

Anteromedial Osteoarthritis – A surgical perspective of incidence, progression and risk factors.



A Dissertation Submitted to the
University of Oxford
in partial fulfillment of the requirements
for the degree of
Doctor of Philosophy

By

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Trinity 2014

Acknowledgements

Andrew Price and David Beard have been my supervisors and I will be forever indebted to them for their ideas, support, guidance and friendship throughout the time of my research. I have learnt so much from each of them and I have greatly enjoyed my time working with them.

I would like to thank all my colleagues in the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences. In particular Ben Kendrick, Raj Rout, Luke Jones, Chetan Jayadev and Paul Monk who have provided support, friendship and laughter throughout my time in the Department.

I feel honoured to have worked with and learnt from so many talented people during the time of my research. By providing advice and collaboration they have really enabled the work that follows and I would like to thank them here; Eugene McNally, Stephen Mellon, Knut Beardsson, Cameron Brown, David Hunter, Kassim Javaid, Michael Nevitt and Kirsten Leyland.

Finally I want to thank my family. To my Mother and Father for providing me with the support and opportunity to succeed. Most importantly I wish to thank Caroline, George and Arthur; my wife and two sons to whom I dedicate this work. Caroline is a truly special person without whose love, understanding and patience this work would never have been completed. To George and Arthur, thank you for continually reminding me of what is most important in life and yes, Daddy has finished his book.

Abstract

Anteromedial osteoarthritis: A surgical perspective of incidence, progression and risk factors

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Worcester College

Doctor of Philosophy
Trinity Term 2014

Anteromedial osteoarthritis of the knee (AMOA) has been defined anatomically, histologically and radiologically and yet little is known about the epidemiology of the disease or the risk factors involved in the development of the disease.

The broad aim of this thesis was to combine clinical insight with the utilisation of modern, large epidemiological datasets to provide information to inform better the clinical management of patients with AMOA. Specifically, the prevalence and incidence of AMOA, the time taken to progress from early disease to severe disease that may require surgical intervention, the radiological characterisation of disease and the assessment of mechanical risk factors implicit in the development of this pattern of disease are investigated.

A cross-sectional study of the radiological prevalence of AMOA in a symptomatic cohort in a specialist secondary care knee clinic showed that AMOA was the commonest pattern of knee OA, present in more than 60% of symptomatic subjects. Less than 25% of subjects with AMOA presented with advanced or 'bone-on-bone' disease, emphasising the clinical importance of understanding the progression from earlier stages of disease to this advanced stage.

A 20-year longitudinal radiographic study was performed on 1000 women to describe the prevalence, incidence and progression of AMOA. The prevalence of AMOA was 43% and the incidence over 20-years was 0.4. Life table analysis showed that the risk of developing advanced AMOA in a previously normal knee was 2.6%. Of those subjects with early radiological AMOA, 11% progressed to advanced 'bone-on-bone' disease within 10 years and 37% within 20 years.

The role of mechanical risk factors in the development of AMOA showed that both anatomical limb and proximal tibial alignment were significantly more varus aligned in those that developed AMOA at 20-years. Assessment of the shape of the medial tibial plateau in a longitudinal MRI study showed that the angle of the upslope at the anterior aspect of the plateau was significantly increased in the group that subsequently developed AMOA. To enable AMOA to be studied in future MRI studies, the MRI description of the disease was defined.

In summary, AMOA was shown to be the most common pattern of knee OA both in symptomatic surgical cohorts and in the community. The progression of the disease from an early stage to an advanced stage, which may require surgical intervention, was described for the first time. To enable better the recognition of AMOA in modern epidemiological studies, the MRI description of AMOA was defined and the clinical relevance of modern MRI was discussed. The anatomical alignment of the limb, the alignment of the proximal tibia and the morphology of the tibial plateau were all shown to have a role in the development of AMOA. Addressing these mechanical factors may provide a therapeutic surgical target for the management of patients with AMOA.

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1 Background

1.1 The compartmental pattern of knee arthritis and anteromedial osteoarthritis

The American Rheumatism Association working group defined arthritis as:

“A heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of cartilage, in addition to the related changes in the subchondral region of the underlying bone [1].”

This classification of arthritis is based on criteria from the history, examination and radiographs meaning that any diagnosis of OA requires a balance between symptoms and structural change. Defects in the structural integrity of cartilage are unable to repair spontaneously leading to the description of arthritis as a progressive disease [2], [3]. Arthroscopic and magnetic resonance imaging studies [4-8] have shown that structurally, in the early stages of disease, there is cartilage volume loss and subsequently full thickness cartilage loss until bone on bone disease is visible on the plain radiographs. However, this diagnosis is a global description of a joint but the knee has three distinct anatomical compartments. These are the medial compartment, the lateral compartment and the patello-femoral compartment, any of which may have arthritis change either in isolation or in combination with damage to other compartments. The medial tibio-femoral compartment is defined by the medial joint most medially and the medial tibial spine laterally. The lateral tibio-femoral joint is defined by the lateral joint line most

laterally and the lateral tibial spine medially. The patellofemoral compartment is formed by the articulation between the cartilage surface of the patella and the trochlea groove of the distal femur, at the anterior aspect of the knee joint.

It is recognised that different patterns of knee arthritis exist, affecting one, two or all the compartments described above. Anteromedial osteoarthritis is a specific pattern of knee arthritis, described in 1991 as medial compartment cartilage damage, beginning in the anterior aspect of the medial compartment and in the presence of an intact anterior cruciate ligament (ACL) [9]. The integrity of the ACL appears to be key in the pattern of disease in the medial compartment, when the ACL is intact cartilage damage is localized to the antero-medial or centro-medial portion of the medial tibial plateau. Damage to the ACL is correlated to an increasing area of medial cartilage damage [10] [11]. The preserved cartilage at the posterior aspect of the medial compartment is histologically normal and so the pattern on AMOA has been described as “spatial model of progressive cartilage damage” [12]. Since the definition of AMOA is specifically defined anatomically, knees with AMOA have provided an excellent study group for histological and genetic analysis of damaged and normal cartilage from the same knee [11]. In the referenced study from Snelling *et al*, had the pattern or ‘phenotype’ of disease not been tightly controlled, small but important differences between cartilage quality and gene expression would not have been identified.

From the perspective of surgical management of knee OA there is specific importance in recognising different patterns of knee arthritis that potentially require different surgical treatment options. Accurate identification of the different patterns of knee OA has implications to patient choice in selecting treatment surgical options, the affect of that choice on patient outcomes [13, 14] and possible financial implications to the treating health service [15].

Whilst an understanding of the different patterns of knee OA has informed biochemical, histological and surgical studies of knee arthritis, the specific patterns of knee OA have been little reported in the epidemiological literature. Much of the work investigating the incidence and progression of knee arthritis does not distinguish between the patterns of OA. The epidemiology of knee OA is summarised below in section 1.3.

1.2 Radiological scoring systems

There are many different radiological scoring systems used in the epidemiological literature. These are based on the radiological features associated with arthritis, most focusing on the presence and size of osteophytes and degree of joint space narrowing. Osteophytes are defined as a 'bony excrescence or outgrowth of bone' commonly around a joint and at the joint margin. Any reported prevalence and patterning of arthritis might depend on the definition and of the markers used to assess radiological arthritis [16-19].

The work of Altman et al [1] outlined above showed that using the presence of osteophytes distinguished better patients with painful OA from those with knee pain from any cause than joint space narrowing alone. However, McAlindon [20] argued that the control group in that particular study was of younger subjects with rheumatoid arthritis (RA), suggesting that osteophytes may just be a better discriminator between RA and OA since joint space narrowing is common to both these disorders whereas osteophytes are unique to OA. However, the radiological definition of OA appears to be a balance between joint space and osteophytes, with joint space perhaps being a better guide towards severity [16] and osteophytes being more specific to osteoarthritis. In this section, three of the main radiological scoring systems are described and their use to define the pattern and radiological severity of OA is defined. These are the Kellgren and Lawrence (KL) [21, 22], Ahlback [23] and OARSI [24] scores. These have been selected because the KL score is the most widely used both historically and clinically, the Ahlback score is based primarily on joint space and may avoid problems with scoring based on osteophytes and the OARSI score is a more recent score which assesses the individual features of OA separately.

1.2.1 The Kellgren and Lawrence score (KL)

The KL score has been the most widely used of all radiographic scoring systems in the knee. In 1952 Kellgren and Lawrence [21] first described the prevalence of “Rheumatism in Miners” by the use of an X-Ray score but it was not until 1957 [22] that their “Radiological assessment of osteo-

arthrosis” defined a radiological atlas whereby the severity of OA could be graded and this was later published as the Empire Rheumatism Council atlas of standard radiographs. Five grades of OA were defined and are outlined in Table 1-1.

No OA	0
Doubtful Possible osteophyte. No JSN	1
Minimal Definite osteophyte. Possible JSN	2
Moderate Multiple osteophytes. Definite JSN	3
Severe Large osteophytes, definite sclerosis, severe JSN and change of bone ends	4

Table 1-1 - Summary of the Kellgren and Lawrence Radiological score [22]

Grade 0 therefore indicated a definite absence of OA and Grade 2 indicated the definite presence of OA although of minimal severity. The KL assigns a score based on the balance of interpretation of the size of the osteophyte and the degree of joint space narrowing. However, the balance of this interpretation has changed subtly over time. Originally the guidance was that Grade 2 was defined as:

“The presence of definite osteophytes with minimal joint space narrowing
[21]”

Yet in a subsequent paper the definition of Grade 2 disease was:

“Definite osteophytes but joint space unimpaired [25]”

An issue with the latter definition is that it places the osteophyte at the beginning of the OA process and it is not known if this is correct [26]. The KL is therefore considered to be osteophyte-centric and the role of the osteophyte in the diagnosis of compartmental disease is controversial since it may not be specific to disease in the compartment in which it is present.

1.2.2 Ahlback Score

In 1968, Ahlback [27] described a radiological staging system for OA of the knee and this is outlined in Table 1-2. The score is based entirely on joint space loss and therefore does not include any reference to osteophytes. Grade 1 is the lowest grade at which OA is present and the higher grades all describe more advanced OA. Grades 3 and higher describe severe and so with many grades all describing severe disease, the Ahlback score can be thought as being historical. More recent scores focus on defining a difference between the earlier stages of OA but it is included here since it is a well validated [28] and accepted score based on joint space and therefore acts as a balance to the newer OARSI score. Previous work has shown good agreement between K&L grade 2-3 and Ahlback grade 1 (Kappa 0.76) and K&L and Ahlback 2 (Kappa 0.78) [29].

Normal	0
Reduction joint space	1
Obliteration of joint space	2
Tibial plateau attrition<5mm	3
Attrition 5-10mm	4
Severe subluxation of tibia	5

Table 1-2 - Summary of the Ahlback Radiological score [27]

1.2.3 The OARSI Score

The Osteoarthritis Research Society International (OARSI) is an organisation focused on the prevention and treatment of OA. In 2007, Altman described the OARSI atlas of individual radiographic features in osteoarthritis [24]. This is a radiographic atlas, which can be used as a template and guide for grading radiographs. Osteophytes on the femur and tibia in both the medial and lateral compartment of the knee, joint space in the medial and lateral compartment and sclerosis and attrition are scored as outlined in Table 1-3

An advantage of this score over the KL score and the Ahlback score is that the features in the OARSI score are graded individually so that there need be no assumption regarding the chronology of OA. Additionally, in the analysis of the results the individual features can be separated.

Marginal Osteophyte	Medial femoral condyle	0-3
	Medial tibial plateau	0-3
	Lateral femoral condyle	0-3
	Lateral tibial plateau	0-3
Joint Space Narrowing	Medial compartment	0-3
	Lateral compartment	0-3
Other	Medial tibial attrition	Absent/Present
	Lateral femoral sclerosis	Absent/Present
	Medial tibial sclerosis	Absent/Present

Table 1-3 - Summary of the OARSI Radiological score [24]

1.2.4 Radiographic Views

Radiographs depict a 3 dimensional structure as a 2 dimensional image and it is well known that for diagnostic purposes, two radiographs in orthogonal planes should be assessed. The common radiographic views for assessment of the knee are the antero-posterior view and the lateral view [30]. Radiographs can be either fluoroscopically guided or aligned on anatomical landmarks. It has been shown that for longitudinal studies, fluoroscopically guided techniques may provide improved reproducibility of patient positioning at the different study time-points [31, 32].

1.2.5 Radiographic severity of arthritis

It is accepted that a patient with significant symptoms and loss of radiographic joint space may benefit from joint arthroplasty [33] [34], yet it has also been shown that the outcome of joint replacement in patients who

do not yet have bone on bone disease is more variable than those who have complete joint space loss [35]. However, patients may become significantly symptomatic from earlier stage structural OA that is not amenable to joint replacement. The proportion of people who have symptomatically arthritic knees who do not yet have bone on bone disease suitable for joint replacement is unknown. An understanding of the burden of the stage of disease as defined at the time of referral to secondary care is important since as a clinical community there is no consensus as to how best to manage these patients.

1.3 The epidemiology of knee arthritis

1.3.1 Diagnosis of arthritis

The American Rheumatism Association released guidance in 1986 to aid in the consistent diagnosis of osteoarthritis of the knee [1] and the clinical and radiographic features are summarised in Table 1-4.

<i>Radiological</i>	<i>Clinical</i>	
Osteophytes	Knee Pain	
	At least one of three	Age >50 years
		Stiffness <30 mins
		Crepitus

Table 1-4 Summary of American Rheumatism Association radiological and clinical criteria for osteoarthritis

Since this guidance the importance of joint space narrowing (JSN) and subchondral cyst formation has been incorporated into guidance for the diagnosis of arthritis [36]. The presence of both JSN and osteophytes as a

marker for osteoarthritis specifically in longitudinal studies has been validated and it is recommended to use radiological scores (summarised in section 1.2), which incorporate both of these markers of osteoarthritis [18]. Indeed, the change of the size of an osteophyte over time has been shown to correlate to worsening pain [26].

1.3.2 The prevalence of knee arthritis

Studies based on *post-mortem* examinations have shown a degree of cartilage damage and bony change consistent with arthritis in 60% of men and 70% of women. Advanced cartilage loss was seen in 17% of men and 38% of women [37]

There have also been many studies assessing the prevalence, incidence and progression of arthritis in *living* population studies. Van Saase *et al* [38] reported a prevalence of arthritis of 54% in a population from a village in Holland. The prevalence increased with age, for example the prevalence of knee arthritis in women aged between 50 and 60 years was 20% and for women over 80 was almost 70%. The prevalence was higher in women than men. Another study from Holland reports prevalence of knee OA of 15.6% in men and 30.5% in women aged over 55 years of age [39]. This gender difference has also been reported in different ethnic groups, Muraki *et al* [40] reported a prevalence of 47% in men and 70% in women over the age of 60 years in a cohort from Japan.

Whilst the gender difference in knee OA prevalence appears to be consistent between ethnic groups, the reported overall prevalence of

arthritis does appear to be change defendant on ethnic group. For example, the reported rates in the study from Japan are higher than those generally reported from other regions of the world. The Framingham study, based in the USA, reports a prevalence of knee OA of 27% in a population under 70 years of age and 44% in a population over 80 years. Another study from a different region of the USA reported a prevalence of radiographic OA in women as 42.1% [41]. However studies reporting *symptomatic* OA in a population in the USA have reported much lower rates of OA of 16.3%, which is similar to the prevalence of painful knee of 10% in a population over 55 years in the UK [42].

Despite all the research into the epidemiology of knee arthritis, there is no data in the literature to describe the prevalence of anteromedial osteoarthritis, either in a generalised population or a symptomatic surgical population.

1.3.3 The incidence and progression of knee OA

The incidence of knee OA is defined as the number of new cases of OA in a population over a specified time period out of the total number without knee OA at the beginning of the time period. To describe an incidence of OA, a study must be longitudinal, have high follow-up rates and use the same diagnostic criteria for OA at the beginning and the end of the study. A change in the radiological technique may change the reported rates of arthritis [43] [16]. Due to these constraints, there are far fewer reports of the incidence of OA than the prevalence. The Framingham Study described a 2% per year incidence of knee OA [44]. A five-year study by Cooper *et al*

described an incidence of 2.5%, which was greater in the obese and those sustaining a knee injury. The first 15 years of the Chingford study [45] described an incident rate of 2.3% per year.

When assessing progression or worsening of arthritis in subjects who already have knee OA, the Framingham study described 4% of subjects progressing per year, Cooper *et al* describe 3.6% per year and the Chingford Study describes a 2.8% per year progression over 15 years. In a twenty-year study of 265 knees, Sahlstrom *et al* [46] reported that 60% progressed at least one radiological grade, however in this study those subjects that progressed to a knee arthroplasty were excluded from the study since their radiographs could not be examined. If these had been included the percentage of progression would likely have been higher.

Not one of the major epidemiological studies outlined above describes the progression in terms of clinical grades of arthritis. There is no data in the literature to allow a surgeon to counsel a patient as to the time it may take to progress from early changes of arthritis to changes that may be treated with surgical intervention, such as arthroplasty.

1.3.4 Epidemiology and the pattern of knee OA

The specific pattern of knee OA reflects the interaction of different risk factors and will progress and may be treated in different ways. The prevalence of osteoarthritis affecting the different compartments of the knee has been described by Ledingham *et al* [47]. Only 1% of cases showed isolated lateral compartment disease, 24% isolated patello-femoral disease

(PFJ) and 10% isolated medial compartment disease. McAlindon [48] reported the prevalence of disease in men as 2% lateral disease, 11% PFJ and 21% medial disease and in women as 3% lateral, 24% PFJ and 12% medial. However, neither of these studies used the recognised diagnostic radiological scoring systems for assessment of the PFJ, since the reproducibility was poor. The PFJ results may, therefore be inaccurate. There is very little data in the literature to provide a clear description of the compartmental pattern of knee OA. As described in section 1.1, the pattern of knee OA reflects the integrity of the underlying structures. Therefore for a surgeon to understand the burden of disease and the likely progression of disease, the individual patterns of knee OA need to be described separately. The epidemiological studies outlined above in this section provide no data to inform our understanding of the incidence, the progression and the risk factors of different patterns of knee osteoarthritis.

1.4 Risk factors for knee arthritis

1.4.1 Patient factors

One of the factors most linked with knee arthritis development is the body mass index (BMI). The BMI is a measure of weight based on the height (metres) and mass (kg) of a subject. Specifically, the BMI is defined as:

$$\text{BMI} = \frac{\text{mass (kg)}}{\text{height (m)}^2}$$

The BMI has been linked to increased knee OA prevalence in many studies [3, 45, 49-51].

Many studies have reported an increase in knee OA after trauma. Davis *et al* linked OA with previous knee trauma [52] and more specifically, Jacobsen [53] showed increased knee OA after ACL rupture. The meniscus has been linked to both knee OA development and progression. In animal studies, damage to the meniscus is well reported as a model for initiating arthritic change [54]. Jackson [55] has shown the prevalence of Knee OA after meniscectomy to be 21% whereas the rate in the subjects other knee was only 5%. Many other studies have shown a link between meniscectomy in human knees and subsequent OA development [56-58].

1.4.2 Limb Alignment and knee osteoarthritis

Osteoarthritis of the knee is often associated with abnormalities of the lower limb in the frontal plane [59], for example bilateral varus knee alignment found in association with bilateral medial knee arthritis. However, the temporal relationship between arthritis and mal-alignment is still not well understood. This is in part due to the small number of long-term longitudinal studies in which alignment may be assessed prior to development of any disease.

It is well described that varus or valgus malalignment increase the risk of radiographic progression of established knee OA [60-63] and that malalignment also increases the risk of further chondral damage [64-67] and progression of chondral defects [68] in knees with established OA.

A difficulty in assessing the role of alignment in the development of arthritis is that the overall limb alignment is affected by damage to intra-articular structures. For example bony attrition and cartilage loss [60] loss of meniscal tissue [69] and even more specifically, meniscal root tears [70] have all been shown to affect the joint space. Alignment studies in knee arthritis have attributed mal-alignment to joint space loss [71, 72] and those whose arthritis progresses radiologically as measured by the Kellgren and Lawrence Score have been shown to become more mal-aligned [73]. Therefore any study to investigate the role of alignment in the development of OA needs to assess a radiograph prior to the development of any significant arthritic change.

An eight year longitudinal study has shown an increase risk of arthritis development in knees with a radiographic varus deformity [74], however another 8 year study showed that varus alignment did not predict new cases of OA [75]. The same cohort reported 6 years later shows an increase risk in the development of lateral OA in knees with valgus alignment [76] but does not report the risk of medial OA in varus alignment.

1.4.3 Proximal tibial alignment and knee osteoarthritis

Differences in the anatomy of the proximal tibia potentially change the orientation of the articulation of the knee joint and therefore may affect the mechanical alignment of a limb and the forces through the joint.

The term “tibia vara” was first reported in 1937 by Blount [77] to describe an abnormality of the proximal tibia in children and is now associated with an

anatomic condition “characterised by an abrupt angulation of the tibia into varus deformity in the proximal end of the bone” [78] However the term does not imply a specific aetiology [79] and can be secondary to developmental, post-traumatic or post-infectious causes. Therefore, tibia vara develops in the growing limb and is secondary to a slowing in the growth of the proximal medial growth plate of the tibia.

Four main types of the condition have been described. These are infantile, adolescent, late onset and secondary to focal fibrocartilaginous dysplasia [80] [81]. The infantile and adolescent sub-types were originally described by Blount [77]. Subsequently the term late onset [82-84] was introduced to describe a later onset adolescent sub-type and to separate this along with the existing adolescent sub-type from the more common infantile sub-type. Whilst the fibrocartilaginous dysplasia sub-type is based on specific histopathological findings, the other three are based on the age at diagnosis.

