 1.06$ (0.70, 1.60) $p = 0.78$ Exon 8 G/A Btg I polymorphisms: $\chi^2 = 1.20$ (0.80, 1.78) $p = 0.37$ *In late onset OA subjects compared to controls-* Difference in genotype distributions of: Intron 1 T/C Pvu II polymorphisms: $\chi^2 = 0.67$, $p = 0.71$ Intron 1 A/G Xba I polymorphisms: $\chi^2 = 0.68$, $p = 0.71$ Exon 8 G/A Btg I polymorphisms: $\chi^2 = 5.40$, $p = 0.07$ Difference in allele frequency of: Intron 1 T/C Pvu II polymorphisms: $\chi^2 = 1.00$ (0.68, 1.46) $p = 0.99$ Intron 1 A/G Xba I polymorphisms: $\chi^2 = 1.82$ (0.50, 1.33) $p = 0.42$ Exon 8 G/A Btg I polymorphisms: $\chi^2 = 1.63$ (1.07, 2.46) $p = 0.021$ *In subjects with mild OA compared to controls-* Difference in genotype distributions of: Intron 1 T/C Pvu II polymorphisms: $\chi^2 = 3.58$, $p = 0.17$ Intron 1 A/G Xba I polymorphisms: $\chi^2 = 3.32$, $p = 0.19$ Exon 8 G/A Btg I polymorphisms: $\chi^2 = 0.30$, $p = 0.19$ Difference in allele frequency of: Intron 1 T/C Pvu II polymorphisms: $\chi^2 = 0.77$ (0.55, 1.09) $p = 0.14$ Intron 1 A/G Xba I polymorphisms: $\chi^2 = 0.66$ (0.42, 1.04) $p = 0.07$ Exon 8 G/A Btg I polymorphisms: $\chi^2 = 1.42$ (0.98, 2.07) $p = 0.06$ *In subjects with severe OA compared to controls-* Difference in genotype distributions of: Intron 1 T/C Pvu II polymorphisms: $\chi^2 = 2.99$, $p = 0.22$ Intron 1 A/G Xba I polymorphisms: $\chi^2 = 4.76$, $p = 0.09$ Exon 8 G/A Btg I polymorphisms: $\chi^2 = 1.92$, $p = 0.38$ Difference in allele frequency of: Intron 1 T/C Pvu II polymorphisms: $\chi^2 = 1.22$ (0.83, 1.79) $p = 0.31$ Intron 1 A/G Xba I polymorphisms: $\chi^2 = 1.45$ (0.94, 2.26) $p = 0.09$ Exon 8 G/A Btg I polymorphisms: $\chi^2 = 1.31$ (0.84, 2.05) $p = 0.23$	There was a significant association between polymorphisms of ESR1, in particular exon 8 G/A Btg I polymorphisms, and late onset OA.

Table 5 (*Continued*)