Infantile tibia vara is also known as “Blount’s Disease” and is multifactorial in origin, there is a strong family history [85, 86] and the affected are usually overweight [78]. The children affected by the late onset adolescent sub-type are almost always overweight and have a slowly progressive varus deformity [83, 87], which is similar radiologically to infantile tibia vara. Children with non-late onset adolescent tibia vara are seen to have premature closing of the proximal medial tibial growth plate secondary to trauma or infection. This occurs without the preceding radiological findings seen in late onset and infantile disease and is usually unilateral [88] [86].

The only similarity with the infantile and late onset sub-types is the sharp angulation at the proximal tibia.

Henderson et al [89] have shown that the prevalence of tibia vara in overweight teenagers is 2.5% and has described tibia vara as a complication of adolescent obesity.[90], This means that the prevalence of tibia vara is likely to increase further.

Levine et al [91] originally described the technique to measure the proximal tibial deformity seen on the plain radiograph in tibia vara. The measurement was described as the metaphyseal diaphyseal angle (MDA) and was the angle formed by the intersection of a line drawn along the lateral cortex of the tibia and a line drawn along the proximal tibial metaphysis. An angle less than 90° described a varus angulation of the growth plate. It has since been shown that the same angle may be measured using the anatomical axis of the tibia, from the centre of the tibial spines to a point in the centre of the tibial shaft, with no significant alteration to the measurement or reproducibility [92] [93]. However, rotation of the limb in the radiographic beam may alter the angle measured by as much as 2.5° [94], so any assessment must control for the rotation of the limb.

Tibia vara with onset in childhood is an extreme example of the alteration of the anatomy of the proximal tibia and this causes an overall varus mal-alignment to the limb in adulthood. The mechanical alignment of the limb is shifted more medially and increases the force passing through the medial plateau [72]. Lesser changes to the anatomy of the proximal tibial plateau,

which may not be diagnosed in childhood, will also affect the overall limb alignment. Alteration in the anatomy of the tibial plateau may therefore be a risk factor in the development of knee arthritis and the angle between the tibial shaft and the tibial plateau have been investigated in adult populations. Cooke et al investigated this proximal tibial angle in adult populations both with and without arthritis [59, 72] but found no difference between a group with arthritis and a group without arthritis. However the study was not longitudinal and all measurements were made after the development of arthritis.

1.4.4 The anatomy of the medial tibial plateau and knee osteoarthritis

The tibial plateau comprises two tibio-femoral articulations with a central area between consisting of the tibial spines. The shape of the medial and lateral tibial plateaus differs to each other. The medial tibial plateau is concave in both sagittal and coronal planes. The lateral tibial plateau is convex when viewed in the sagittal plane.

There is much debate as to the correct description of the kinematics of the tibio-femoral articulations of the knee joint and detailed analysis of this is beyond the scope of the thesis. However, an understanding of the anatomy and its relevance to both movement and weight bearing is important. Much of this work was undertaken to understand better the kinematics of the knee joint to inform knee arthroplasty design, but is also relevant when investigating risk of developing disease.

The evolutionary origins of the knee joint can be traced back hundreds of millions of years and the asymmetry of the medial and lateral tibial plateau is common to many mammals [95]. Whilst the basic bony anatomy of the knee joint is shared between many species, the specific form and function of the human knee is unique, for example the terminal 20° of extension of the human knee joint appears to be unique to bipedal gait. Although the gross anatomy of the human knee joint has been studied for many hundreds of years [96] a close understanding of the kinematics has only really become possible since the advent of modern radiological techniques.

The movements of the knee joint have been studied by several methods including intra-cortical pins [97-99] and goniometers [100, 101][100, 101][100, 101][100, 101] but kinematic modeling may have many inherent errors [102, 103] and does not allow visualisation of the joint surface interaction.

The traditional model of knee kinematics is that of the 'Four-bar linkage'. A mathematical model [104] of a rigid four bar system comprised of the femur, tibia, anterior cruciate ligament and posterior cruciate ligament with six vectors of force from the quadriceps, hamstrings, gastrocnemius, ACL, PCL and the tibio-femoral constraint predicts the gross bony anatomy and relative movements of the tibia and the femur. The lateral tibio-femoral articulation is seen to have relatively more antero-posterior movement and in deep flexion the lateral femur is seen to roll backwards to the posterior edge of the lateral tibia.

Shapeero *et al* [105] in 1988 used 'ultra-fast' CT techniques to map the movement of the femur relative to the tibia and confirmed the mixed roll and glide of the tibio-femoral articulation. In their work the roll:glide ratio of the femur in the lateral compartment was 1:1.2 and for the medial compartment was 1:3.8; again describing relatively more roll back on the lateral side. Further work [106, 107] used magnetic resonance imaging to describe the role and movement of the meniscus and the bony articulation.

Development of the technique described by Niitsu [107] using an open MRI scan allowed the assessment of the moving knee. Refining this process, Freeman and Pinskerova presented a series of work on the kinematics of the knee joint and the related anatomy [108-110]. This work was summarised in a later review article [111]. Three arcs of movement were described. The first was that from hyperextension to 20° of flexion, the second between 20°-120° and the third 120° into deep flexion. The arc between 20°-120° was termed 'The functional arc' since most activities of daily living occurred in this sector and this, together with the deep flexion arc, were reported as sharing the same centre and arc of rotation. The first arc, that which enables hyperextension, was reported as having a greater arc of rotation. The centre of this arc of rotation was positioned close to the origin of the medial collateral ligament, proximal and anterior to the centre of rotation of the other arcs. The greater radius of the arc was explained by a larger anterior femoral facet, which in turn articulated with the upslope of the anterior portion of the convex medial tibial plateau. This larger femoral facet

was termed the extension facet and the upslope of the anterior medial tibial plateau was therefore also termed the extension facet.

This area is also called the “medial tibial upslope”, since a consensus that this area only has a role in extension, is lacking. This tibial upslope is present only on the medial side, providing asymmetry between the medial and lateral tibial plateaus. Freeman postulates that it is this asymmetry that has allowed the human knee to escape from bony capture and enable full extension. The position of the tibial upslope is outlined in Figure 1.1.

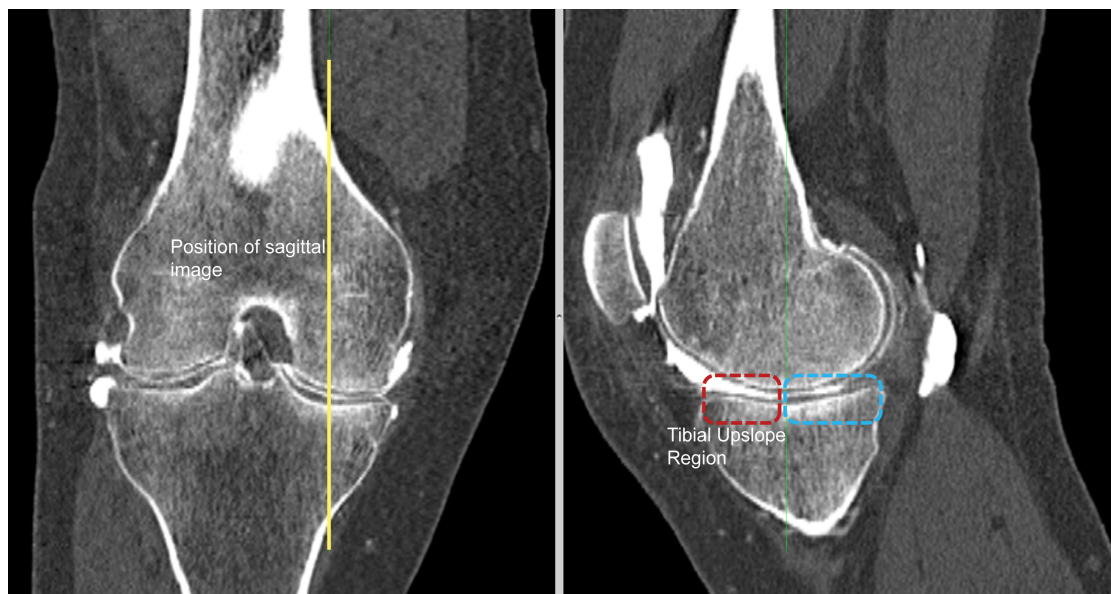


Figure 1.1 – An annotated CT scan showing a coronal image on the left identifying the position of the sagittal image shown on the right. The tibial upslope region is identified within the red box.

Whilst the relative merits of the different kinematic models of the knee joint are not for discussion here, this is an important functional anatomical description since it is the first study to ascribe names and specific functions to the elements of the concavity of the medial tibial plateau. The upslope of

the medial tibial plateau and the flat region posterior to it create an angle and describing this angle provides a surrogate for the description of the morphology of the medial tibial plateau.

Finite element analysis work shows that increasing the anterior tibial upslope of the medial tibial plateau results in an increase in the stress to the cartilage [112]. Interestingly, this stress rise is maximal at the inflection point between the two regions, an area 30-45% from the anterior rim of the tibial plateau which correlates well to previous intraoperative findings mapping the position of cartilage loss in the arthritic knee [113].

There is good clinical evidence that variations in the morphology of the tibial plateau exist [114] and that these alter the risk of ligament damage within the knee joint [115]. In these studies an increase in the posterior tibial slope (a line from the most superior point on the anterior plateau to the most inferior point on the posterior plateau) or decrease in the tibial plateau depth are linked to risk of anterior cruciate ligament rupture. Matsuda [116] shows that the posterior tibial slope is increased in varus knees but does not prove a link to arthritis. Indeed, whilst there is strong evidence that specific morphological abnormalities in the knee are linked to ligament damage and around the hip joint are linked to the development of arthritis, there is little evidence of a specific link to arthritis around the knee joint [117, 118].

1.4.5 Summary of anatomical risk factors for AMOA

There is no clear consensus in the literature as to the association of varus mal-alignment and the development of medial or anteromedial knee OA.

Additionally, there have been no longitudinal studies assessing the role of the medial proximal tibial angle in the development of AMOA. Whilst there are anatomical and theoretical investigations into the role of the tibial plateau anatomy in the development of AMOA, there is no longitudinal data in the literature that assess this in a living subjects.

1.5 The radiographic assessment of lower limb alignment

The accepted gold standard assessment of limb alignment is a standing antero-posterior long-leg radiograph. The entire limb is captured on one radiograph and since the subject is weight bearing, a line from the centre of the rotation of the hip to the centre of the talus approximates the direction of force through the limb.

The mechanical axis of the femur runs from the center of the hip to the centre of the knee joint. The mechanical axis of the tibia runs from the centre of the knee to the centre of the talus at the ankle. The angle between these two axes is termed the hip knee angle (HKA). The anatomical axis of the femur is different to the mechanical axis, running from a point along the femoral shaft to the centre of the knee. The difference between the anatomical and mechanical axes of the femur is due to the lateral offset of the femoral shaft from the femoral head by the femoral neck. The anatomical axis of the tibia is often very similar to the mechanical axis of the tibia, running from the centre of the knee down the tibial shaft. The angle between the anatomical axis of the femur and tibia is termed the anatomical axis of the limb.

1.5.1 Selection of landmarks on plain radiograph

To measure the anatomical alignment reproducibly, the anatomical points from which to measure the axis in each long bone and at the knee need to be defined precisely. The commonest method to determine the point in the femoral or tibial shaft is to use the midpoint between the edges of the cortex of the long bone shaft [119]. The majority of the studies validating short leg radiographs to measure anatomical alignment have assessed the mid-cortical point 10 cm from the joint line [120, 121].

There is more than one landmark described to assess the centre of the knee. The centre of the tibial spines was the most reported landmark of the proximal tibial measurement [119, 122, 123]. The tibial spines may also be used for the anatomical landmark to determine the distal femoral point [124]. However, if the joint were to be subluxed, measuring the femoral axis to a point on the tibia may artificially alter the anatomical axis. Measurement of the femoral angle to the centre of the femoral notch has therefore been shown to be more reproducible than measurement to the centre of the tibial spines [121].

The tibial anatomical and mechanical alignment axes are measured from the same anatomical points, meaning there is no discrepancy between them when measured on a long leg radiograph. Since there is no offset between the anatomical and mechanical axis in the tibia, the problems inherent in using a short leg measurement instead of a long leg measurement are smaller when assessing the tibia than the femur. However, a discrepancy

may still occur on a short-leg film if there is extra-articular malformation of the tibia.

1.5.2 Short-leg radiographs and the assessment of limb alignment

Whilst it is accepted that the gold standard assessment of limb alignment is the long leg radiograph, the use of short leg radiographs to assess limb alignment has been validated and the literature is summarised below. Importantly, short leg assessment provides only a direct measure of the anatomical alignment of the limb and not of the mechanical alignment.

Kraus *et al* [120] performed a comparative assessment of limb alignment using long leg and short leg radiographs and clinical assessment. This showed that the measure obtained from assessment of the short leg radiograph anatomical alignment correlated well with the long leg measure anatomical leg alignment. This anatomical leg alignment measure did not equal the mechanical alignment but it correlated well, meaning as one increased the other also increased. In an attempt to enable anatomical alignment to be converted to mechanical alignment, a gender specific conversion from the anatomical alignment to the long leg mechanical measure was calculated. However, the confidence intervals were wide and so direct use of this conversion was not recommended. As a consequence, mathematical conversion from anatomical to mechanical alignment is not commonly performed.

Other studies have since validated the use of short leg radiographs [125] [126] by comparing the measurement to long leg radiographs. Several

studies have used this validation work to defend the use of short leg radiographs to describe the anatomical alignment of the lower limb [127] [75]. Khan *et al* [128] assessed short leg radiographs to show that increasing mal-alignment of the limb was related to deteriorating arthritis, as assessed by the Kellgren and Lawrence score.

There have been arguments against the use of short leg radiographs to assess limb alignment [129, 130]. The main point of argument was to emphasise the effect of the femoral offset, such that a co-linear anatomical alignment is not the same as co-linear mechanical alignment. An anatomical alignment of neutral would mean that the mechanical axis would be at least four or five degrees further in valgus.

1.6 The use of magnetic resonance imaging in arthritis

1.6.1 Review of magnetic resonance imaging

Magnetic resonance imaging (MRI) is an imaging modality providing excellent soft tissue visualisation and allowing multi-planar reconstructions of the area imaged. Unlike many other imaging modalities which are based on an exogenous energy source passing through tissue, a magnetic resonance image is generated by capturing the energy response of cells to a radiofrequency pulse in the presence of a steady magnetised field. A detailed discussion of the physics of MRI is beyond the scope of this thesis, however, an understanding of the processes and compromises involved in

the capture of images is important for the understanding of the use of MRI in the assessment of arthritis.

The human body is weakly magnetic due to the intrinsic spin of the nuclei of some molecules generally due to the presence of nuclei with odd numbers of protons and neutrons [131]. In the human body these are most abundantly hydrogen, with each water molecule consisting of two hydrogen molecules and one molecule of oxygen. When placed in a strong magnetic field there is a net magnetisation as the protons align themselves with the magnetic field, a process known as precession [132]. The direction of this first field is termed B_0 . A second radiofrequency pulse, B_1 , at a specific frequency (the Larmor frequency) is applied at an angle to B_0 and this causes the protons to precess in a different direction and are now in a higher energy state. This changes the net magnetisation and once the angle of spin reaches 90° to B_0 , the MRI scanner can detect this. The strength and duration of the B_1 field affects the net magnetisation and therefore alters the signal detected by the scanner. As the B_1 field is turned off the nuclei return to their lower energy state, aligned to B_0 and as they do so release energy to the surrounding molecules. The time by which 63% of the nuclei have returned to be aligned with B_0 is termed the T_1 relaxation time and is a description of energy decay. Since MRI was originally described with materials in a lattice, this is also termed spin-lattice relaxation as the energy is released to the surrounding tissue. The T_1 relaxation time is normally between 200-3000 milliseconds and is not only tissue specific but also increased at higher magnetic field strengths.

Once the field B_1 is stopped, the spin of protons may interact with each other causing them to slip out of phase. The phase then gradually decays and the time taken for 63% of the spin to be out of phase is termed the T_2 relaxation or spin-spin relaxation time. T_2 relaxation is tissue dependent but not dependent on the strength of the field. Since all interactions between protons will cause T_2 relaxation but only interactions that cause alignment back to B_0 will cause T_1 relaxation the time for T_2 relaxation is much shorter.

A magnetic resonance imaging scanner therefore consists of a large magnet to create an homogenous magnetic field, a radiofrequency coil to emit a signal into the part of the body being imaged and a further coil to detect returning signal, gradient coils to alter the field so that spatial information can be generated and a computer to translate the signals to an image. Changing the timing of the RF signal, termed the pulse sequence, changes the information gathered. Therefore, the contrast of the MRI depends on the relaxation time outlined above and the pulse sequence. The two main parameters set in the pulse sequence are the repetition time (TR) and the echo time (TE) and these can be utilized in two main ways; either as a spin echo or a gradient echo sequence.

The spin echo sequences vary the TR and TE to produce three main sequences. These are the T_1 weighted, T_2 weighted and proton density weighted sequences. The T_1 weighted sequence is programmed with short TR and short TE and tissues with a short T_1 relaxation time will be bright. This includes fat and bone marrow, whereas cortical bone will be dark. The T_2 weighted sequence is programmed with long TR and long TE and tissues

with long T_2 relaxation will be bright, especially water containing tissues and tissues with short T_2 relaxation time, such as cortical bone, will be dark. The PDWI is programmed with a long TR and a short TE and again water will be bright.

Gradient echo sequences (GRE) are based on changing the pulse sequence design rather than just the tissue response to the radiofrequency pulse. Their main advantage is that they provide a faster scan time. The three main types are incoherent, partially coherent and coherent acquisition sequences. To achieve this dephasing or rephrasing gradients are added towards the end of the sequence. In addition, the angle of the radiofrequency (B_1 as outlined above) is changed from the usual 90° to between $10-80^\circ$. This angle is termed the flip angle and by using different angles the TR time may be dramatically reduced. The faster scan timings allow acquisition of higher detailed 3D images.

The MRI sequence changes the information gathered from different tissues, therefore different sequences will provide different information about different tissues. It is important to design an MRI sequence that will provide the correct information for the purpose the image was taken, however, MRI scans are expensive and time consuming so there is often a compromise in the design of the sequences used. The image provided must provide images of the entire anatomical area of interest in sufficient detail and quality enough to enable assessment of the tissue of importance in multiple planes.

With respect to MRI in arthritis research, the Osteoarthritis Research Society International (OARSI) released guidance [133] to ensure that a correct balance of sequences could be attained. The anatomical areas of importance were articular cartilage, bone marrow abnormalities and both meniscal and ligamentous integrity. Of these, the cartilage assessment was defined as the most important.

A voxel is the smallest package of MRI data. It is a volume of the scan calculated by the product of the slice thickness and the pixel size. A smaller voxel will allow for greater spatial resolution over the scan but each voxel will have fewer protons and therefore lower detail (a smaller signal:noise ratio). A small voxel size can be accommodated by increasing the energy of the scan or measuring sooner after the energy is applied (decreasing the echo time) [133]. Cartilage visualisation is optimal when the voxel is oriented perpendicular to the cartilage, meaning that the shortest side of the voxel aligns with the shortest dimension of the cartilage [134]. The orientation of the voxel in relation to the cartilage plane changes dependent on the orientation of the slice. Axial slices provide higher quality assessment of the patella cartilage, coronal slices provide high quality assessment of the tibial cartilage and sagittal images assess the cartilage on the curve of the femur. If only one orientation is to be assessed, the sagittal view is recommended.

Therefore, when designing an MRI protocol for assessing knee arthritis it is recommended that axial, sagittal and coronal sequences be performed.

1.6.2 Diagnosis of OA using MRI

MRI is now increasingly used both clinically and in the research of osteoarthritis of the knee. In 2011 the OARSI imaging work group updated the guidance above for use on the MRI diagnosis of knee OA [7] and the summary of recommendations are shown in Table 1-5. Other groups have attempted to describe the MRI findings of early knee OA [135]. These guidelines are also based on cartilage damage, meniscal damage and bone marrow lesions.

Group A Criteria	Group B Criteria
Both Group A criteria or one Group A criteria with 2 or more Group B criteria	
Definite osteophyte formation	Subchondral bone marrow lesion
Full thickness cartilage loss	Meniscal subluxation, degeneration or maceration
	Partial thickness cartilage loss (when no full thickness loss)
	Bone attrition

Table 1-5 Summary of MRI diagnostic criteria for knee osteoarthritis [7].

1.6.3 MRI scoring systems for knee arthritis

MRI assessment of OA of the knee may performed by semi-quantitative or quantitative techniques [136]. Semi-quantitative techniques assign a score or grade to a marker of interest. The score is usually a scale of severity, for example, a score from a range of 0-3, which allows comparison of the interval change in severity or size of the marker in longitudinal studies or between cases in cohort studies. Quantitative studies involve quantification or direct measurement of tissue, for example thickness of cartilage [137-139] or size of osteophytes or bone marrow lesions [140].

Semi-quantitative techniques have allowed detailed study of the progression of OA using conventional MRI techniques and acquisition sequences. No further specialist equipment is needed but the observers must be trained to ensure reproducibility [141, 142]. Quantitative techniques require specialist training and equipment. Additionally, in large cohort studies they may be too time consuming to examine entire datasets [143]. However, quantitative assessments may be more sensitive to change when assessing cartilage damage and BML progression, as shown in one direct comparison over 24 months [144].

The most cited MRI scoring system for the knee is the Whole Organ Magnetic Resonance Imaging Score or WOMBS[145]. This was described in 2004 and has been the main score of the largest population based MRI studies such as the Osteoarthritis Initiative and the Multicentre Osteoarthritis Study [5, 146, 147]. The knee is separated into thirteen sub-regions and each of these is scored for eleven independent articular features that are listed in Table 1-6.

Articular Feature	Score
Cartilage signal and morphology	0-6
Subarticular bone marrow abnormality	0-3
Subarticular cysts	0-3
Subarticular bone attrition	0-3
Marginal osteophytes	0-7
Medial and lateral meniscal abnormality	0-6
Anterior and posterior cruciate integrity	0-1 each
Medial and lateral collateral integrity	0-1 each
Synovitis	0-3
Loose bodies	0-3
Periarticular cysts/bursae	0-3

Table 1-6 Summary of WOMBS scoring system [145]

In 2005 Kornaat *et al* [148] described the Knee osteoarthritis Scoring System or KOSS. This is similar to WOMBS except for small differences in the sub-region selection and the assessment of meniscal extrusion. The Boston Leeds Osteoarthritis Knee Score (BLOKS) was described by Hunter *et al*[149] and measures the same features as the WOMBS but scores the features differently and does not assess the patellofemoral joint. In order to compare and attempt to unify the scoring systems, the BLOKS and WOMBS scored were directly compared [150, 151] which showed that although there was no significant difference in the assessment of cartilage between the two scores, the BLOKS was able to better predict progression of OA due to the more refined meniscal system scoring system.

The authors of the WOMBS and BLOKS score subsequently developed the MRI Osteoarthritis Knee Score (MOAKS) [152] to refine the cartilage, bone marrow lesion and meniscal scoring systems. Whilst this is a newer scoring

system it shows reasonable inter-rater agreement with a range of Kappa agreements of 0.36-0.8. Importantly, the authors feel that they are assessing the important components of knee OA, especially the meniscus, in more detail.

Despite all of this guidance on the recognition of MRI 'biomarkers' which lead to the diagnosis of arthritis and the multitude of MRI scoring systems there are no published descriptions to aid the recognition or diagnosis of specific patterns of arthritis. For example, the MRI description of the patterns of arthritis that are recognised surgically, such as AMOA, have never been described. This means that modern epidemiological studies utilising MRI as the main imaging tool do not describe or investigate the different patterns of knee arthritis, so only limited information regarding these patterns of OA is available.

1.7 The DICOM System and OsiriX

The capture, storage and presentation of medical imaging has progressed from printed films to digital systems over the past 30 years. The industry standard for handling, storing and transmitting information in medical imaging is the DICOM system. This is an acronym for Digital Imaging and Communication in Medicine and was developed by the American College of Radiology in conjunction with the National Electrical Manufacturers Association [153]. First described in 1985 and majorly updated in 1993 this is now the standard format from which images are displayed. The DICOM system allows for the image itself, the data pertaining to the image and

relevant patient data to be stored, transmitted and viewed as one file. There are now many DICOM viewing software packages commercially available and OsiriX (Pixmeo, Geneva) is one of the most popular open-source DICOM viewers available with over 40,000 users. It was specifically designed for navigation and visualisation of multidimensional images, especially those from CT and MRI. Due to its wide user base and on recommendation from the radiological department at a specialist orthopaedic hospital (Nuffield Orthopaedic Centre, Oxford, UK); OsiriX was selected as the DICOM viewer for MRI and CT for this thesis. Embedded within the OsiriX program are image tools allowing direct measurements of distances and angles on the DICOM file of the captured imaging. Any selection of the specific MRI or plain radiographic images and the subsequent measurement of angles are reliant on these in built tools and so their accuracy and precision are assessed in this thesis (Section 6.3)

1.8 Synthesis of the literature

Knee arthritis is an important cause of morbidity throughout the world, causing pain and limitation of function. The prevalence of knee arthritis is reported to be as high as between 40% and 80% of the population over 60 years of age [38, 40, 41, 49, 154]. Rather than one pattern of disease it is increasingly reported that arthritis may affect just one or two, or all of the three compartments of the knee joint [47, 48]. These compartments are the medial and lateral compartments, separated by the intercondylar eminences in the central region of the tibial plateau and the patellofemoral

compartment, formed by the patella articulation with the trochlea groove of the femur.

The different patterns of knee arthritis are likely to reflect different disease processes, with different risk factors and treatment options. Early research into knee arthritis may not have recognised the importance of this patterning of knee arthritis and unfortunately, the investigation of the risk factors of knee arthritis as a single disease may mask the subtle risk factors implicit in the development of specific patterns of arthritis. The work in this thesis therefore controls for these potential confounders by investigating a specific pattern of knee arthritis with an accepted anatomical definition. This pattern of arthritis is anteromedial osteoarthritis (AMOA), and was defined in 1991 as medial compartment arthritis in the presence of a functioning anterior cruciate ligament (ACL) [9, 155]. The tibial cartilage damage begins in the anterior medial quadrant of the medial tibial plateau and, in the continued presence of a functioning ACL, is associated with a preserved posterior rim of tibial cartilage. The study of AMOA isolates a specifically defined disease to investigate the risk factors for its development but it is also a disease that has important implications for an academic surgeon. Since AMOA affects just the medial compartment in a stable knee it is a disease that may be treated with interventions such as partial knee replacement and osteotomy, whereas knees with arthritis in two or more compartments may not be suitable for these treatments [15, 156].

The definition of knee arthritis in the literature describing the epidemiology of knee arthritis is based on the radiographic appearance of the knee,

specifically the presence of osteophytes and loss of the joint space between the articulating surfaces [1, 157]. Osteophytes are outgrowths of new bone formation at the margins of the joint and their presence is suggestive of arthritis within the joint [17]. The assessment of the loss of joint space on a plain radiograph is a surrogate marker for the compound assessment of cartilage thickness and meniscal competence [16]. The threshold of diagnosis for knee arthritis in epidemiology is often the first appearance of a marginal osteophyte or early joint space loss [22-24]. However, for a surgeon investigating arthritis of more interest is the severity of arthritis since this will influence the potential treatment options [35].

Since much of the epidemiology research into knee arthritis has not defined the specific pattern of disease, the incidence and prevalence of AMOA in long-term studies has not been described before. Whilst previous investigation into limb alignment as a risk factor for knee arthritis have investigated medial disease, many of the studies have investigated the role of mal-alignment in the progression of disease rather than its development [61] [60, 63, 64, 158], mostly because the latter would have necessitated the study to have begun prior to the development of disease, which is unusual. The role of malalignment in the development of the results have been surprisingly mixed with some studies reporting no correlation with alignment and others showing it be an important risk factor [72, 74, 159].

Whilst MRI is now a common tool in the research of knee arthritis [7, 160] [136] it has not yet been used in long-term epidemiological studies and its

role in the diagnosis of arthritis and in clinical decision-making is still not clear [7, 161, 162] .

When attempting to understand knee arthritis and specifically AMOA from a surgical perspective, there are questions about which the literature provides no or limited data. The assumption from the surgical community is that AMOA is a common disease; however there is no data in the literature as to how common AMOA is in the community or what proportion of patients in surgical clinics have AMOA. It is unknown at what age a person might expect to develop AMOA or the risk of developing AMOA as they age. There is no data to help inform how long it may take for early disease to progress and so there is no information to guide the timing the timing of surgical intervention, this is of great importance to a surgeon treating patients with AMOA.

In terms of treatment and intervention, to enable the development of new targets for treatment and disease modifying surgery, the surgical community needs to understand the risk factors for the development of AMOA. Mechanical factors seem to have a role in the development of knee OA and alteration of the mechanical axis of a limb is an accepted treatment of AMOA, however, the risk of limb alignment in the development of AMOA is not known. Additionally, the literature shows that the morphology of the tibial plateau affects the mechanics of the knee joint yet there is no good data to define the risk of altered tibial plateau morphology on the risk of developing AMOA.

MRI is a common tool used clinically by surgeons to assess patients and in research studies by scientists to investigate disease. However, no one knows or has described the criteria to define AMOA on an MRI scan. This means that it cannot be reliably recognised in research studies and indeed there is little data as to whether MRI is actually useful in the clinical assessment of AMOA.

1.9 Scope of this thesis

The scope of this thesis is to attempt to answer some of the unknown questions about AMOA raised above. The aim is to try and improve a *clinicians* understanding of the disease to better inform decisions about the timing and type of intervention for AMOA. The studies will now be described under five general aims with specific studies outlined.

1. To investigate if anteromedial osteoarthritis is a common problem that presents to secondary care in the NHS.
 - a. To investigate the proportion of anteromedial osteoarthritis in symptomatic patients with knee arthritis presenting to a specialist knee clinic in the NHS.
 - b. To describe the spectrum of radiographic severity of disease in patients with symptomatic AMOA.
 - c. To investigate if the pattern of knee arthritis reported from an NHS clinic depends on the radiological scoring system used to assess the radiograph.

2. To investigate, using an appropriate and generalisable population, the incidence and progression of AMOA.
 - a. To describe the prevalence and incidence of AMOA and the normal age range of each radiographic stage of disease in a 20-year longitudinal study.
 - b. To describe the 20-year risk of developing AMOA and the radiographic severity of disease progressed to during this time
 - c. To describe the time taken for early radiographic AMOA to progress to advanced radiographic AMOA, which may require surgical intervention, in a 20-year longitudinal study.
3. To investigate the role of lower limb alignment in the development of AMOA in a longitudinal cohort.
 - a. To investigate the role of anatomical limb alignment in the development of AMOA in a 20-year longitudinal study.
 - b. To investigate the role of proximal tibia vara in the development of AMOA in a 20-year longitudinal study.
4. To investigate the role of proximal tibial morphology in the development of AMOA
 - a. To investigate the role of an increased medial tibial upslope in the development of AMOA in a 30-month longitudinal MRI study
5. To define the role of 3-Tesla MRI in the assessment of AMOA.
 - a. To define the MRI description of AMOA
 - b. To investigate the role of MRI in the clinical assessment of AMOA.

The specific details of each experiment are now outlined in the following chapters.

1.10 Structure of this thesis

This thesis is organised using the following chapters:

- Chapter 2 investigates the compartmental pattern of symptomatic knee arthritis presenting to one surgical clinic over one year, compares the effect of using different radiographic knee scores on the reported compartmental patterns of knee arthritis and investigates the radiological severity of symptomatic arthritis.
- Chapter 3 describes the prevalence of AMOA in different age groups and the incidence of disease in the Chingford Study, a 20-year population based longitudinal radiographic study. The time taken for subjects with early medial OA to progress to advanced disease is described and the risk of progression is presented.
- Chapters 4 and 5 explore the role of limb alignment in the development of AMOA. Chapter 4 describes the design and validation of KneeMorf, a software application to measure and store the limb alignment and bone morphology of the lower limb. Chapter 5 describes a 20-year longitudinal nested case control study to investigate the role of anatomical limb alignment and proximal tibial alignment in the development of AMOA.
- Chapters 6 and 7 explore the role of the morphology of the medial tibial plateau in the development of AMOA. Chapter 6 describes the

validation of the method to assess the medial tibial upslope and Chapter 7 describes a nested case-control MRI study to investigate the role of an increased tibial upslope in the development of AMOA.

- Chapter 8 defines the 3-Tesla MRI description of end-stage anteromedial osteoarthritis of the knee and discusses the role of this imaging modality in the research and clinical arenas.
- Chapter 9 discusses the results of the thesis.
- Chapter 10 emphasises the clinical relevance and importance of this work and discusses further work

2 The surgical burden of anteromedial osteoarthritis of the knee

2.1 Aims

The aims of this chapter are

- 1 To validate the use of a radiological scoring atlas.
- 2 To investigate the compartmental pattern of knee arthritis presenting to a secondary care specialist knee clinic during a calendar year.
- 3 To investigate the effect of radiological scoring systems in common use in the epidemiological literature on the reported patterning of knee arthritis.
- 4 To describe the radiological severity of knee arthritis presenting to a secondary care specialist knee clinic.

2.2 Introduction

Whilst epidemiological studies have reported incidence and prevalence of overall knee arthritis [40, 44, 45, 163] there are very few reports of the compartmental patterning of knee arthritis [47] and little discussion regarding the implications on surgical management options [164].

There is great benefit to a surgeon understanding the different patterns of arthritis but it is also important for the research community investigating risk factors for development and progression of knee arthritis to understand the

different phenotypes of arthritis, which may each have some phenotype specific pathophysiology involved in initiation and progression of the disease. Different patterns of arthritis develop due to different environments and risks, for example there is good evidence that there is a genetic risk complicit in the development of hip and knee arthritis in general [165-167] and specifically in anteromedial osteoarthritis of the knee (AMOA) [168]. Mechanical and anatomical factors in the limb may also affect the compartments of the knee affected by arthritis [62, 76, 169]. If there are indeed different risks involved in both the development and rate of progression of the different patterns of knee OA then epidemiological studies investigating arthritis risk which ignore these patterns may miss subtle specific risk factors.

This chapter investigates the different patterns of knee arthritis presenting to a surgical clinic, describes the proportions of patients with each pattern and reports the radiological severity of arthritis.

2.2.1 Assessment of the anterior cruciate ligament

The development of AMOA is thought to depend on a functionally intact anterior cruciate ligament (ACL) [9]. There have been radiological studies [170] which have assessed the integrity of the ACL on the lateral radiograph. Therefore an assessment of the ACL integrity was undertaken as part of this study.

2.2.2 Radiographic Views

The radiographs in this study were not fluoroscopically aligned but they were performed according to a strict protocol, which has been shown to improve reproducibility [45]. The importance of this is that rotation of the X-Ray beam may affect the interpretation of the joint space and osteophytes. To minimise this further a strict anatomical definition of the point at which the joint space area should be assessed was included as part of the radiological atlas used for the study. Specifically, the joint space on both the medial and lateral compartments should be at the anterior rim of the tibial plateau.

2.2.3 Radiographic severity of arthritis

As outlined in section 1.2.5, the proportion of people who have symptomatically arthritic knees who do not yet have bone on bone disease suitable for joint replacement is unknown. This chapter therefore also investigates the radiological severity of anteromedial osteoarthritis in symptomatic patients attending a secondary care specialist knee clinic.

2.3 Validation of radiographic assessment

2.3.1 Intra-observer Analysis

2.3.1.1 Method

The intra-observer assessment study was performed on 25 radiographs by this author, working from a radiographic atlas. This atlas was based on the original examples and atlases for the three scores being used [22, 24, 27] and was used to improve reproducibility [171]. Two separate readings were performed on each radiograph a week apart from each other to lessen the possibility of individual radiographic features being recalled from previous assessment, which might have led to measurement bias [172]. The results were tabulated and Kappa statistic calculated. Kappa assessment was used since the data is categorical with no hypothesis to be tested. This has been described as a 'chance corrected proportional agreement' [172]. Maximum agreement is 1.0 and a value of 0 indicates an agreement no better than chance. The formula for Kappa is as follows:

$$\kappa = \frac{P_o - P_e}{1 - P_e}$$

Where κ = kappa

P_o = Observed frequency of agreement

P_e = Expected frequency of agreement

There is no universally agreed value of Kappa that represents a satisfactory level of agreement, since the value is not only affected by the percentage of agreement between the observers but also by the number of categories in

the data. However, guidelines have been published [172] which suggest the following interpretation:

<i>Value of κ</i>	<i>Strength of Agreement</i>
<0.2	Poor
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Good
0.81-1.00	Excellent

Table 2-1 Summary of the suggested strength of agreement of the Kappa statistic

2.3.1.2 Results

The results were tabulated for each score and are shown in Table 2-2.

<i>Score</i>	<i>Kappa</i>
KL Medial	0.86
KL Lateral	0.69
KL PFJ	0.67
Ahlback Medial	0.66
Ahlback PFJ	0.66
Ost Medial Femur	0.87
Ost Medial Tibia	0.75
Ost Lateral Femur	0.57
Ost Lateral Tibia	0.72
JSN Medial	0.74
JSN Lateral	0.59
Medial Tibial Attrition	1.00
Medial Tibial Sclerosis	0.74
ACL Intact	0.42
Bone on Bone	0.81

Table 2-2 – Intra-observer Kappa statistic assessment for different radiographic scoring systems

The Kappa results show either excellent or good agreement for all score assessments except the assessment of ACL integrity and lateral joint space

and osteophyte component of the OARSI score, which were moderate agreements.

2.3.2 Inter-observer analysis

The inter-observer assessment study was performed by the author and another Orthopaedic research fellow. Twenty-five radiographs were assessed and scored by each assessor using the agreed atlas of scores. Prior to the study a teaching set of ten radiographs were assessed independently and the results reviewed together to ensure that individual features were scored consistently. The results of the inter-observer analysis are summarised in Table 2-3.

Score	Kappa
KL Medial	0.82
KL Lateral	0.81
KL PFJ	1.00
Ahlback Medial	0.8
Ahlback Lateral	1.00
Ahlback PFJ	0.74
Ost Medial Femur	0.68
Ost Medial Tibia	0.66
Ost Lateral Femur	0.62
Ost Lateral Tibia	0.63
JSN Medial	0.67
JSN Lateral	0.75
Medial Tibial Attrition	0.65
Lateral Tibial Attrition	1.00

Table 2-3 - Inter-observer Kappa statistic assessment for different radiographic scoring systems

The results show a good or excellent agreement for all scores. The Kappa statistic results for both the inter-observer and intra-observer studies validated both observers to assess the radiographs in the main study.

2.4 The compartmental pattern of knee arthritis presenting to a specialist knee clinic.

2.4.1 Introduction and aims

The compartments of the knee are the medial, lateral and patellofemoral compartments and their radiographic assessment has been described in section 2.2. Arthritis may affect any one of these compartments, either in isolation or in combination with other compartments. This section investigates the compartmental pattern of symptomatic knee arthritis in a secondary care specialist knee clinic, the Nuffield Orthopaedic Centre (NOC).

The NOC is a specialist Orthopaedic Hospital in Oxford, UK. It serves both as a local referral centre for the surrounding area for primary orthopaedic complaints as well as specialist referral centre for more complex orthopaedic surgery. The work in this chapter investigated the radiographic pattern of knee arthritis presenting for management of a painful, arthritic knee to the knee clinic at the Nuffield Orthopaedic Centre over one calendar year. The aims were to describe the compartmental pattern of symptomatic knee arthritis and to investigate the effect of using different radiographic scoring systems on the reported pattern of arthritis.

Oxford is a City in central southern England, 60 miles North West of Central London. Its population at the 2001 census was 134,248 and this is expected to grow to 154,500 by 2020. Since OA affects older people more commonly than younger people, in order to extrapolate any findings from the

population referred to clinic it was important to assess if there was any difference between the population of Oxford and that of the country as a whole. Data from the Office for National Statistics summarised in Figure 2.1 shows that there is no overall difference in the population structure between the Oxford Population and the General Population.

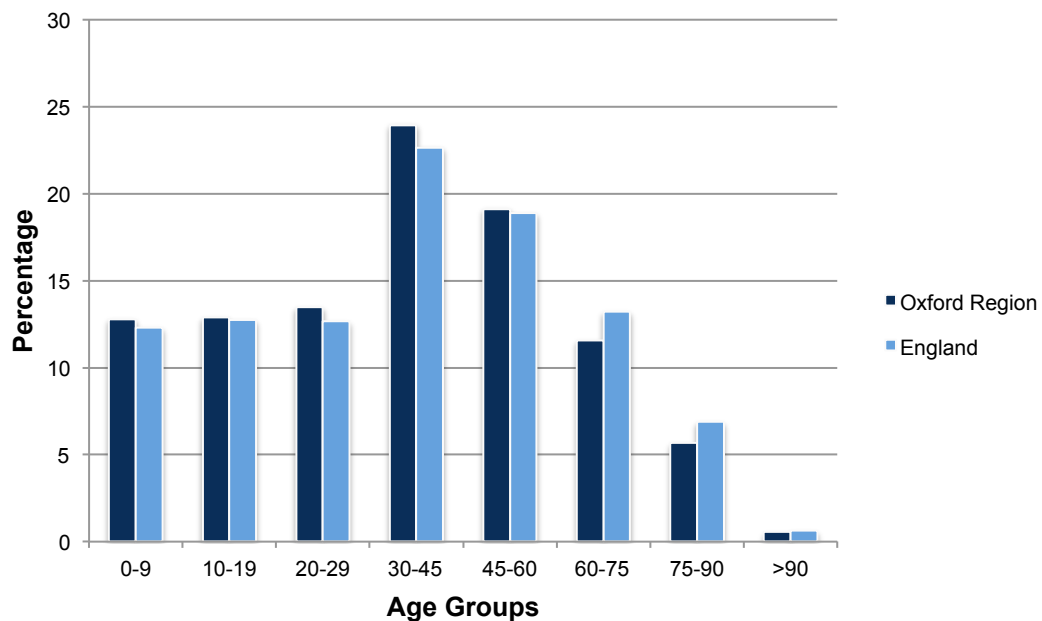


Figure 2.1 – Graph to show the comparison between the national population demographics and those of the Oxford region

2.4.2 Method

All primary referrals by local family doctors to the knee clinic at the NOC during a calendar year were assessed. Tertiary referrals, second opinions and primary referrals from out of region were excluded to ensure there was no bias from the hospitals position as a specialist referral centre. Exclusion criteria were intra-articular fracture, inflammatory arthropathy and previous

knee surgery to ensure that only primary referrals were assessed. The inclusion criteria were a primary diagnosis of symptomatic knee osteoarthritis after clinical assessment and all imaging had been completed. This is summarised in Figure 2.2 and is based on the recent diagnostic criteria of OA defined by Zhang *et al* on behalf of the European League Against Rheumatism (EULAR) [36]

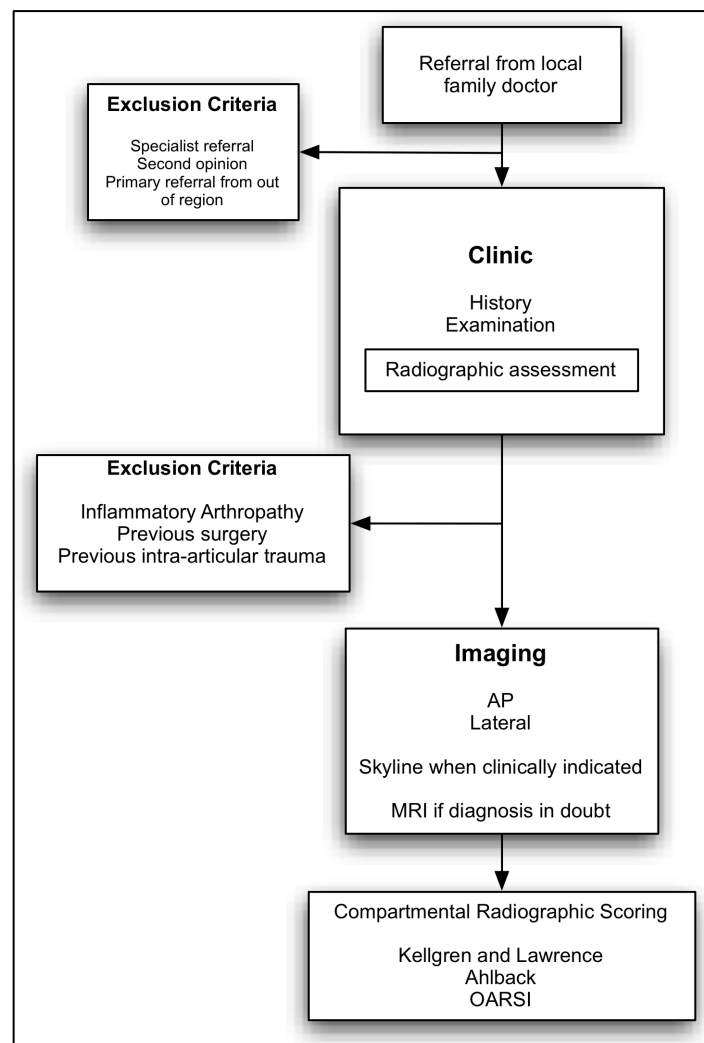


Figure 2.2 – Outline of the study design for assessing the compartmental pattern of knee arthritis

All patients were assessed with a focused clinical history, examination and radiological assessment. All patients were symptomatic, complaining of moderate or severe knee pain, which affected their activities of daily living. The radiological assessment consisted of plain radiography, specifically a standardised standing antero-posterior and lateral radiograph with an additional patella skyline Merchant view performed at 30° when the clinical assessment indicated anterior knee symptoms or patello-femoral arthritis. Magnetic resonance imaging (MRI) was utilised to assess only those knees where the diagnosis was unclear from the clinical and plain radiological assessment.