Author (year), Ref.	Risk factor	Outcome	Results	Summary of significant findings
Lian et al. (2007) [30]	Pvu II genotypes Xba I genotypes	Radiographic hip OA, osteophytosis and JSN	Risk of OA for: Pvu II T/C v.T/T genotype: OR 0.87 (0.71, 1.08) Pvu II C/C v. T/T genotype: OR 0.71 (0.54, 0.94) Xba I A/G v. A/A genotype: OR 0.88 (0.73, 1.08) Xba I G/G v. A/A genotype: OR 0.77 (0.56, 1.05) Risk of osteophytosis for: Pvu II T/C v. T/T genotype: OR 0.93 (0.62, 1.41) Pvu II C/C v. T/T genotype: OR 0.85 (0.50, 1.42) Xba I A/G v. A/A genotype: OR 1.16 (0.79, 1.69) Xba I G/G v. A/A genotype: OR 0.85 (0.46, 1.60) Risk of JSN for: Pvu II T/C v. T/T genotype: OR 0.86 (0.65, 1.13) Pvu II C/C v. T/T genotype: OR 0.67 (0.46, 0.96) Xba I A/G v. A/A genotype: OR 0.79 (0.61, 1.03) Xba I G/G v. A/A genotype: OR 0.72 (0.47, 1.09)	ESR1 polymorphisms, in particular Pvu II polymorphisms but not Xba I polymorphisms, were associated with reduced odds of prevalent hip OA and JSN.
Lian et al. (2007) [30]	Pvu II genotypes	Incidence of radiographic hip OA	Risk of OA for Pvu II T/C v. T/T genotype in: ERT users: OR 0.81 (0.59, 1.12), non ERT users: OR 0.91 (0.68, 1.21) Risk of OA for Pvu II C/C v. T/T genotype in: ERT users: OR 0.66 (0.44, 0.99), non ERT users: OR 0.78 (0.54, 1.13)	Pvu II polymorphisms of ESR1 were associated with reduced odds of incident hip OA in ERT users.
Fytili et al. (2005) [32]	ESR1, oestrogen receptor beta (ESR2) and androgen receptor (AR) microsatellite repeat polymorphisms	Radiographic knee OA	Mean (SE) CA repeat polymorphism of the ESR2 gene: Cases 21.3 (0.1) controls 20.4 (0.1), p for difference <0.0001 Mean (SE) TA repeat polymorphism of the ESR1 gene: Cases 17.5 (0.3), controls 16.5 (0.2), p for difference =0.005 Mean (SE) CAG repeat polymorphism of the AR gene in women: Cases 21.7 (0.2), controls 22.2 (0.2), p for difference =0.086 Mean (SE) CAG repeat polymorphism of the AR gene in men: Cases 19.9 (0.9), controls 21.6 (0.5), p for difference =0.076 Odds for OA for ESR2 genotype: SL (one short one long) v. SS: OR 6.2 (1.1, 34.7) p = 0.037 Odds for OA for ESR2 LL v. SS: OR 3.1 (1.33, 7.45) p = 0.009 Odds for OA for AR SL v. SS in women: OR 0.25 (0.05, 1.2) p = 0.082 Odds for OA for AR LL v. SS in women: OR 0.017 (0.001, 0.16) p < 0.001	There was a significant association between ESR1 and ESR 2 polymorphisms and radiographic knee OA.
Riancho et al. (2010) [36]	Aromatase gene (CYP19A1) and ESR1 SNPs	Severe radiographic hip and knee OA requiring joint replacement	Risk for knee OA for the GC genotype at rs1062033 of CYP19A1: Women: OR 1.28 (1.04, 1.57, p = 0.02), men: not significant, data not shown Risk for knee OA for the CC genotype at rs2234693 of ESR1: Women: OR 0.76 (0.59, 0.97, p = 0.028), men: not significant, data not shown Risk for hip OA for the GC genotype at rs1062033 of CYP19A1: Women: OR 1.12 (0.95, 1.33, p = 0.18), men: not significant, data not shown Risk for hip OA for the CC genotype at rs2234693 of ESR1: Women: OR 0.84 (0.69, 1.02, p = 0.07), men: OR 1.28 (1.02, 1.59, p = 0.029)	In women, polymorphisms of ESR1 and the aromatase gene CYP19A1 were associated with knee OA. In men, polymorphism of the ESR1 was associated with hip OA.

OA, osteoarthritis; TMJ, temporomandibular joint; K/L, Kellgren/Lawrence; JSN, joint space narrowing; SNP, single nucleotide polymorphism; OR, odds ratio.

resulting in chondroprotection [43]. Currently there is insufficient evidence from only one study to support an association between endogenous sex hormones and radiographic OA, albeit from a high-quality cohort with a long follow-up time and a large sample size.