The medial and lateral compartment of the tibio-femoral joint and the patellofemoral joint were each scored using the three radiological systems outlined above.

The diagnosis of osteoarthritis was based on the definition of the American Rheumatism Association [1] described earlier in Section 1.1. Therefore, the patient would have reported symptoms in the clinical history suggestive of OA as well as evidence of “defective integrity of cartilage” on radiological assessment. Arthritis was diagnosed as a symptomatic knee with radiographic changes consistent with arthritis. Two of the radiological scoring systems had well described criteria in the epidemiological literature for the diagnosis of arthritis. The KL score definition of arthritic change is a score ≥ 2 [174] [22] and the Ahlback definition of arthritic change is a score ≥ 1 [27]. However the OARSI score has no formal description of the definition of arthritis. Review of the literature of other compartmental scores

based on joint space narrowing and osteophytes showed that both an isolated joint space narrowing (JSN) score of 1 [26, 175] and a score of both osteophyte score of ≥ 1 and a JSN of ≥ 1 [58] were validated definitions of arthritis [28].

When MRI was utilised, the diagnosis of arthritis was based on the presence of full thickness cartilage loss in at least one surface of a joint compartment. Those with symptoms but with no full thickness cartilage lesions at MRI were excluded. The MRI assessment enabled diagnosis of arthritis but was not used for the compartmental pattern description, which was based on the plain radiological changes only to ensure consistency both within the study and with other epidemiological studies.

2.4.3 Results

The radiographs of five hundred and eighty four knees in 526 consecutive patients with osteoarthritis as defined by the criteria above, 58 with bilateral disease were assessed. Two hundred and eighty eight patients were female (54.8%), 238 were male (45.2%). The mean age was 65 years (standard deviation 11 years).

The distribution of radiographic arthritis for the different scoring systems is shown in Table 2-4 and summarised graphically in Figures 2.3 - 2.6. Across all the scores, the predominant pattern was arthritis in the medial compartment either with, or without, PFJ involvement. The next most common pattern was tricompartmental arthritis, then lateral arthritis either

with or without patellofemoral disease and then isolated patellofemoral disease.

For the KL score the percentage with medial disease was 62.2%, for the Ahlback score the percentage was 70.2% and for the OARSI score the percentages were 70.9% and 69.1% for the JSN and JSN with osteophyte scores respectively.

Further interpretation of the data showed that for the KL score 34.6% of OA was an isolated unicompartamental pattern; either isolated medial, isolated lateral or isolated PFJ, 39% were unicondylar tibiofemoral disease with PFJ involvement; and 26.4% were bi-condylar tibiofemoral disease with or without PFJ involvement. Using the Ahlback score 40.4% of disease was unicompartamental, 40% either medial or lateral tibiofemoral disease with PFJ disease and 18.6% bicondylar tibiofemoral disease.

	KL SCORE		AHLBACK SCORE		OARSI JSN only		OARSI JSN and osteophyte	
	N	%	N	%	N	%	N	%
Medial	158	28.4	205	35.9	393	70.9	344	69.1
Lateral	17	3.1	20	3.5	52	9.4	58	11.6
Medial and Lateral	19	3.4	18	3.2	109	19.7	96	19.3
Medial and PFJ	188	33.8	196	34.3				
Lateral and PFJ	29	5.2	28	4.9				
Tricompartamental	129	23.2	91	15.9				
PFJ	17	3.1	13	2.3				
Total	557	100	571	100	554	100	498	100

Table 2-4 - Pattern of knee arthritis in the clinic group. The pattern described by each of the scoring systems is presented.

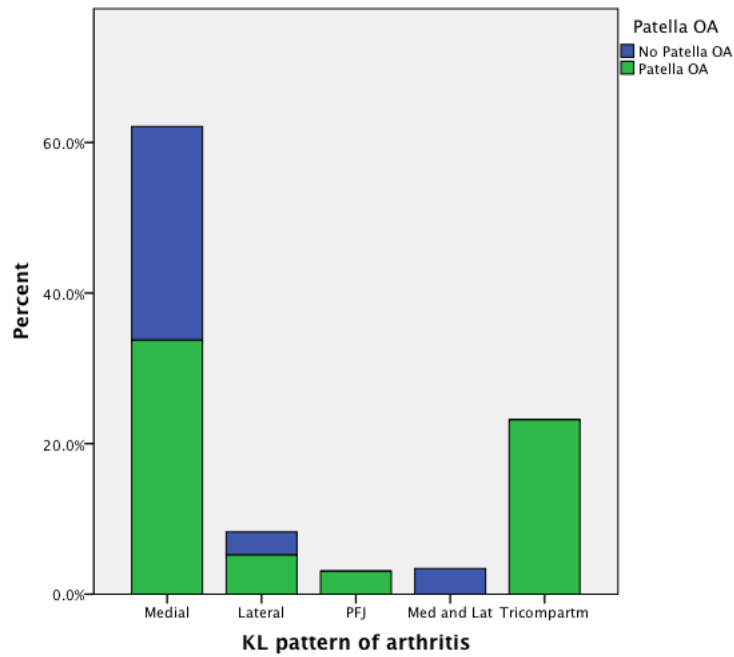


Figure 2.3 – Summary of the compartmental pattern of knee arthritis when using the Kellgren and Lawrence score. Cases with PFJ arthritis are shown in blue and those with no PFJ arthritis are shown in green.

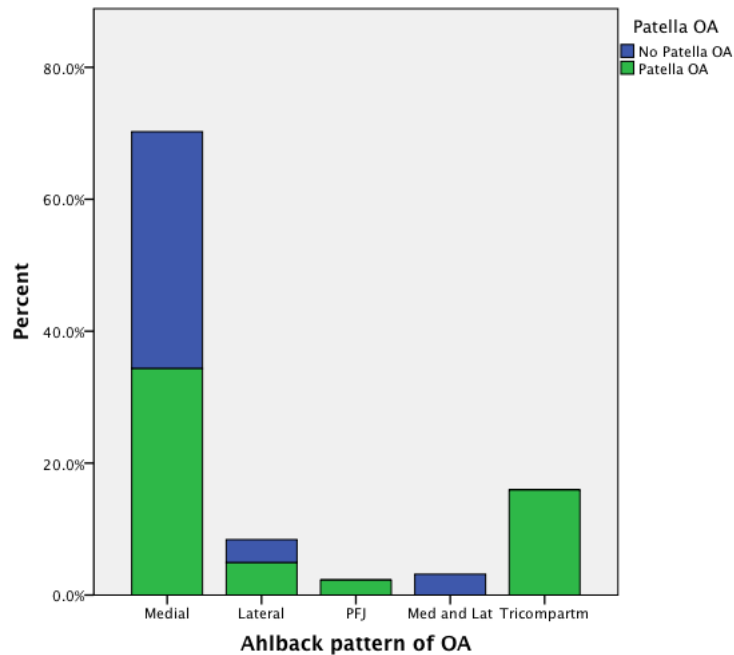


Figure 2.4 - Summary of the compartmental pattern of knee arthritis when using the Ahlback score. Cases with PFJ arthritis are shown in blue and those with no PFJ arthritis are shown in green.

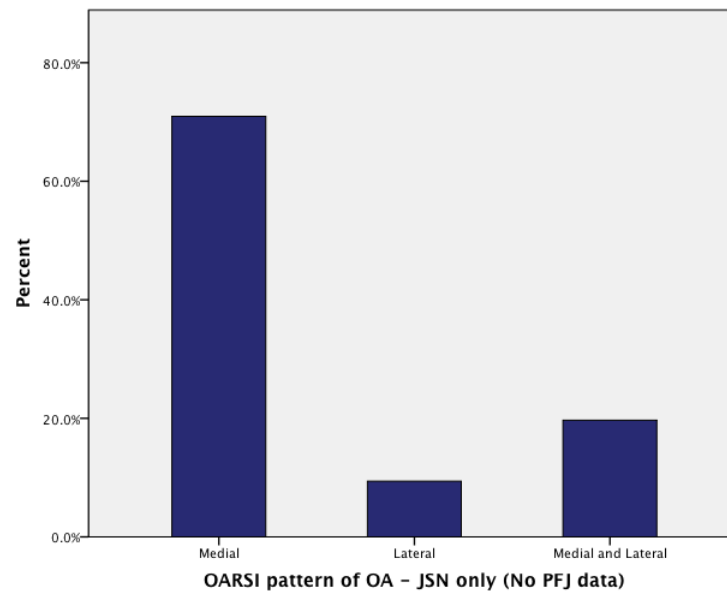


Figure 2.5 - Summary of the compartmental pattern of knee arthritis when using the OARSJ joint space narrowing score. Note that this score has no PFJ component.

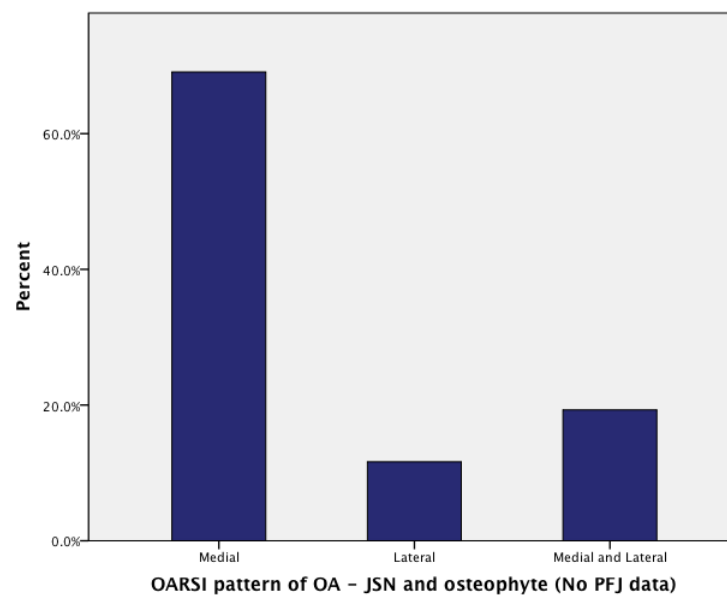


Figure 2.6 - Summary of the compartmental pattern of knee arthritis when combining the OARSJ joint space narrowing and osteophyte score. Note that this score has no PFJ component

The total number of knees with a medial pattern of disease as defined by the KL score was 346 and the lateral radiograph assessment showed that in

92% the ACL was intact. This shows that the predominant pattern of medial arthritis was anteromedial arthritis with an intact ACL.

2.5 The effect of different radiological scoring systems on the reported pattern of knee arthritis

2.5.1.1 Introduction and aim

Section 2.4 above described the compartmental pattern of symptomatic knee arthritis in a secondary care specialist knee clinic. The aim of this section was to investigate if the pattern of disease described was dependent on the radiological score used to assess the knee. Any difference in the pattern of arthritis from the different scores would have wider implications both for the interpretation of the results of other epidemiological studies and for clinical decision-making.

2.5.1.2 Method

The compartmental pattern of arthritis as defined by each of the three radiographic scoring systems was tabulated and compared using Wilcoxon rank statistical analysis. The Wilcoxon rank was used since the data was categorical and not normally distributed [172]. Since the OARSI score does not contain a PFJ component, to enable direct comparison with the KL and Ahlback the isolated PFJ disease from the latter two scores were excluded from the analysis and the PFJ disease that occurred with medial or lateral disease was included as medial or lateral disease only.

2.5.1.3 Results

Table 2-5 shows the comparison between the different radiological systems and the pattern of arthritis described. The Wilcoxon rank test result is summarised in Table 2-6. This shows that there is no significant difference between the pattern of medial and lateral disease described by the OARSI and the Ahlback scores. However, the KL score is significantly different to both of the other scores. The KL described relatively less isolated medial disease and relatively more combined medial and lateral disease. This is due to KL score scoring osteophytes as one of the main determinants of disease. Therefore studies that use scores based on osteophytes and JSN rather than just JSN are likely to show an increase in bicompartamental disease in comparison to the other scores.

Score	Compartment		
	Medial (%)	Lateral (%)	Medial and Lateral (%)
Kellgren and Lawrence	64	8.5	27.5
Ahlback	71.2	8.9	19.9
OARSI	70.1	9.7	20.1

Table 2-5 – Comparison between the OARSI, KL and Ahlback radiological scores and the distribution of compartmental pattern of knee arthritis.

	Ahlback		OARSI		OARSI
KL	p<0.001	KL	p<0.001	Ahlback	p=0.590

Table 2-6 – Summary of the Wilcoxon rank assessment of the difference in the described patterning of knee OA between the three OARSI, KL and Ahlback radiological scoring systems.

2.6 The radiological severity of anteromedial arthritis

2.6.1 Introduction and aim

The epidemiological literature will often describe the incidence of arthritis but rarely does the literature focus on the radiological severity of arthritis. The epidemiological diagnosis of arthritis is based on radiological findings and the threshold is often set at a KL score of 2, which equates to a radiograph with minimal joint space narrowing and a small osteophyte. To a surgical academic the severity of disease presenting for assessment in a clinic is of great interest because this guides the treatment options available for the management of the patient. For example, a patient with KL 2 changes on the radiograph would have different surgical management options to a patient with KL 4. A symptomatic patient with bone on bone changes may be managed by knee arthroplasty whereas the results of arthroplasty without bone on bone changes may be variable. Those patients with earlier structural changes may be suitable for different surgical interventions, for example an high tibial osteotomy to mechanically offload the affected compartment. A clinical interpretation of the radiological scores is shown in Table 2-7.

<i>Radiological Scoring System</i>	<i>Score</i>	<i>Clinical Definition</i>
KL	0	Normal
	1	Failing Knee
	2	
	3	
	4	End Stage
OARSI	0	Normal
	1	Failing Knee
	2	
	3	End Stage
Ahlback	0	Normal
	1	Failing Knee
	2	End Stage
	3	
	4	
	5	

Table 2-7 – Summary of the radiological scoring system with the clinical category that each score correlates to.

The aim of this section was to describe the radiological severity of all patients with symptomatic anteromedial arthritis presenting to a surgical clinic over a calendar year.

2.6.2 Method

All patients with anteromedial osteoarthritis as defined in Section 2.4 above were included. Concurrent disease in the patello-femoral joint was not a contra-indication and so these cases were included. The individual radiological scores for these patients were tabulated and those for the KL score were represented graphically.

2.6.3 Results

The assessment of the radiographic severity of the different patterns of OA is shown in Table 2-8. Analysis of the KL score shows that the 38.2% of cases were KL 2, 37.3% KL 3 and only 24.6% were KL 4. Therefore, 75.4% of symptomatic knees presenting to clinic for surgical management could be classified clinically as “failing” knees, where the outcome of arthroplasty may be variable. The KL results are shown graphically in Figure 2.7 This result has implications for the planning of surgical interventions and suggests that emphasis needs to be placed on the management of the failing knee, without bone on bone radiographic changes.

	<i>OARSI</i>		<i>KL</i>		<i>Ahlback</i>	
	N	%	N	%	N	%
1	119	30.3	N/A		252	62.8
2	147	37.4	132	38.2	108	26.9
3	127	32.3	129	37.3	38	9.5
4	N/A		85	24.6	2	0.5
5	N/A		N/A		1	0.2

Table 2-8 – Radiographic severity of symptomatic anteromedial osteoarthritis presenting to a surgical clinic. Results for OARSI, KL and Ahlback scores are shown.

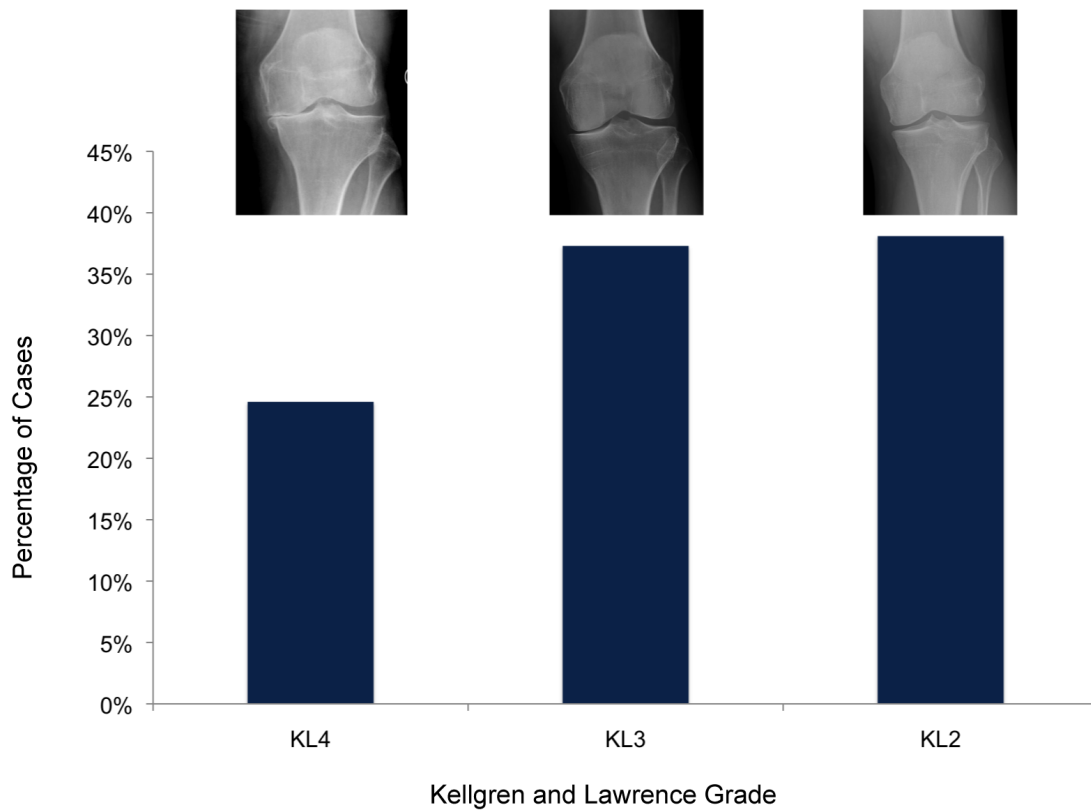


Figure 2.7 - Radiographic severity of anteromedial arthritis as defined by the Kellgren Lawrence score. Shown with radiographic examples of each score.

2.7 Summary of results

This Chapter validated the use of the radiological atlas based on the KL, Ahlback and OARSI scores by more than one person in the assessment of multiple radiographs. Many of the categories assessed showed excellent reproducibility and for the inter-observer assessment all the categories were rated as either excellent or good agreement.

The study has identified a number of patterns of disease that commonly present to secondary care. The commonest pattern was of medial disease, almost all of which were seen to have an intact ACL on plain radiographic assessment. Approximately half of the medial disease also had concurrent

PFJ disease and more than half of the lateral disease also had PFJ disease. Isolated PFJ arthritis was uncommon and tricompartmental disease accounted for between 15% and 23% of all disease.

The overall pattern of disease changed according to the scoring system used. The KL score significantly increased the diagnosis of concurrent medial and lateral disease in comparison to the Ahlback and OARSI scores. This is due to the incorporation of the osteophyte into the KL assessment of arthritis. Understanding the role of the osteophyte in the diagnosis of disease is important in both the clinical and research setting. Clinically, the interpretation of the osteophyte may change the type of treatment offered to a patient, for example when discussing joint preserving surgery. In research, the interpretation of the results of other population based studies reporting pattern of knee arthritis must take account of which scoring system was used and how osteophytes were scored.

The majority of patients attending a surgical clinic with knee arthritis do not have bone on bone disease. Knee arthroplasty is known to be a reliable and effective treatment for these patients but this study shows that the majority of patients are requiring treatment for an earlier stage of disease. The treatment options for this majority of patients are less clear and the timescale of progression towards end stage disease is not known. The time that a knee may take to progress from the earliest radiological signs of arthritis to advanced bone on bone arthritis is of great importance in a clinical setting. An understanding of this timing of arthritis progression would enable a more detailed counseling process between a surgeon and their

patients. This timescale is investigated in a 20-year longitudinal cohort in the next chapter.

3 The incidence and progression of anteromedial osteoarthritis - A twenty year longitudinal study

3.1 Introduction

The previous chapter described the compartmental pattern of knee arthritis in symptomatic patients attending a surgical clinic, which showed that anteromedial osteoarthritis was the most common pattern of disease. The work in this chapter investigates anteromedial arthritis in a 20-year longitudinal radiographic study. Specifically, the prevalence of AMOA and the longitudinal incidence of AMOA over 20 years and the timescale of progression from early to advanced arthritis are investigated. This has not been described before.

The clinical importance of defining the time it may take to progress to an advanced stage of arthritis is that patients will often ask the time in which they might expect to progress from early arthritis to advanced arthritis, necessitating a joint arthroplasty. At present the surgical community does not have any data to inform an evidence-based response to this question

3.2 Aims

The aims of this chapter are:

- 1 To describe the prevalence of anteromedial OA at each five year visit in a 20-year longitudinal cohort
- 2 To describe the age distribution of subjects in each radiographic stage of anteromedial osteoarthritis.
- 3 To describe the incidence of arthritis over a 20-year period, specifically:
 - a. The incidence or chance of developing anteromedial knee OA over 20 years
 - b. The time period over which these incident cases of arthritis develop.
 - c. The radiological grade of arthritis the incident cases progress to.
- 4 To describe the time taken to progress from early radiographic anteromedial OA to advanced anteromedial OA.

The work in this chapter was based on the Chingford Study of 1000 women, which is outlined below. In summary, this is a twenty-year longitudinal study with radiographs performed on each subject every five years. All the radiographs from all the five-year visits were scored and assessed to describe the prevalence, incidence and progression of arthritis outlined above.

3.3 The Chingford 1000 Women Study

3.3.1 Introduction

The Chingford 1000 Women Study was established in 1989, initially as a retrospective case-control study to investigate the prevalence of osteoporosis and osteoarthritis in a general population of middle aged women. From that time it has developed into a prospective study of this group with detailed musculoskeletal data and high participant retention of 77% at 20 years. The study has generated over 70 peer review publications and is an important resource not only for the study of progression and classification of osteoarthritis [157, 176, 177] but also for osteoporosis [167, 178] and fracture risk [179, 180].

3.3.2 Recruitment to The Chingford Cohort

One thousand and three female volunteers aged between 45 and 64 years of age were recruited from one General Practice in the town of Chingford, which is situated in North East London, England. The participants were born between March 1922 and December 1946 and the average age of women in the study at the baseline visit was 54.2 years. The area is predominantly populated by Caucasian middle class people but socio-economic profiling shows a range of all social groups [181]. The Chingford study group is statistically similar to UK women of their age group in terms of their height, weight, rates of smoking and hysterectomy [177], which are all risk known to affect bone health..

3.3.3 Radiographic assessment of the Chingford Cohort

Standard radiographic assessment protocols were established prior to the baseline assessment and this method was continued for all subsequent assessments. The assessments from baseline to year 15 were captured using plain film technology. The year 20 radiographs were captured using digital technology.

The same radiographer on the same equipment performed the baseline to year 15 assessments on both knees of each attendee. For the baseline to year 15 plain film radiographs, the protocol described weight-bearing antero-posterior views with the beam centered 2.5cm below the patella and with the knee in contact with the cassette and tube-to-film distance of 100cm [163]. This adherence to strict radiological protocols is known to be important in standardising radiological results in longitudinal cohorts [16].

At the year 20 visit, digital radiographic equipment with the same positioning protocol was used. A KIDA calibration object was included in the film field to allow calibration [182]

3.3.4 Radiographic scoring systems in the Chingford Study

The radiological scoring systems used in the Chingford Study were the Kellgren and Lawrence (KL) arthritis score and the Chingford Radiographic atlas.

3.3.4.1 The Kellgren and Lawrence Score

The KL score [21, 22, 25] has become part of the key classification criteria for OA of the knee [1, 157] and is summarised in Table 3-1. Of note, in the Chingford Study the presence of a knee arthroplasty was categorized as a score of 5, which is a departure from the original classification. This enabled those knees that have undergone arthroplasty to remain within the longitudinal cohort.

Kellgren Lawrence Score	Description
0	Normal
1	Possible osteophyte No joint space narrowing
2	Definite osteophyte Possible joint space narrowing
3	Multiple osteophytes Definite joint space narrowing Sclerosis and possible deformity of the bone ends
4	Large osteophytes Marked joint space narrowing Severe sclerosis and definite deformity of the bone ends
5	In the Chingford Study coding this represented a knee with joint arthroplasty in situ

Table 3-1 - Summary of the Kellgren Lawrence knee arthritis score [22]

The baseline to year-15 readings ascribed a global KL score to the whole knee with no information regarding the compartmental pattern of the arthritis. The year 20 recorded both a global KL score and additionally a KL score for both the medial and lateral compartment was ascribed. This is not the usual protocol in longitudinal studies although has been reported before [20] and is becoming more common as the assessment of the specific compartments affected by arthritis has become part of inclusion criteria to National Institute for Health clinical trials.

3.3.4.2 *The Chingford Radiographic Atlas*

The Chingford Atlas is a validated arthritis score for the knee [157] and assesses joint space narrowing in the medial and lateral tibiofemoral compartments, osteophyte size, subchondral sclerosis and tibial spiking [183]. Joint space narrowing was scored from 0 (normal), 1 (joint space narrowing), 2 (definite joint space narrowing, not bone on bone disease) 3 (bone on bone joint space narrowing). Osteophyte size was scored from 0 (no osteophyte), 1 (small osteophyte), 2 (medium sized osteophyte) and 3 (large osteophyte).

3.3.5 Reproducibility of the Chingford radiographic assessments.

Two observers, Prof Tim Spector (TS) and Dr Debbie Hart (DH), had previously assessed the Baseline to Year 15 radiographic scores [163]. These observers were not involved in the assessment of the Year 20 radiographs and therefore reproducibility between the baseline to year 15 and the new year 20 assessments were performed and this showed 85% agreement [184]

The reproducibility assessments of the year 20 readings have been reported elsewhere [184] and showed excellent intra-observer reliability with Kappa scores of greater than 0.90 for KL scoring and joint space assessments which are at least as good as those reported by other longitudinal studies [185]

Observers blinded to the clinical details of the subjects, except the case number and the year of the visit, scored the Year 20 radiographs. The

radiographs for each five yearly visit were scored together, which is a validated method of assessment of radiographs in longitudinal studies [186].

3.4 Definition of anteromedial arthritis for this study

The radiographic assessment of knee arthritis has been based on the KL score since 1957 [22] and the original cut-off of $KL \geq 2$ as a definition of radiographic arthritis has been used in analyses since [187, 188]. This definition has been validated by the American Rheumatism Association [1]. This study therefore used the same criteria to define arthritis. However, the original definitions of joint space narrowing and osteophytes for each grade of the KL are often reported differently in different literature [19] so contemporary guidance is that an atlas consisting of examples of each radiographic stage is used to ensure reproducibility. Therefore an atlas was constructed for this study and all radiographic readers were trained on this.

This chapter investigates the presence of and compartments affected by arthritis in the Chingford Study. Whilst the year 20 radiographic readings were assessed for KL score in each of the lateral and medial compartment, the baseline to year 15 readings were ascribed a global knee score. Therefore, to describe which compartments were affected by arthritis, the joint space and osteophyte data from the Chingford Radiographic Atlas was also used. The use of osteophytes [189],[157] and joint space narrowing [18, 48] to define arthritis has been described and validated before. The

algorithm to define anteromedial arthritis using joint space narrowing and osteophytes is outlined below in Figure 3.1.

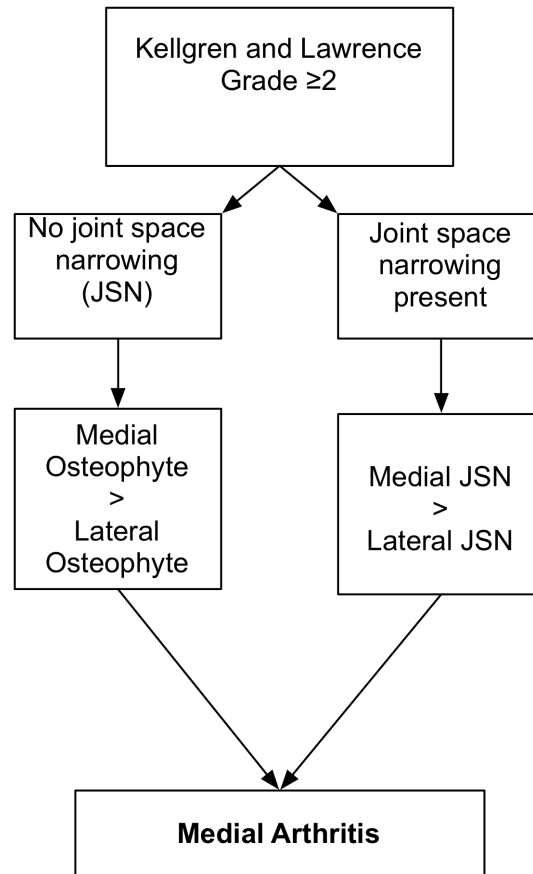


Figure 3.1 – Algorithm for definition of medial arthritis using osteophyte and joint space narrowing data as defined by McAlindon [190] and Spector [191].

3.5 Summary of Chingford radiographic data

3.5.1 Demographics of Chingford radiological data

One thousand and three subjects were recruited at baseline as outlined in section 3.3.1. The number of knee radiographs performed at each visit and the age demographics of the population at each visit are summarised in Table 3-2.

In the Chingford Study, of the 1940 knees assessed at baseline, only 868 were radiologically assessed at all of the five subsequent time-points. Nine hundred and ninety four knees were assessed radiologically at year 20, which is a 51% radiological follow up at 20 years.

	<i>Year of Study</i>				
	<i>Baseline</i>	<i>5</i>	<i>10</i>	<i>15</i>	<i>20</i>
Number of Knees	1940	1663	1638	1227	994
Mean Age	54.2	59.1	64.0	68.3	72.8
Std. Deviation	5.9	5.9	5.9	5.7	5.5
Median	54	59	63	68	72
Range	22	22	22	22	20
Range	22	22	22	22	20
Minimum	44	49	54	59	64
Maximum	66	71	76	81	84

Table 3-2 Table to show the number of knees assessed and the age demographics at each of the Chingford visits

3.5.2 Radiographic summary of each Chingford Study visit

The radiographic scores from each year of the Chingford study for all subjects are summarised in Figure 3.2 and the compartmental pattern of OA as defined by the algorithm above (Figure 3.1) is summarised in Table 3-3.

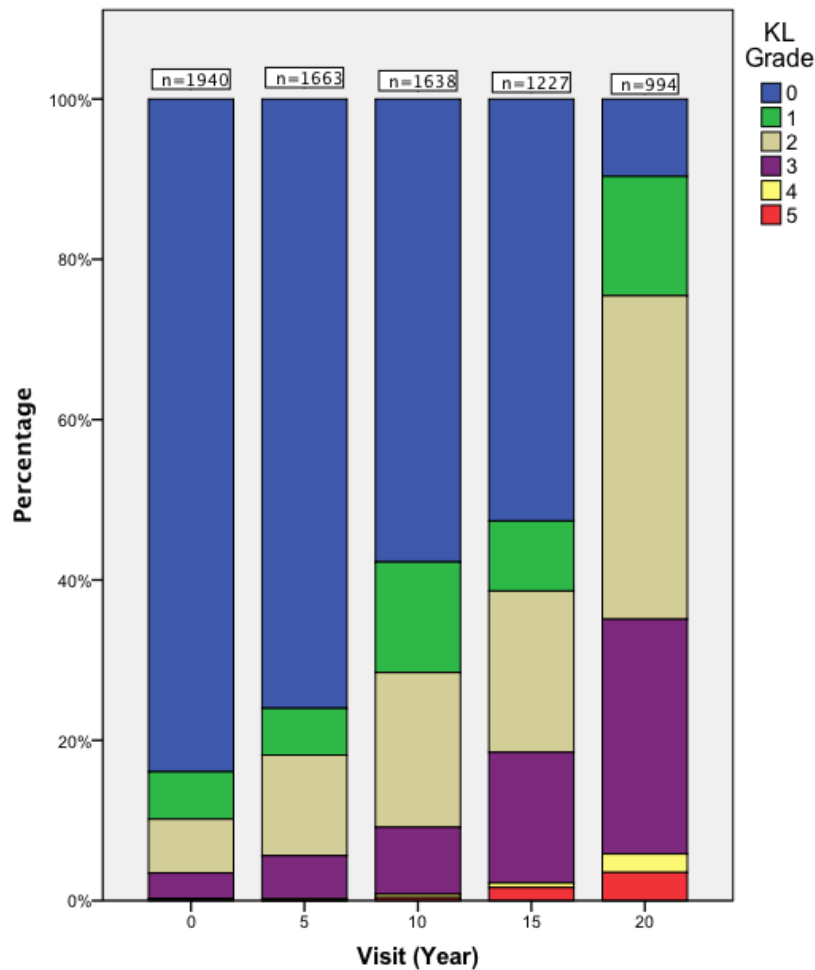


Figure 3.2 - Bar chart to show percentage of each global KL radiographic stage at each visit for all knees. (Number of knees assessed at each visit is annotated)

	Baseline		Year 5		Year 10		Year 15		Year 20	
	N	%	N	%	N	%	N	%	N	%
Medial	113	57.7	207	68.5	302	64.8	350	73.8	533	71.2
Lateral	83	42.3	95	31.5	164	35.2	124	26.2	216	28.8
Total	196	100	302	100	466	100	474	100	749	100

Table 3-3 – The knee compartments affected by OA, shown by each 5-year visit.

The overall change of knee KL score for all knees is shown below in Table 3-4. The rows outline the KL score at baseline and the columns outline the score at the last radiographic assessment. The final KL score is the last

recorded score for each subject, which does not necessarily imply that this is at the 20-year visit. For example, some subjects had no further radiographs after year 10. Table 3-4 shows that 3 knees had a knee arthroplasty in situ at baseline. A further 44 knees progressed to a knee arthroplasty during the study. At baseline 1628 knees (84%) were scored as KL 0 and whereas at the respective final follow-up only 644 (33.2%) were still scored as KL 0. During the time in the study, the KL score of 795 knees did not progress from the baseline value.

		<i>Final KL Score</i>						<i>Total</i>
		0	1	2	3	4	5	
Entry KL Score	0	644	221	417	305	16	25	1628 (84%)
	1	0	32	43	32	2	6	115 (5.9%)
	2	0	1	63	54	5	8	130 (6.7%)
	3	0	0	0	51	6	5	62 (3.2%)
	4	0	0	0	0	2	0	2 (0.1%)
	5	0	0	0	0	0	3	3 (0.1%)
Total		644 (33.2%)	253 (13%)	523 (27%)	442 (22.8%)	31 (1.6%)	47 (2.4%)	1940

Table 3-4 - Crosstable of KL score from Chingford baseline (Rows) to final radiographic assessment (Columns). Row and column totals shown as both value and percentage of overall tota

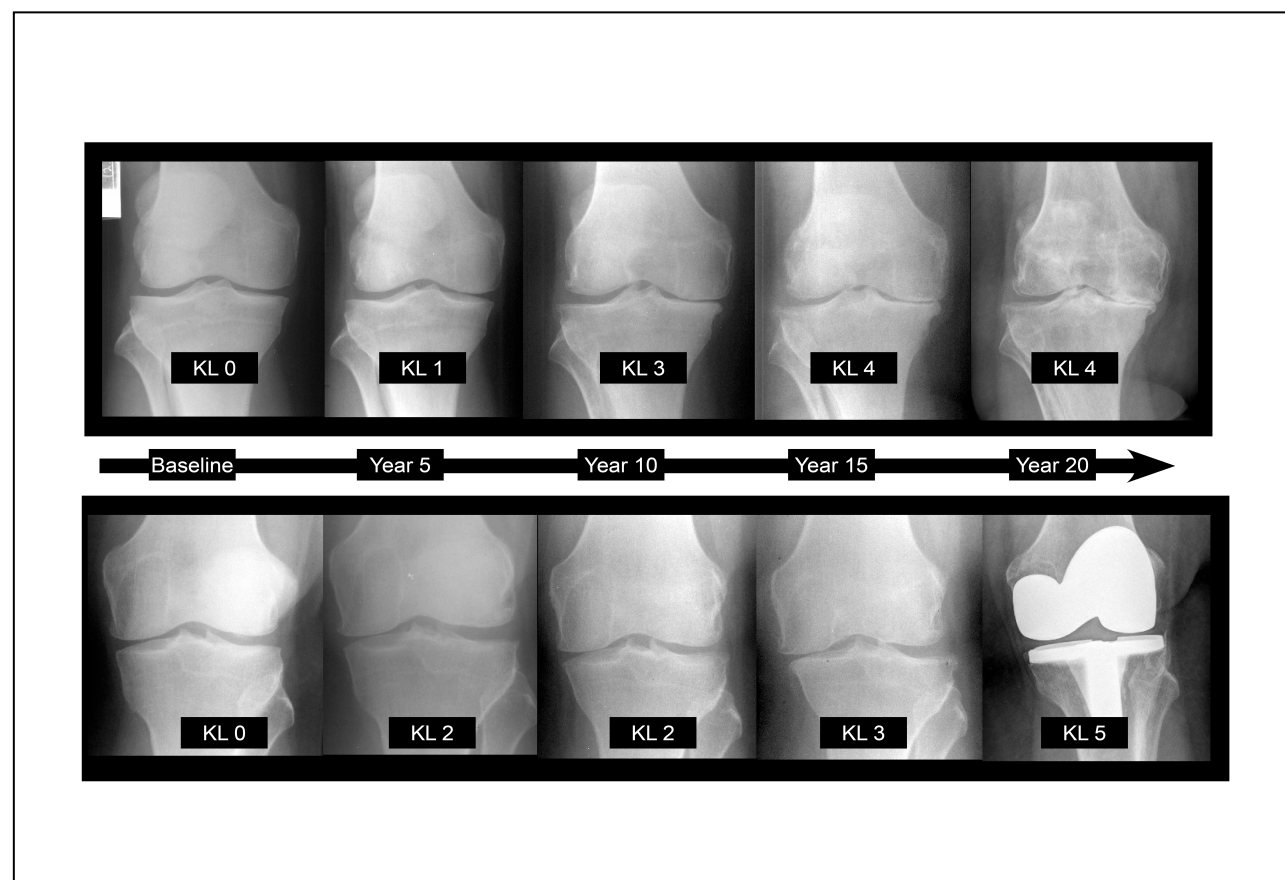


Figure 3.3 – Examples of arthritis progression in the Chingford Study. This shows the knees of two different subjects (one right and one left) during the 20-year study.

3.6 Prevalence of arthritis in the Chingford Study

3.6.1 Introduction

Prevalence is defined as the total number of cases with disease within the total in the population over a defined time period. Over a longitudinal study the point prevalence describes the prevalence at a given time point. For this study the point prevalence is reported for each five-year visit to show the increasing burden of arthritis on the Chingford population. The period prevalence is the prevalence over the entirety of the study. The definition of knee arthritis for this prevalence is a KL score greater or equal to 2.

3.6.2 Results

The prevalence for all patterns of knee arthritis is shown in Table 3-5.

	Year of Study				
	Baseline	5	10	15	20
Point Prevalence (%)	10.2	18.2	28.4	38.6	75.5
Period Prevalence (%)	53.7				

Table 3-5 - Prevalence of knee arthritis (defined by KL score) by year (point prevalence) and over period of study (period prevalence)

The point prevalence of knee arthritis increases from 10.2% at baseline to 75.5% at year 20. There is a large increase in point prevalence between year 15 and year 20, from 38.6% to 75.5% respectively. The mean age of

subjects at the two visits is 68.3 years at the year 15 visit and 72.8 years at the year 20 visit and the standard deviation remains similar at 5.7 and 5.5 years respectively.

The period prevalence shows that during the study 53.7% of all knees show radiographic signs of arthritis.

The pattern of whether the medial or lateral compartment of the knee has arthritis at each time-point has already been outlined above in Table 3-3 above. Table 3-6 below expands both on Table 3-3 and Table 3-5 to show the prevalence of arthritis by knee compartment. This shows that the period prevalence for medial arthritis is 43% and for lateral arthritis is 10.7%.

		Baseline	5	10	15	20
Point Prevalence (%)	Medial	5.9	12.5	18.4	28.5	53.8
	Lateral	4.3	5.7	10	10.1	21.7
Period Prevalence (%)	Medial	43.0				
	Lateral	10.7				

Table 3-6 – Compartmental prevalence of knee arthritis in the Chingford Study

Interestingly, at baseline the point prevalence for both medial and lateral disease is similar, 5.9% and 4.3% respectively. However, at each progressive visit the point prevalence of medial disease shows a much greater increase than that for lateral disease. At the year 20 visit 53.8% of knees show signs of medial arthritis whereas 21.7% of knee show signs of lateral arthritis.

3.7 Age of arthritis

3.7.1 Introduction

The work outlined in this section has two main aims. The first is to investigate the KL grade distribution within the whole Chingford Study cohort when it is categorised by age. This provides a population overview of the KL grade by age and so provides an expected burden of disease of knee OA in a general female population.

The second aim is to investigate specifically the age of subjects in each KL grade with AMOA or who subsequently developed AMOA. The data regarding the ages of subjects with AMOA may then be used to define a normal age range of the population with knee arthritis. Any subsequent findings regarding the timescale of progression of knee arthritis will then relate to this normal population. Should subjects outside of this study develop arthritis significantly sooner or later than these ages, it may be that they have a different type of disease, which may not progress according to patterns described here.