3. Association with OA-related MRI-assessed structures

One small, high-quality, 2-year cohort study and 2 small-to-moderately sized, low-quality cross-sectional studies have examined the association between endogenous sex hormones and MRI structures in asymptomatic populations. Cross-sectionally, there was a positive association between testosterone and tibial cartilage volume in men whilst, in women, an association between SHBG and patella bone volume [17]. Indeed in vitro examination of human chondrogenic progenitor cells (CPCs) in arthritic tissue during late stages of OA found that physiologic testosterone concentrations decreased the gene expression of type I collagen in CPCs, indicating a positive influence on the regenerative potential of CPCs from men

[44]. Interestingly, although increased testosterone was associated with greater cartilage volume cross-sectionally, it was also associated with increased cartilage loss over 2 years [13]. This suggests that any cross-sectional benefit of testosterone on tibial cartilage is only temporary, and whilst the evidence is based on a small cohort of 28 men, the study was of high-quality with a low risk of bias and blinded measurements. Nevertheless a larger cohort followed over a longer period of time is required to confirm these results.

4. Association between aromatase and hip OA

   One low-quality case–control study of 104 men and women has reported significantly lower aromatase RNA levels in hip OA patients [39]. Aromatase converts androstenedione, an adrenal androgen, to oestrone and oestradiol [45]. Low aromatase levels in OA may indicate decreased oestrogen availability, which could facilitate cartilage damage [39]. Although this suggests that low aromatase levels may be a risk factor for hip OA, this is based on evidence from only one low-quality study thus providing insufficient evidence to support an association.

5. Summary

   A total of 6 studies examined endogenous sex hormones as risk factors. The limited evidence in general suggests a likelihood for an association between endogenous sex hormones. In particular this relates to associations between oestrogens and both cartilage turnover and radiographic OA. In contrast the association between serum testosterone and cartilage volume remains unclear and there is insufficient evidence for an association between aromatase and hip OA.

4.2. Exogenous sex hormones

1. Association with bone and cartilage biomarkers

   Three RCTs with moderate sample sizes and one large, low-quality cross-sectional study have assessed the effect of exogenous sex hormones on bone and cartilage turnover. The findings of the RCTs, two of which were of high-quality, indicate decreased CTX-I and II levels with oestradiol therapy [19], as well as decreased CTX-I and II levels with levormeloxifene use over one year [29] and a reduction in CTX-I levels with tibolone use over 2 years [28]. This was also supported by the findings of the cross-sectional study. Since oestradiol is the primary oestrogen in women pre-menopause [14], and both tibolone [28] and levormeloxifene [40] possess oestrogenic properties, it appears that there is a strong level of evidence provided by controlled trials and one observational study supporting an association between exogenous oestrogen and bone and cartilage turnover.

2. Association with radiographic OA

   The association between exogenous sex hormone and radiographic OA has been examined by 2 low-quality cross-sectional studies, reporting no association with patterns of OA [27] and a positive association with hand OA severity, but not with prevalence of OA [23]. The lack of association may in part be attributable to the type of hormones used in the HRT. Progestins or progesterone may counter the efficacy of oestrogen via modulation of oestrogen receptor expression when used in conjunction [46]. Nevertheless, current evidence suggests no association between HRT and radiographic OA, though it may play a role in severity of hand OA.

3. Association with OA-related MRI-assessed structures

   One high-quality, 2.5-year cohort of 81 community-based women and 3 cross-sectional studies, one of which was of high-quality, have examined the association between exogenous sex hormones and MRI structures. Whilst cross-sectionally there was a protective effect of exogenous sex hormones on risk of bone attrition [21] and greater tibial cartilage volume in users of oestrogen [26], this was in contrast to the findings of one cohort and one cross-sectional study which reported no association between ERT and patella cartilage volume [22] and tibial cartilage loss [20]. Similar to the effect of endogenous testosterone on tibial cartilage in men [13,16], it might be that any positive effect of exogenous oestrogen on tibial cartilage in women is only short-term or the study may have been too small or too short to show an effect. This may also suggest that oestrogen affects the patellofemoral and tibiofemoral compartments differently. Current evidence for an association between exogenous sex hormones and tibiofemoral structures remains conflicting.