3.7.2 Method

To investigate the first aim of KL grade distribution by age of the entire Chingford Study cohort, the age and KL grade of each subject at each visit were tabulated. The ages of the subjects were categorised into age brackets, each of 5 years. The stacked variables of a bar chart were the

increasing age brackets and the segment variables were the increasing KL grades.

The rest of the section investigated only those subjects who either commenced the study with AMOA or those who developed AMOA during the study. The selection criteria of AMOA were based on the flow diagram in Figure 3.1, which provided 860 knees for study.

Every subject is included at least once but some subjects are included more than once. This is because as an individual subject progresses through the KL stages their age at each KL stage will be included in the statistics for that specific KL stage.

For example.

A subject with the following radiographic findings:

KL0 at the baseline and year 5 visits

KL2 at year 10

KL3 at year 15

The age at baseline and year 5 will be included in the KL0 data; age at year 10 in the KL2 data and the age at year 15 will be included in the KL3 data.

The results were tabulated and a box and whisker plot was drawn to display the results graphically. Analysis of variance was calculated to investigate if there was a significant difference in the mean age between the increasing KL grades.

3.7.3 Results

The summary of the KL distribution by age (separated into 5 year age brackets) is shown in Table 3-7 and summarised in Figure 3.4.

Age Range (Years)	KL Grade	Frequency	Percent
<50	0	659	92
	1	23	3.2
	2	26	3.6
	3	8	1.1
Total		716	100
50-55	0	888	84.7
	1	61	5.8
	2	71	6.8
	3	28	2.7
Total		1048	100
55-60	0	1048	74.2
	1	132	9.3
	2	155	11
	3	72	5.1
	4	2	0.1
	5	3	0.2
Total		1412	100
60-65	0	1011	62.6
	1	157	9.7
	2	280	17.3
	3	150	9.3
	4	11	0.7
	5	7	0.4
Total		1616	100
65-70	0	598	44.2
	1	170	12.6
	2	379	28
	3	174	12.9
	4	14	1
	5	17	1.3
Total		1352	100
70-75	0	271	32.9
	1	95	11.5
	2	239	29
	3	185	22.5
	4	9	1.1
	5	25	3
Total		824	100
75-80	0	96	25.4
	1	41	10.8
	2	113	29.9
	3	114	30.2
	4	6	1.6
	5	8	2.1
Total		378	100
>80	0	9	7.8
	1	14	12.1
	2	40	34.5
	3	48	41.4
	5	5	4.3
Total		116	100

Table 3-7 – Summary of KL distribution by age for all subjects in the Chingford Study

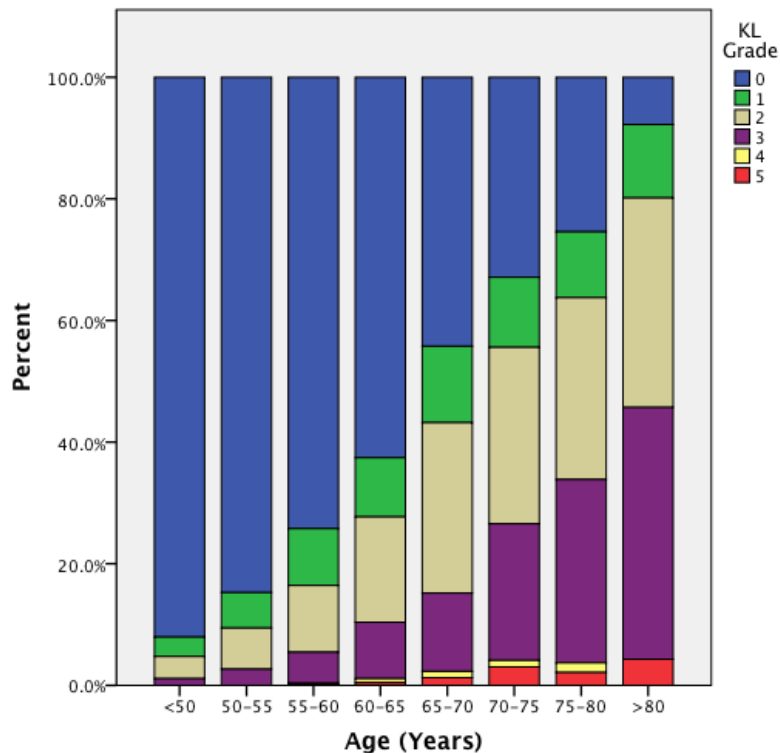


Figure 3.4 – Bar chart showing the KL distribution in 5-year age group brackets for all subjects in the Chingford Study

In the under-50 age group, 95.2% of subjects had no radiographic signs of arthritis and not one subject under the age of 55 years had radiographic bone-on-bone or end stage disease. By comparison only 44.5% of 70-75 year olds and 36.2% of 75-80 year olds were seen to have no radiological signs of arthritis. More than 80% of over eighty year olds, 64% of 75 to 80 year olds and 55% of those between 70 and 75 years had radiographic knee OA. Four percent of those over 70 years and 2% of those between 65 and 70 years were seen to have either advanced arthritis or to have already undergone knee replacement.

The age of subjects who developed AMOA at any stage during the Chingford Study was investigated. Table 3-8 summarises the average age at each grade for all those in this group.

	<i>KL 0</i>	<i>KL 1</i>	<i>KL 2</i>	<i>KL 3</i>	<i>KL 4</i>	<i>TKA / KL 5</i>
Mean Age (Years)	57.6	61.8	66.6	68.9	68.6	71.1
Median Age (Years)	57	61	67	69	67	72
Std. Deviation	7.2	6.5	7.4	7.6	5.3	5.6
Variance	51.2	42.1	55.1	57.8	28.1	31.6
Range	35	33	39	38	19	24
Minimum	44	46	45	46	59	59
Maximum	79	79	84	84	78	83

Table 3-8 - Age (years) by Kellgren Lawrence radiographic stage for all subjects who develop AMOA

Figure 3.5 shows a box and whisker plot depicting the age difference for the different KL stages graphically. This shows the increasing age of the subjects as the KL grade increases.

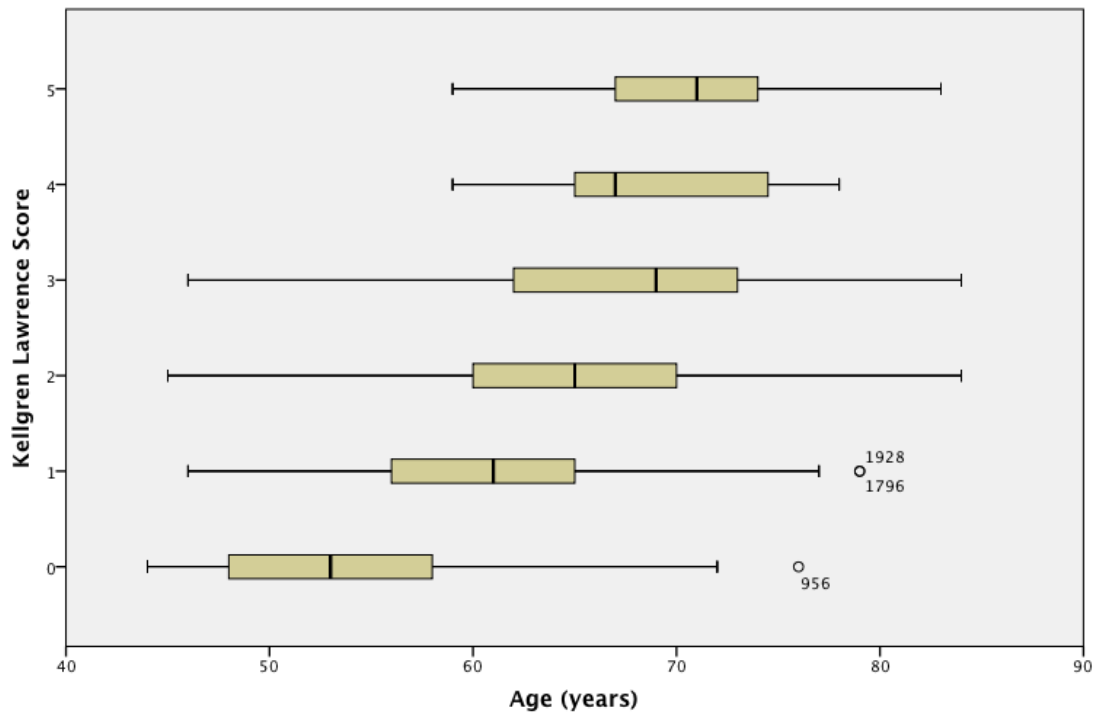


Figure 3.5 – Box and whisker plot showing the age of subjects in each KL grade.

Analysis of variance (ANOVA) showed a significant difference in the mean age between the KL grades. The ANOVA score is summarised in Table 3-9.

	<i>Sum of Squares</i>	<i>df</i>	<i>Mean Square</i>	<i>F</i>	<i>Significance.</i>
Between Groups	90600.092	5	18120.018	347.019	<0.001
Within Groups	199361.564	3818	52.216		
Total	289961.656	3823			

Table 3-9 – Analysis of variance between the mean age of each Kellgren Lawrence Grade

The mean age increased from 57.6 years for those with KL grade 1 to 68.6 years for those with KL grade 4 and 71.1 years for those with knee arthroplasty. The minimum age for KL grades 0 to 3 were very similar,

between 44 and 46 years but the minimum age for those with KL grades 4 and 5 was significantly increased at 59 years.

Kellgren and Lawrence grade 2 is the grade at which a diagnosis of knee OA is made. Figure 3.6 shows a histogram of the age distribution of those subjects with KL grade 2, which is normally distributed. The youngest subject was 45 years old and the oldest was 84 years old. The mean age is 66.7 years and the median is 67 years.

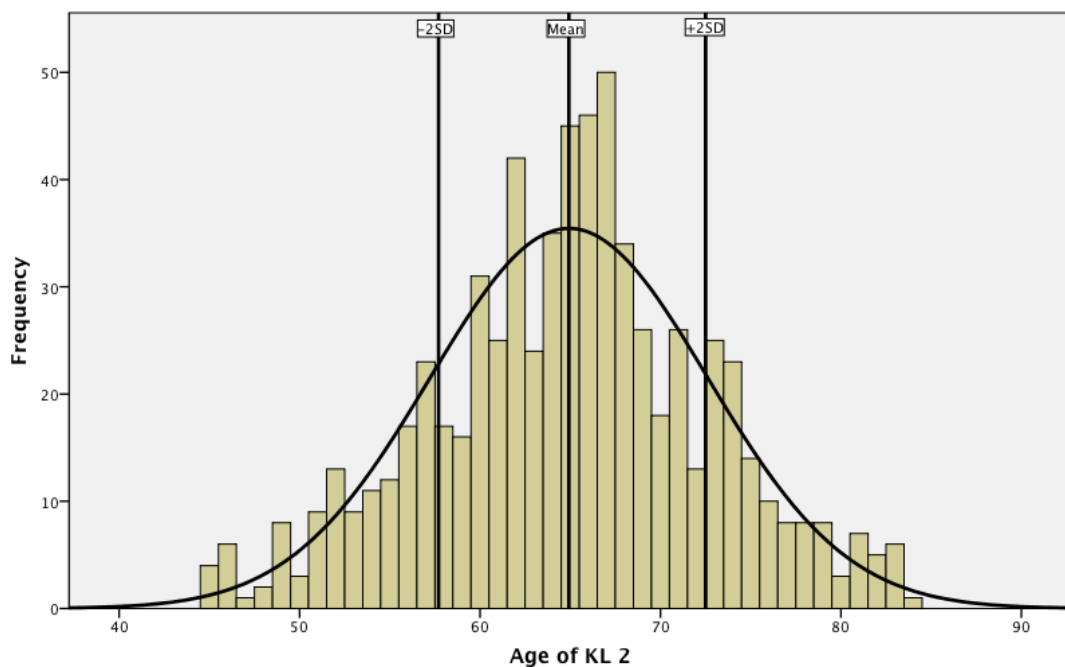


Figure 3.6 – Histogram of the age distribution of those subjects with KL grade 2 arthritis. Two standard deviations are marked on the chart.

3.8 Incidence of arthritis in the Chingford Cohort

3.8.1 Introduction

Incidence is a measure of new cases of disease during a defined time period. The incidence rate is the number of new cases at the end of a time

period divided by the total number at risk of developing the disease at the beginning of the time period. The new cases that progressed from a normal knee to at least a KL grade 2 were termed the incident group and those that did not progress were termed the non-progressor group.

$$\text{Incidence rate} = \frac{\text{Number of new cases at end of time period}}{\text{Number without disease at beginning of time period}}$$

In this section the overall incidence rate of arthritis in *any* compartment was calculated and then the incidence was further refined to describe the incidence of *either* medial or lateral knee OA in the Chingford study. The incidence rate was calculated for the overall 20-year Chingford study time period. In addition, the incidence rate for each 5-year time period between visits was also calculated.

3.8.2 Method

The definition of OA used was that defined in Section 3.4. In summary, those with KL grade 0 or 1 were classified as without OA and those with KL ≥ 2 were classified as with OA. The definition of medial and lateral OA was as outlined by the algorithm described in Section 3.4 and shown in Figure 3.1.

The incidence rate was calculated for each 5-year time-point. This enabled both the overall incidence rate for the 20 year Chingford Study and the

incidence rate between each 5-year time-point to be calculated. For each of these incident rates the inclusion criteria at the *beginning* of each time period was the same; the subject's KL grade was either 0 or 1. The number of subjects in this group at the beginning of each time period provided the total number for the denominator of the incidence rate calculation. Those subjects whose KL grade increased to ≥ 2 during the time period were the incident group and formed the numerator of the incidence rate calculation. Those that did not progress were the non-progressor group. This is summarised in Figure 3.7.

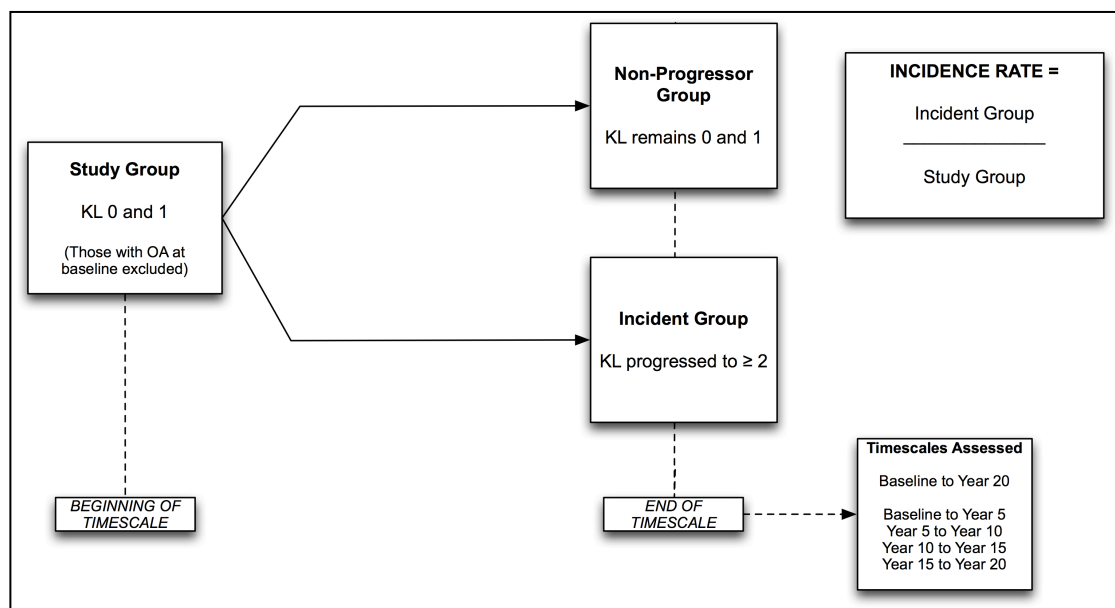


Figure 3.7 – Overview of the terminology and the calculation of the incidence rate for knee arthritis in the Chingford Study

The time periods over which the incidence rates were calculated were:

- Baseline to development of disease at any point in the 20 year study
- Baseline to Year 5
- Year 5 to Year 10
- Year 10 to Year 15
- Year 15 to Year 20

For each of the five time periods listed above, the entry criteria were that the subjects' radiographic KL grade was 0 or 1. Since not all subjects attended all visits, the study group for visit-to-visit incidence rate includes only those who attended the next visit for radiographic assessment. The summary of the incidence rate study structure is shown in Figure 3.8.

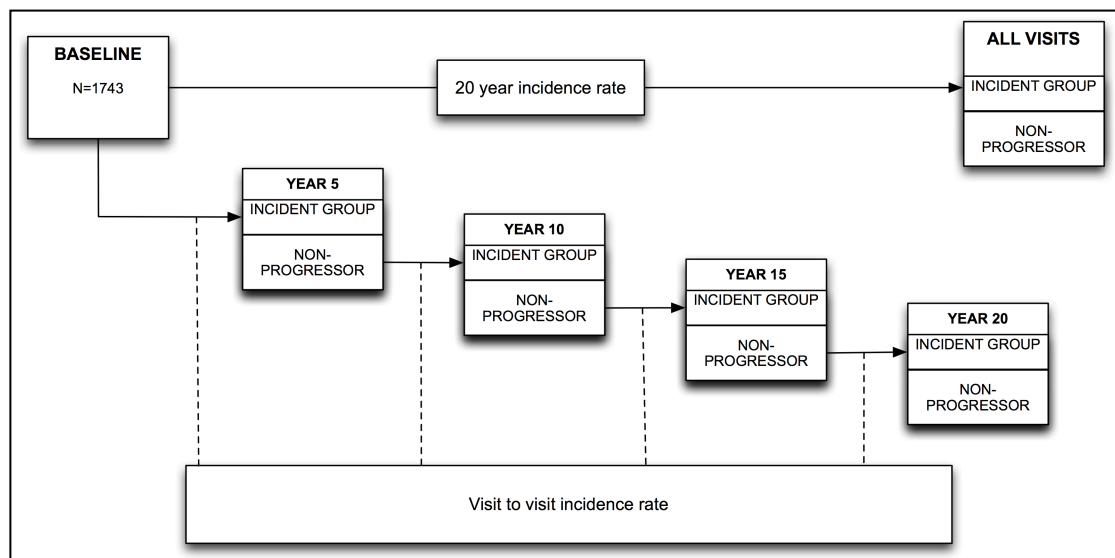


Figure 3.8 - Summary of incidence rate study structure, with the 20 year incidence rate study and the visit to visit to incidence rate study outlined.

3.8.3 Results

3.8.3.1 Overall incidence of OA in Chingford

The overall incidence rate of knee OA during the Chingford Study was 0.49 (summarised in Table 3-10). This means that subjects with no OA at the beginning of the study had a 49% chance of developing OA during the study. Eighty-two percent of the OA that developed during the study was medial OA, with an overall incidence rate of 0.40.

Study Group (N)	Incident Group (N)	Overall Incidence	Compartmental Pattern	N (% of incident Group)	Incidence by joint compartment
1743	846	0.49	Medial	695 (82)	0.40
			Lateral	151 (18)	0.09

Table 3-10 - Incidence of OA over whole Chingford Study- Baseline to maximum KL measured during study. Overall incidence rate and incidence rate by knee compartment are shown.

3.8.3.2 Visit to Visit Incidence of knee OA in the Chingford Study

The incidence rate from visit-to-visit in the Chingford study is summarised in Table 3-11. The mean age of the incident and the non-progressor groups are summarised in Table 3-12.

<i>Visit</i>	<i>Study Group (N)</i>	<i>Incident Group (N)</i>	<i>Overall Incidence Rate</i>	<i>OA Compartment Pattern</i>	<i>N (% of incident Group)</i>	<i>Compartmental Incidence</i>
Baseline - Year 5	1508	148	0.1	Medial	102 (69)	0.067
				Lateral	46 (31)	0.033
Year 5 to Year 10	1255	175	0.14	Medial	123 (70)	0.1
				Lateral	52 (30)	0.04
Year 10 to Year 15	872	144	0.17	Medial	97 (67)	0.11
				Lateral	47 (33)	0.06
Year 15 to Year 20	590	357	0.61	Medial	246 (69)	0.42
				Lateral	110 (31)	0.19

Table 3-11 – Incidence of knee OA in the Chingford Study - Visit-to-Visit. Overall incidence rate and incidence rate by knee compartment are shown.

The incidence rate gradually increases from 0.1 between baseline and year 5 to 0.14 and 0.17 in the subsequent 5 yearly visits before a large jump in incidence to 0.61 between year 15 and year 20. The mean age of the incident groups increases from 60.5 years for the baseline-to-year-5 group to 72 years for the year-15-to-year-20 group.

Visit	Group	Mean Age (Years)
Baseline - Year 5	Non-Progressor	58.5
	Incident	60.5
Year 5 to Year 10	Non-Progressor	63.2
	Incident	65.3
Year 10 to Year 15	Non-Progressor	67.5
	Incident	67.3
Year 15 to Year 20	Non-Progressor	72
	Incident	71.4

Table 3-12 – Summary of the age in years of the non-progressor and incident groups in the Year-to-Year incidence rate study.

3.8.4 Severity of incident OA development

Table 3-13 summarises the final KL grade of the medial OA incident group. Thirty-one subjects (4.5%) who had no knee OA at the beginning of the study progressed to a knee replacement during the study. The majority of the subjects (55.5%) who developed OA during the study ended the study as KL grade 2. Thirty eight percent and 2% progressed to KL grades 3 and 4 respectively.

	Final KL Score				Total
	2	3	4	5	
Medial OA Incident Group N (%)	385 (55.4%)	265 (38.1%)	14 (2%)	31 (4.5%)	695

Table 3-13 – A table showing the KL grade to which the medial OA incident group progressed during the Chingford Study

3.9 The timescale of progression of anteromedial OA

3.9.1 Introduction

This section investigated the timescale of medial OA progression. The two patterns of progression investigated were:

- 1 Normal knee (KL 0,1) to any OA (KL 2,3,4,5)
- 2 Early OA (KL 2,3) to more advanced OA (KL 4,5).

The aim of this part of the study was to translate the study of incidence described above in section 3.8 to clinical situations and to be able to counsel patients in a clinical setting about the risk of arthritis progressing and the timescale over which it may progress. Whilst there were several methods available to describe the progression of arthritis the aim was to be able to provide a risk of progression that could be explained to patients. Therefore, the method used was a life table analysis since this provided a percentage of cases that progressed over a time period.

The specific KL score cut offs to investigate were chosen because KL4 is the grade at which the surgical management options would include joint replacement and KL5 is when the knee joint has already undergone joint replacement. These are the stages of disease about which patients with an earlier stage of disease often enquire and want to know the time that it may take for them to progress to this stage of disease. Outcome data has shown that knee arthroplasty performed on knees without bone on bone changes may have proportionately less post operative improvement in comparison to

those subjects with established bone on bone changes to their native joint improvement [35].

3.9.2 Method

Life table analysis is a statistical technique usually associated with survival analysis of joint replacements [192]. To construct a life table the number of subjects being investigated and the number of both failures and withdrawals are determined for each year after the commencement of the study. The number withdrawn must include those who have died, lost to follow up or have reached the end of their period of assessment in the trial. The first year therefore starts with the total number in the study and in subsequent years the number falls away gradually. The definition of failure, called a terminal event, must be set at the beginning of the study. This process of calculating a life table is summarised in Table 3-14.

To transfer this technique to the progression of arthritis the definition of a terminal event was set as progression of arthritis. The study design is outlined in Figure 3.9. Specifically, the definition of terminal event for the first aim; assessment of progression from a normal knee to arthritis of any grade, was the point at which the KL score of a subject progressed from either KL 0 or 1 to $\geq$ KL 2. A sub-study further investigated the incident group timescale of progression dependent on the final KL score progressed to during the study. One group progressed to early or moderate arthritis (KL 2 or 3) and the other group progressed to advanced arthritis or arthroplasty (KL 4 or 5).

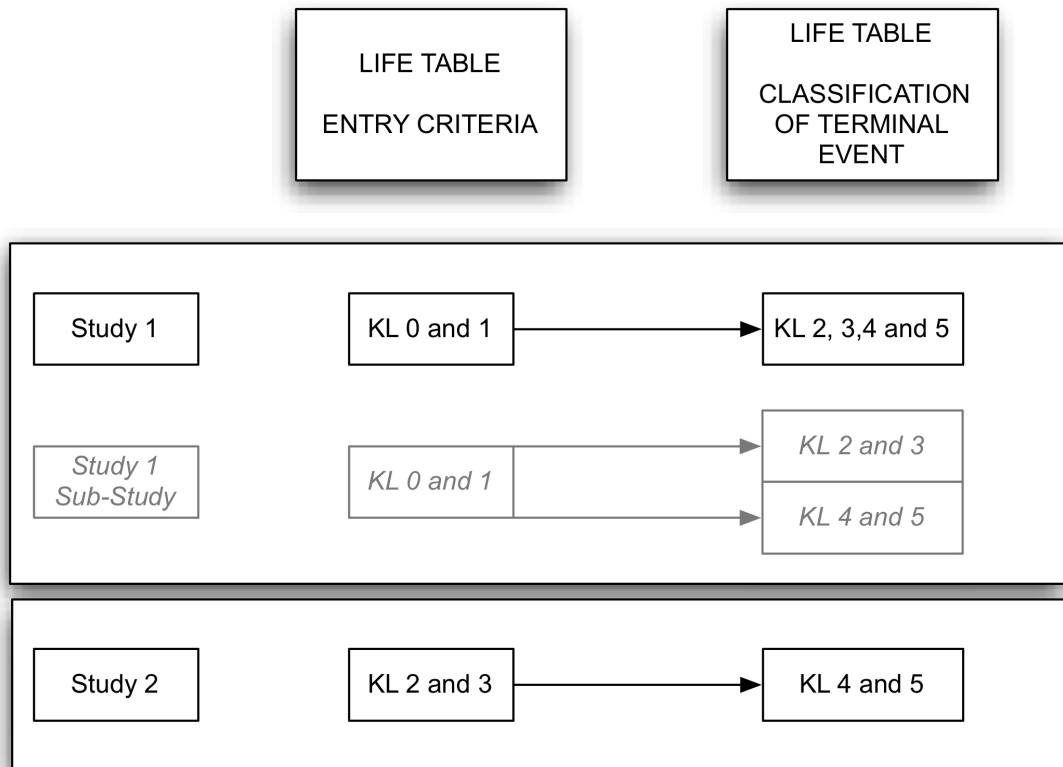


Figure 3.9 – Outline of the life table inclusion criteria and definition of terminal event for the study of the timescale of progression of arthritis in the Chingford Study.

The definition of terminal event Study 2 outlined in Figure 3.9 above; assessment of progression from early arthritis to advanced arthritis was the point at which the KL score of the subject progressed from KL 2 or 3 to KL 4 or 5.

Life tables were constructed and the number of cases progressing at each five-year time point were reported.

<i>Interval Start Time</i>	<i>N</i>	<i>Withdrawn</i>	<i>At Risk (N)</i>	<i>Terminal Events (N)</i>	<i>Proportion Terminating</i>	<i>Proportion Surviving</i>	<i>Cumulative Proportion Surviving at End of Interval</i>	<i>Cumulative Percentage Arthritis Progression</i>
Visit Number	Total number of cases at the beginning of the time period	Withdrawn due to death, loss to follow up and end of study	Number entering interval subtract half the number of withdrawals	Number of subjects with arthritis progression	Number terminating divided by number at risk	1-proportion terminating	Product of present and all previous proportion surviving	(1-cumulative proportion)x100

Table 3-14 – Summary of the method of constructing a life table

3.9.3 Results

3.9.3.1 Progression of incident group

The life table analysis of the progression of the incident group is shown in Table 3-15. As a reminder, the incident group is defined as those that entered the study with no radiographic OA and subsequently developed OA whilst in the study. Understanding the definition of the incident group explains why the life table shows that all cases develop OA by 20 years. The cumulative percentage risk of progression in the incident group was 19% at five years and almost half of the group (45%) had progressed by ten years. Overall there were 143 new cases of progression at five years, a further 194 at ten years, 138 at fifteen years and an increase to 266 at twenty years. This increase between year 15 and year reflects the known increase in incident OA between year 15 and year 20, described in Section 3.8.3.2.

<i>Time (Years)</i>	<i>N</i>	<i>Withdrawn</i>	<i>At Risk (N)</i>	<i>Terminal Events (N)</i>	<i>Proportion Terminating</i>	<i>Proportion Surviving</i>	<i>Cumulative Proportion Surviving at End of Interval</i>	<i>Cumulative Percentage Arthritis Progression (%)</i>
0	741	0	741	0	0	1	1	0
5	741	0	741	143	0.19	0.81	0.81	19
10	598	0	598	194	0.32	0.68	0.55	45
15	404	0	404	138	0.34	0.66	0.36	64
20	266	0	266	266	1	0	0	100

Table 3-15 – A life table to show proportion of the incident cohort (KL 0 or 1 at baseline) progressing to arthritis (KL $\geq$ 2), in 5 year time brackets.

<i>Max KL score</i>	<i>Time (Years)</i>	<i>N</i>	<i>Withdrawn</i>	<i>At Risk (N)</i>	<i>Terminal Events (N)</i>	<i>Proportion Terminating</i>	<i>Proportion Surviving</i>	<i>Cumulative Proportion Surviving</i>	<i>Cumulative percentage progression</i>
2 or 3	0	668	0	668	0	0	1	1	0
	5	668	0	668	86	0.13	0.87	0.87	13
	10	582	0	582	121	0.21	0.79	0.69	31
	15	461	0	461	146	0.32	0.68	0.47	53
	20	315	0	315	315	1	0	0	100
4 or 5	0	45	0	45	0	0	1	1	0
	5	45	0	45	0	0	1	1	0
	10	45	0	45	3	0.07	0.93	0.93	7
	15	42	0	42	13	0.31	0.69	0.64	36
	20	29	0	29	29	1	0	0	100

Table 3-16 – A life table separating the incident group into cases that progressed to KL 2 and 3 and cases that progressed to KL 4 and 5.

The life table analysis of the sub-study separating the incident cohort into those that progressed to KL 2 and 3 (early and moderate OA) and those that progressed to KL 4 and 5 (advanced OA and arthroplasty) is shown in Table 3-16. Forty-five cases in the incident group developed advanced OA. No cases developed advanced OA within 5 years and three cases (7%) developed advanced OA by ten years. Thirty-six percent developed advanced disease by 15 years and the remaining 29 cases developed advanced OA by 20 years

The age and the progression of the advanced OA sub-group are shown graphically in Figure 3.10. This shows that there is no overall pattern to the timescale of the progression from no OA to end stage OA.

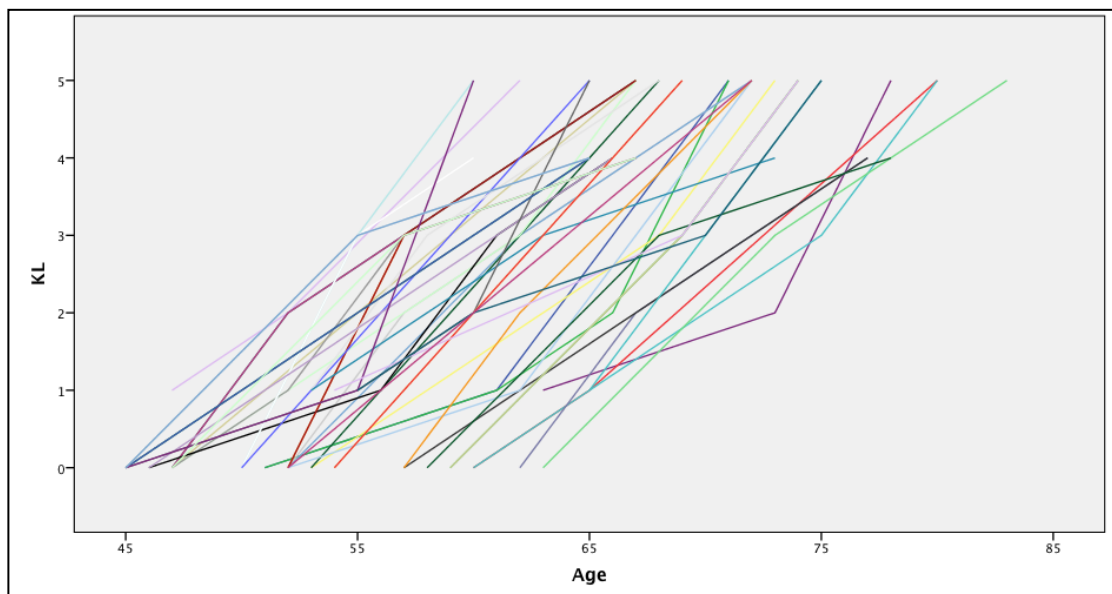


Figure 3.10 – A graph to show the age and KL score of all those in the incident group who subsequently developed advanced arthritis.

3.9.3.2 Progression of early arthritis to advanced arthritis

The progression of early OA to advanced OA for all cases is shown in Table 3-17. This table includes all subjects with early medial arthritis, defined as KL 2 or 3, meaning that both those who already had OA at the beginning of the study and those in the incident group who subsequently developed early medial OA are included. The terminal event is a radiographic KL grade of 4 or 5 (advanced OA). Since not all cases in this group develop advanced OA the cumulative percentage at 20 years is not 100%.

<i>Time (Years)</i>	<i>N</i>	<i>Withdrawn</i>	<i>At Risk (N)</i>	<i>Terminal Events (N)</i>	<i>Proportion Terminating</i>	<i>Proportion Surviving</i>	<i>Cumulative Proportion Surviving at End of Interval</i>	<i>Cumulative Percentage Arthritis Progression (%)</i>
0	545	1	544.5	0	0	1	1	0
5	544	189	449.5	14	0.03	0.97	0.97	3
10	341	133	274.5	22	0.08	0.92	0.89	11
15	186	91	140.5	9	0.06	0.94	0.83	17
20	86	74	49	12	0.24	0.76	0.63	37

Table 3-17 – A life table to show risk of progression from early arthritis (KL 2 or 3) to advanced arthritis (KL 4 or 5), in 5 year time brackets.

The cumulative 20 year risk of progression to bone on bone medial OA from early OA is 37%. The 5-year risk is low at 3% but this increases to 11% at 10 years and 17% at 15 years.

3.10 Summary of results

The aims of this chapter were to describe the prevalence of anteromedial OA in a longitudinal cohort, to define the normal age of each KL grade and to then investigate the incidence of new cases over this twenty-year period and describe the timescale of progression of the disease. The overall aim was to provide information to clinicians to discuss with the general population regarding the time of progression of knee arthritis towards a pattern and severity, which might need treatment with arthroplasty.

The prevalence of knee arthritis generally in the population was 53.7% and that of anteromedial arthritis was 43%. The mean age of the earliest radiographic OA (KL2) was 66.6 years and the mean age of advanced arthritis (KL4) was 68.6 years. The age of those with KL 2 was normally distributed with a standard deviation of seven years. The age of subjects with no arthritis on plain radiograph was significantly younger at 57.6 years.

The incidence of knee OA over the twenty year Chingford Study was 0.49 for any knee arthritis and for anteromedial OA was 0.40. This means that

almost 50% of subjects with no OA at the baseline visit developed radiographic arthritis during the study and eighty percent of this was anteromedial OA. The timescale for progression to arthritis of the 40 % of subjects who were in the incident group was approximately:

- 20% at 5 years,
- 45% at 10 years
- 65% at 15 years
- 100% at 20 years.

Six and a half percent of the anteromedial OA incident group progressed to advanced disease or arthroplasty during the study whereas 93.5% progressed to early or moderate OA. If these results are translated to a standard female population, of those who are age 60 with no signs of OA, 40% will develop anteromedial OA by age 80, 6.5% of which will be end stage or 'bone-on-bone' disease. The population risk of developing end stage OA by age 80 with a normal knee at age 60 is therefore 2.6%, since 40% of the population develop AMOA and 6.5% of this is advanced disease.

In the overall study population, the risk of those with early or moderate knee OA progressing to end stage OA was:

- 3% at five years
- 11% at ten years
- 17% at 15 years
- 37% at 20 years

At age sixty, 27.7% of the Chingford population already had radiographic signs of OA. Only one percent of the OA was end stage OA. The results of the progression of early OA to end stage OA study show that almost 40% of these subjects will have progressed to advanced anteromedial OA by age 80. This equates to ten percent of the whole Chingford Study population (37% risk of progression in 27.7% of the population).

In summary, the 20-year risk of a 60-year-old lady with no OA developing end stage OA is 2.6%. The 20-year risk of a 60-year-old lady with early OA progressing to advanced OA is 37%.

4 KneeMorf – The design and validation of a radiographic angle measurement software

4.1 Introduction

This work in this chapter describes the design and validation of a software application to provide accurate, reproducible anatomical lower limb alignment and proximal tibial alignment measurement from a plain radiograph. The software, KneeMorf, was a collaborative project and this author designed the components to assess limb alignment.

KneeMorf was a software programme designed for two main purposes. The first was to store patient demographics and link this data to radiographic qualitative scores to allow assessment of the epidemiology of arthritis. The second was to measure the bony anatomy and alignment of the plain radiograph and store the results in a database. The aim was to design an application capable of automatic retrieval of a patient specific radiograph from a database and automatic calibration of the radiograph. The software would then enable a validated step-by-step process to measure the bony anatomy of the limb on the radiograph. A long-term aim was not only to use this software to assess the radiographs from the Chingford Study, described in section 3.3 but also to allow future additional modules to enable KneeMorf to be used on other cohorts.

There was no existing software that was capable of fulfilling the needs of radiographic assessment of this thesis. Therefore, KneeMorf was designed

in collaboration by this author with a clinical scientist and a software designer. The specifics of the database design and radiograph calibration have previously been described and validated [184]. This section describes the development of the programming and method used to measure the anatomical limb alignment and proximal tibial alignment and to subsequently validate these measurements. These were the role of this author.

4.2 Summary of literature

The literature regarding limb alignment in arthritis and its assessment using plain radiographs is reviewed in detail Section 1.5 and this is summarised here. Whilst mechanical and anatomical limb alignment are not the same, the literature shows that assessment of anatomical limb alignment correlates to the mechanical limb alignment. Additionally, the assessment of anatomical alignment on a short leg radiograph has been reported and validated against both long-leg radiographs and clinical assessments. However, the anatomical and mechanical alignment cannot be reliably converted to one another without knowledge of the femoral neck offset, which is only possible from a long-leg radiograph.

The measurement point described for assessment of alignment on a short leg radiograph at the femoral and tibial shafts is the mid-cortical point at 10cm from the joint line. The measurement point at the knee for the femur is the centre of the femoral notch and for the tibia is the point in-between the medial and lateral tibial spines.

The Chingford Study radiographs are standing AP radiographs, each taken by the same radiographer on the same equipment using a strict protocol. However, they are not long leg radiographs meaning that the centre of the hip and the centre of the ankle are not included on the radiograph. Therefore direct assessment of the mechanical alignment of the limb was not possible.

4.3 Validation of the use of Chingford short leg radiographs to assess anatomical limb alignment

4.3.1 Introduction

KneeMorf was designed primarily to assess the Chingford Cohort series of radiographs. These radiographs are antero-posterior (AP) radiographs as described in Section 3.3.3 but assessment of limb alignment would ideally be measured from a long leg radiograph including the hip, knee and ankle on one film, as described above in Section 1.5.

Whilst direct assessment of the mechanical alignment of the limb would have been the optimal assessment of limb alignment, the long-term nature of the Chingford Study provided a unique opportunity to investigate the role of limb alignment in the development of knee OA. Therefore, it was decided to accept the limitations that absence of long leg radiographs caused and to investigate the validity of the use of short-leg radiographs, which is described in Section 4.3.

This section investigates if assessment of radiographs performed using the same short leg radiograph protocol as the Chingford Study radiographs provides a precise measure of the anatomical limb alignment when compared to long leg radiograph assessment. If the short leg alignment were significantly different to the long leg alignment, then the use of KneeMorf to assess limb alignment on the short leg radiographs from the Chingford study would not be possible.

4.3.2 Method

A series of limb radiographs of twenty subjects were assessed. Each subject had undergone radiographs of the knee using two techniques. The first technique was an AP radiograph using the same short leg protocol as the Chingford Study radiographs. The second technique was a standardised standing long leg radiograph, including the hip, knee and ankle. These investigations were performed at the same visit.

The software selected to assess the radiographs was OsiriX, Pixmeo, Geneva. This is an open source DICOM viewing software with in-built measurement tools, allowing distance and angle measurements. OsiriX is in worldwide use and has been referenced and validated in over one hundred publications [193-196]. OsiriX was used to measure the anatomical limb alignment on both the short leg and long leg radiographs.

The short leg radiograph alignment was measured as the angle between the anatomical axis of the femur and tibia. The anatomical axis of the femur was from a point at the centre of the femoral shaft 100mm proximal to the

femoral joint line and a point at the centre of the femoral notch. The tibial axis was from the point central to the tibial spines to the point 100mm distal to the tibial joint line. The central point of the femoral and tibial shaft was identified as the centre of a circle, the diameter of which was from each cortical edge of the shaft (Figure 4.1). The long leg femoral axis was from the piriform fossa to the centre of the femoral notch. The long leg tibial axis was from the centre of the tibial spines to the centre of the talus at the ankle (Figure 4.2).



Figure 4.1 – Representation of the technique to assess the anatomical limb alignment on a short leg radiograph. The circles are based on diaphyseal cortical edge and the limb alignment bisects the centre of these circles.

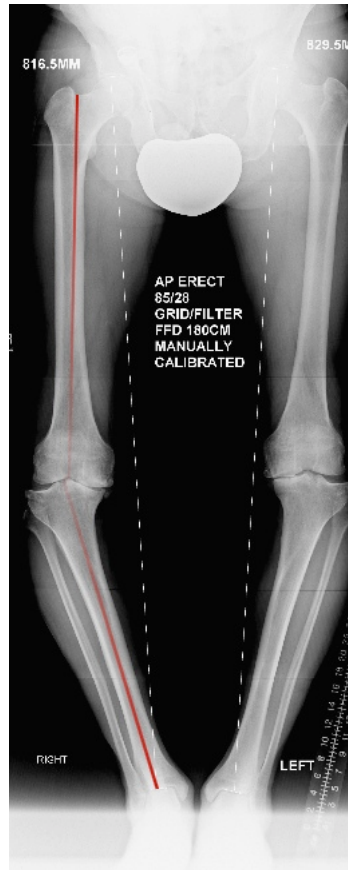


Figure 4.2 – Assessment of the long-leg anatomical axis. Lines are drawn from the piriform fossa to the centre of the femoral notch and from the centre of the talus to the centre of the tibial spines.

The angle measurements for both techniques were tabulated and assessed with a paired t-test, inter-class correlation and the limits of agreement were calculated from the standard deviation.

4.3.3 Results

A paired t-test showed that there was no difference between the long leg and short leg method of anatomical limb alignment assessment on average, with a mean difference of less than 0.5° and p-value of 0.344. The data is summarised graphically in Figure 4.3 with a line of best fit and the raw data

is shown in Appendix A. Inspection of the data shows two clear outliers, Cases 4 and 6. Assessment of the radiographs showed that these two cases had femoral shaft fractures, which were mal-united. These mal-unions were not visible on the short leg radiographs.