4. Association with joint replacement

   One RCT has examined the association between the use of oestrogen ± progesterone and incidence of hip and knee replacement [18]. Women receiving unopposed oestrogen had lower rates of joint replacement, though the same is not true for women receiving oestrogen plus progesterone, which may be due to the previously mentioned modulating role of progesterone on oestrogen. Furthermore the oestrogen plus progestin trial was discontinued ~1 year earlier than scheduled due to adverse events which outweighed the benefits [18]. In contrast, a cross-sectional examination found past hormone use was associated with increased risk of hip OA [24]. However, this study again provided no information on the type of hormone used, and by nature of the study design evidence from a cross-sectional study would be weaker, particularly as both hormone use and the diagnosis of primary OA and hip replacement were self-reported. Thus we conclude that the effect of oestrogen on joint replacement requires further research.

5. Summary

   Whilst evidence suggests a protective effect of exogenous oestrogen on cartilage and bone turnover, whether it also affects radiographic OA, MRI structure, and joint replacement remains unclear. The conclusions are limited by lack of studies of sufficient duration to adequately answer this.

4.3. Oestrogen and androgen receptor gene polymorphisms

1. Association with radiographic OA

   Two large high-quality cohort, 4 low-quality case–control and 2 cross-sectional studies with large sample sizes, one of which was of high quality, have examined the association between ESR1 polymorphisms and OA. ESR1, the gene which encodes oestrogen receptor alpha (ERα), is an important mediator in the signal transduction pathway and its protein is expressed in cells including bone cells and chondrocytes [47]. Two common polymorphisms of this gene are Pvu II and Xba I, which occur in intron 1 on the ESR1. All but one high-quality cross-sectional study [34] showed a positive association between ESR1 polymorphisms and OA, suggesting strong evidence for an association. Nevertheless, the discrepancy in results may be due to the different endpoints used. Whereas the 7 studies showing an association use radiological OA as an outcome [30–33,35,37,38], the study by Loughlin et al. used end-stage idiopathic OA as an outcome, although their idiopathic diagnosis was supported by, amongst others, radiological findings [34]. Two studies also examined ESR2 polymorphisms and its association with severe hand OA [38] and knee OA [32]. Moreover, the study by Fytili et al. also examined androgen receptor (AR) polymorphisms, reporting an association with knee OA. Although the types of ESR polymorphisms examined by the included studies vary, in general the evidence suggests that ESR1, as well as ESR2 and AR polymorphisms are likely to influence radiographic OA.

2. Summary

There is consistent evidence supporting an association between ESR1, ESR2 and AR polymorphisms and radiographic OA.

4.4. Limitations

There is significant heterogeneity in the available data on sex hormones, particularly exogenous sex hormones. For example studies have examined HRT, ERT and oral or transdermal oestradiol, and in often cases the hormones included in the HRT are varied. The definition of OA is also heterogeneous with studies examining different groups of joints and using varied methods for assessment of structure, from biomarkers to radiographic and MRI based measures. As a consequence, we were unable to do a best evidence synthesis. We have however grouped the studies based on 3 main exposures: endogenous hormones, exogenous hormones and receptor polymorphisms; which were then further grouped by outcomes including radiographic OA, MRI structure and joint replacement. We have presented the relevant studies and for each subgroup we have provided a summary of the evidence. A further limitation is that lack of cohort studies of sufficient sample size and duration to confirm or refute some of the cross sectional results. For example, some of the results showing effects of hormones on cartilage serum and MRI biomarkers warrant further investigation.

4.5. Conclusion

Although the heterogeneity of the studies in terms of the type of sex hormone examined and whether it is endogenous or exogenous as well as the different methods for assessing OA means that there is insufficient evidence to form strong conclusions, nevertheless current evidence suggests an association between endogenous and exogenous oestrogen on cartilage and bone turnover. Although endogenous oestrogen may affect radiographic OA, whether similar effects exist with exogenous oestrogen remains unclear. The relationship between oestrogen and OA is supported by genetic studies, which show a relationship between certain ESR1 and 2 polymorphisms and radiographic OA. Given the higher prevalence of OA in women, particularly after the menopause, this area warrants further investigation.

Competing interests

The authors declare that there are no competing interests.

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