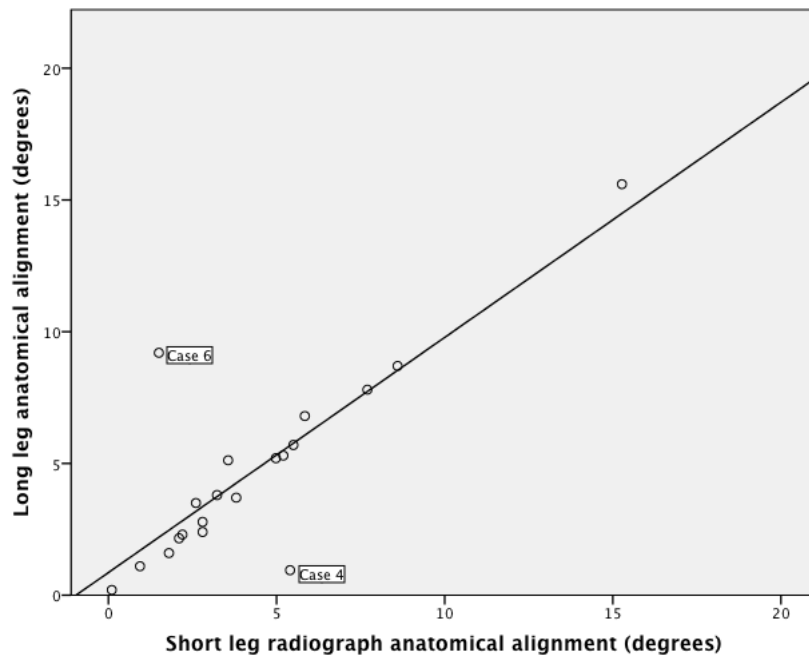


Figure 4.3 – Scatter plot of the long leg and short leg alignment measures from the validation study with a line of best fit. The outliers, with previous extra-articular fractures, are labeled.

Table 4-1 shows the mean and standard deviation (SD) of the long leg and short leg anatomical limb alignment measurements. The data is shown both for all cases and with the cases of fracture mal-union excluded. The SD of the difference between long and short leg radiographs was 2.06° when all cases were assessed. When the mal-unions were excluded the SD of the difference was 0.47° . The data is normally distributed, therefore the 95%

limits of agreement would be $\pm 2SD$ or $\pm 0.96^\circ$ if cases of mal-union were excluded or greater than 4° if mal-unions are present in the data set.

	<i>Long Leg</i> (°)	<i>Short Leg</i> (°)	<i>Difference</i> (°)
Mean (All cases)	4.70	4.30	0.40
SD (All cases)	3.64	3.39	2.06
Mean (Fracture excluded)	4.65	4.39	0.26
SD (Fracture excluded)	3.58	3.51	0.47

Table 4-1 – The mean and standard deviation (SD) of the long and short leg anatomical alignment measurements. The results are presented for all cases and with the post traumatic mal-unions excluded.

The intra-class correlation between the long leg measures and the short leg measures was 0.878, which is rated as an excellent agreement.

4.3.4 Summary of results

On average over a population there is no significant difference between the use of short and long leg radiographs to assess the anatomical limb alignment. However, if cases of mal-union are present the limits of agreement between the two methods are $\pm 4.12^\circ$, which is unacceptably high. If mal-union is excluded the limits of agreement are $\pm 0.96^\circ$, which is acceptable.

These results suggest that over a whole population in a study the use of short leg radiographs is acceptable, however cases of extra-articular malformation may be missed, which on an individual basis may cause alteration of the results between the two techniques. Cases from the Chingford study with past history of femoral or tibial fracture would need to be excluded from any study based on short limb radiographs.

4.4 KneeMorf – Measurement of knee alignment

The literature reviewed above guided the selection of points from which to measure the limb alignment. Additionally, sections 4.3 and 4.8 above have shown that the Chingford radiographs are suitable for assessment of limb alignment assessment.

The workflow of the KneeMorf software application has been described and validated elsewhere [184]. In summary, KneeMorf is programmed to create a database specifically for each study investigated. The database stores the calibration data to calibrate the radiographs from the specific study and visit number of the radiograph, based on the equipment used to capture the original image. The digital files of radiographs are named according to a defined protocol, which identifies the individual study participant and the visit number of the radiograph, for example the baseline or year 5 visits. The radiograph file is automatically opened and calibrated. KneeMorf then enables placement of pre-determined points to assess radiographic morphology. The regions selected are stored and the defined angles calculated. This section describes the definition of the regions to be selected

to assess the anatomical limb alignment and the proximal tibial alignment. The KneeMorf application window is shown in Figure 4.4.

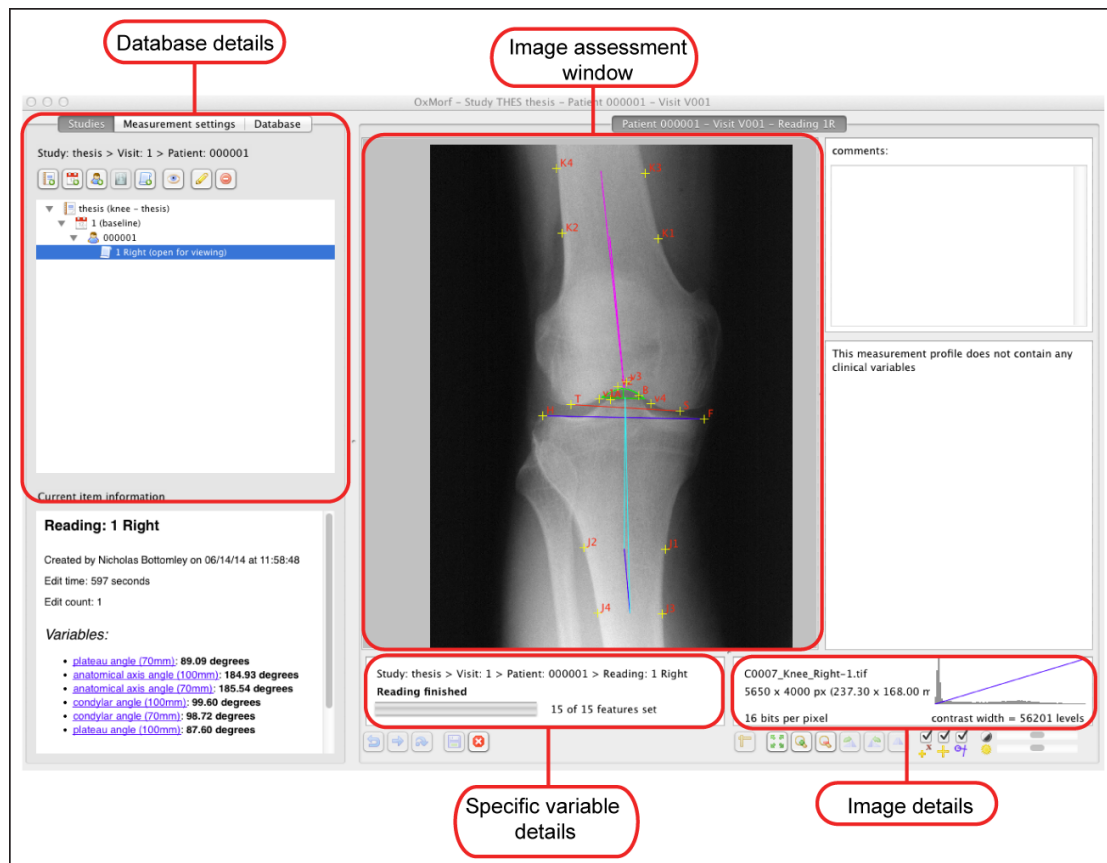


Figure 4.4 – A screenshot of the KneeMorf software application window.

4.4.1 Anatomical alignment assessment measurement points

The selection of the measurement points in KneeMorf were based on the literature outlined above in section 4.2. The anatomical limb alignment was described by the angle between the anatomical axis of the femur and the anatomical axis of the tibia. The anatomical axis of the femur was defined as the axis from the mid-cortical point 10 cm proximal to the knee joint to the point in the centre of the femoral notch. The anatomical axis of the tibia was defined as the axis from the point in the centre of the tibial spines to the mid-

cortical point 10 cm from the joint line. A neutral axis, when the lines from the anatomical axes of the tibia and femur were co-linear, was reported as an anatomical axis of 180° . A varus alignment was when this axis was less than 180° and a valgus alignment was when this axis was greater than 180° . These assessments were repeated to provide an axis based on the mid-cortical points at 7cm from the joint to attempt to include a greater number of Chingford radiographs in the study, since at the KneeMorf design stage it was unknown what proportion of Chingford radiographs would include both the femoral and tibial shafts at 10 cm from the joint

4.4.2 Femoral anatomical axis selection

The centre of the femoral intercondylar notch was defined using Bezier curve mapping of the intercondylar area [184]. The Bezier curve was manually segmented to match the bony anatomy of the intercondylar area and KneeMorf was programmed to select the most proximal point along the Bezier curve. This is shown in Figure 4.5.

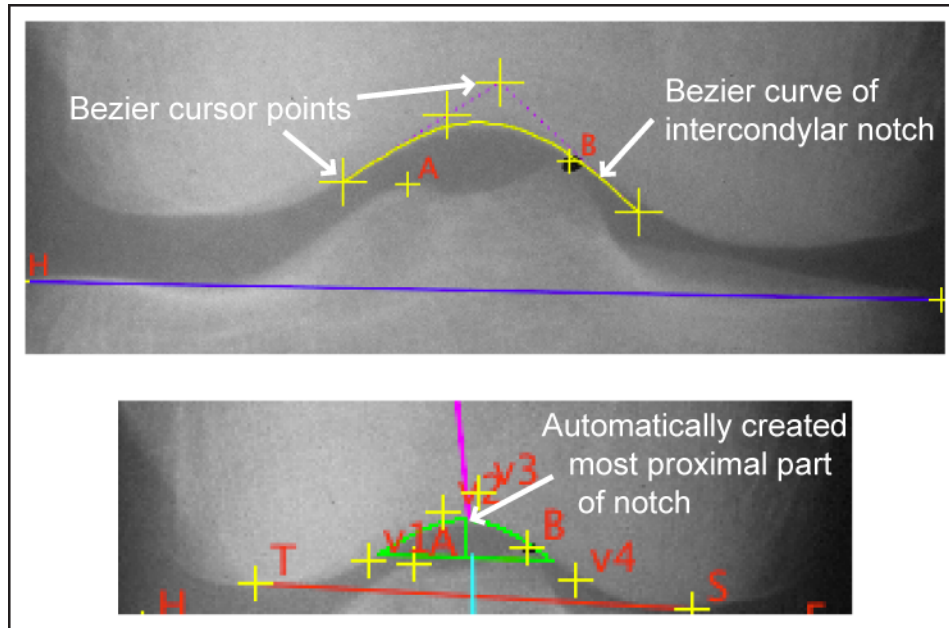


Figure 4.5 – A screenshot of KneeMorf to show the Bezier curve mapping of the intercondylar notch (yellow line in top picture) and the automatic definition of the most proximal part of the notch (green line within the green arc in the bottom picture).

The mid-cortical point was selected at both 7 and 10cm from the distal femur. To define the distal femur the most distal point of both the medial and lateral femoral condyles were manually selected using a specially designed selection cursor. This cursor consisted of a long horizontal bar, to allow accurate assessment of the most distal point of the condyle and a short vertical bar to define the exact distal point. This process is shown in Figure 4.6. The line between the medial and lateral distal femoral points provided the distal femoral axis.

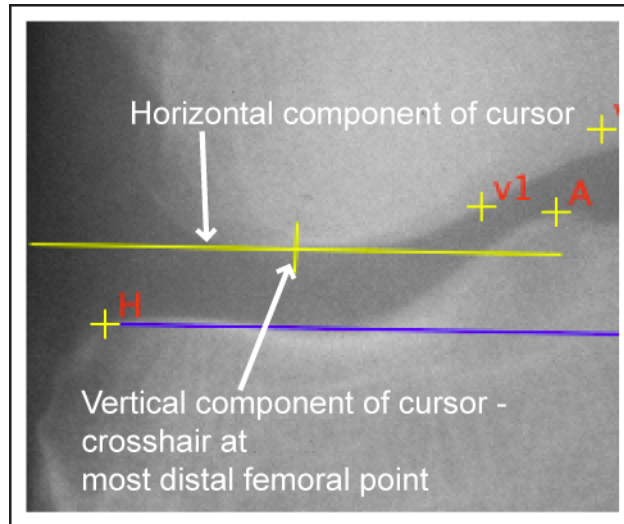


Figure 4.6 – A screenshot to show the cursor positioning to define the most distal point of the lateral femoral condyle.

To define the femoral mid-cortical point at 10cm proximal to this distal femoral axis, KneeMorf automatically calculated a line parallel and 10cm proximal to the distal femoral axis. Selection cursors were limited to movement along this line, ensuring that they remained 10 cm proximal to the distal femur. The medial and lateral cortical edges of the femoral shaft were then manually selected and KneeMorf automatically calculated the mid-point between these two cortical edges to define the mid-cortical point. This process was repeated at 7cm proximal to the distal femur.

The line between the intercondylar notch and the mid-cortical point at 10cm provided the femoral anatomical axis (10cm) and the line to the mid-cortical point at 7cm provided the femoral anatomical axis (7cm). This process is shown in Figure 4.7.

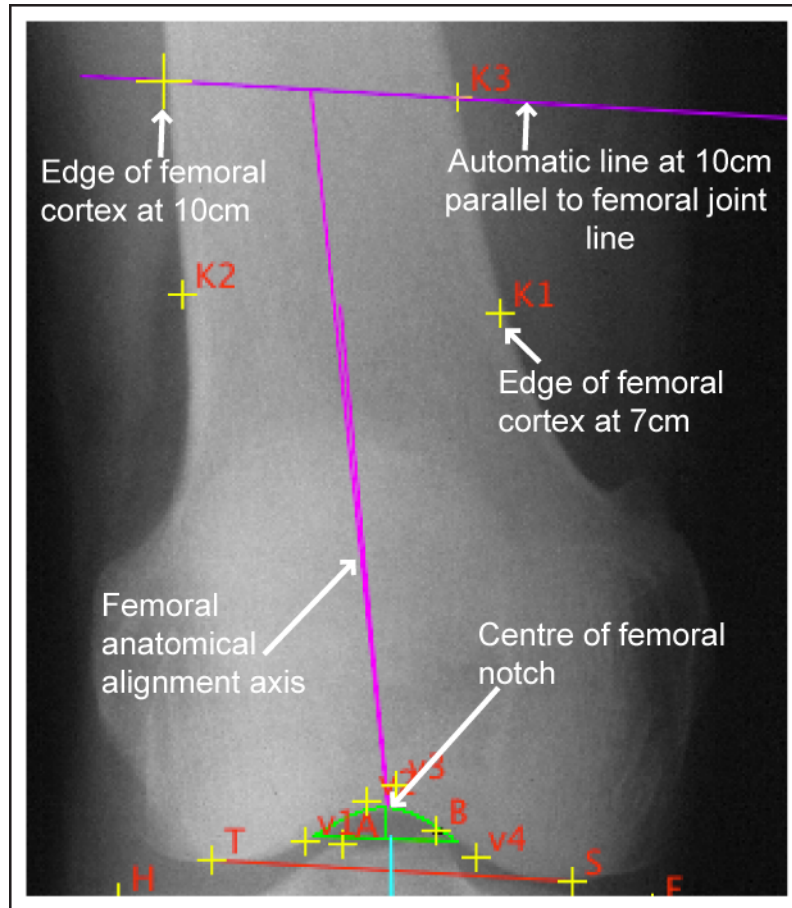


Figure 4.7 – A screenshot to show the selection of the edge of the femoral cortex at 7cm and 10cm proximal to the distal femur. The anatomical femoral axes for 7cm and 10cm femoral measurements are shown in purple.

4.4.3 Tibial anatomical axis selection

The tibial anatomical axis was defined as the point central to the medial and lateral tibial spines to the mid-cortical point at both 7 and 10cm from the tibial surface.

The centre of the tibial spines was defined by manually placing a cursor at the highest point of each of the medial and lateral tibial spines. KneeMorf automatically calculated the mid-point between these two cursors.

The tibial surface was defined as the line between the most medial point of the tibial plateau and the most lateral point of the tibial plateau, excluding osteophytes. These points were manually selected and the line between them was automatically calculated. This is shown in Figure 4.8.

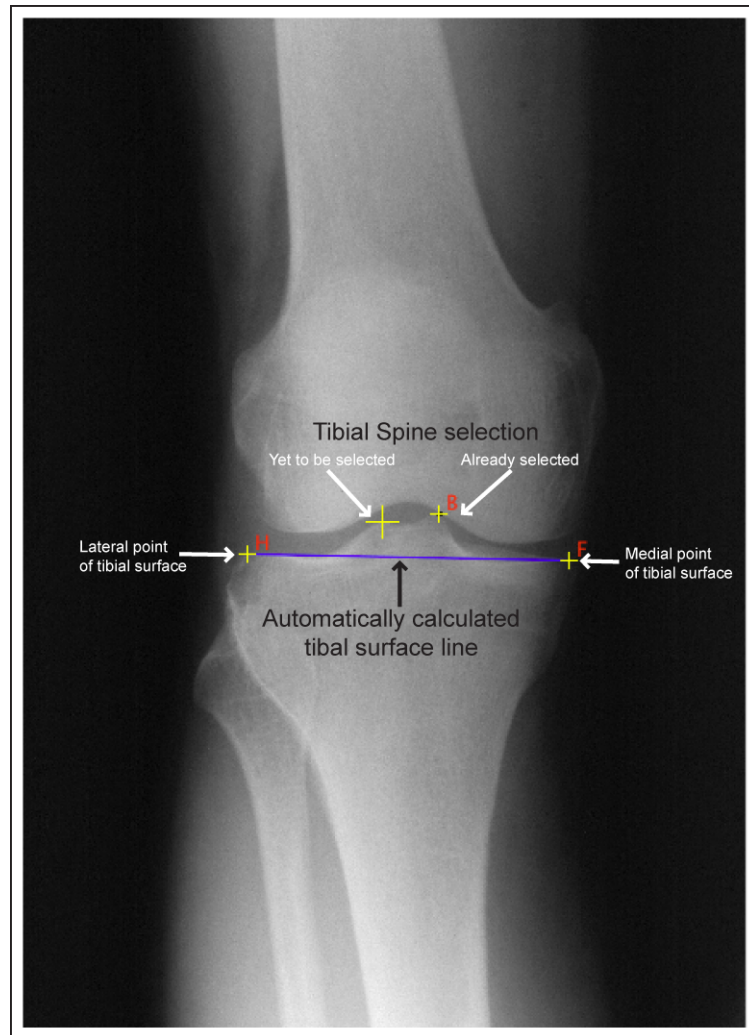


Figure 4.8 – A screenshot to show the selection of the tibial spines and the tibial surface joint line (shown in blue)

KneeMorf automatically calculated a line parallel and 10cm distal to the tibial surface. Selection cursors were limited to movement along this line, ensuring that they remained 10 cm distal to the tibial bony surface. The

medial and lateral cortical edges of the tibial shaft were then manually selected and KneeMorf automatically calculated the mid-point between these two cortical edges to define the mid-cortical point. This process was repeated at 7cm distal to the tibial bony surface.

The line between the centre of the tibial spines (which was automatically generated by KneeMorf) and the mid-cortical point at 10cm provided the tibial anatomical axis (10cm) and the line to the mid-cortical point at 7cm provided the tibial anatomical axis (7cm), shown in Figure 4.9.

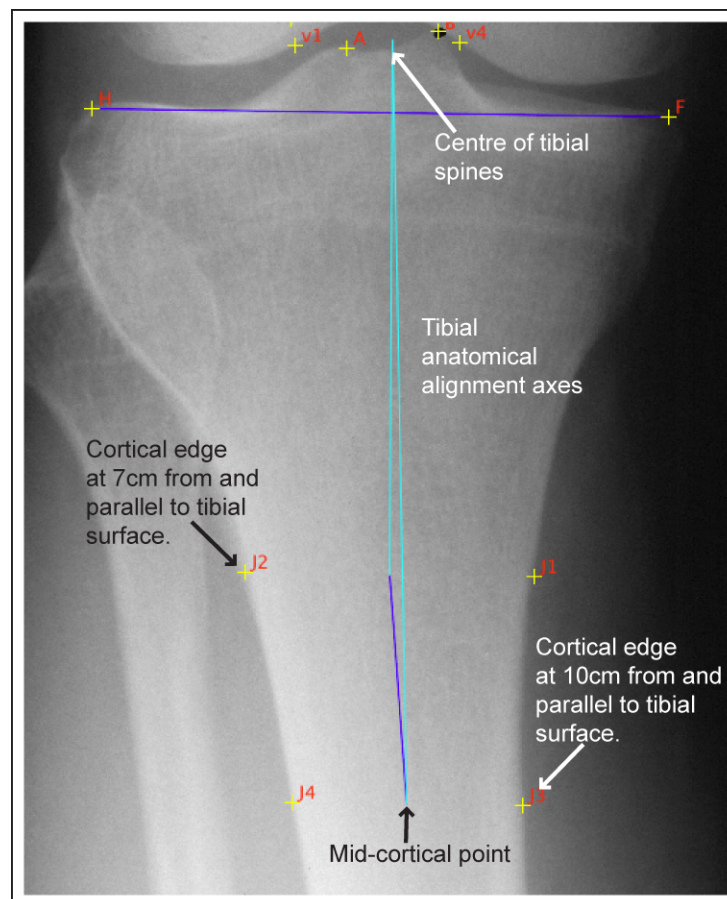


Figure 4.9 – A screenshot to show the tibial anatomical axis (cyan lines) from the centre of the tibial spines to the mid-cortical point at 7cm and 10cm. The cortical edges are selected along a line parallel to the tibial joint line (horizontal blue line).

The limb anatomical axis was defined as the angle between the tibial and femoral anatomical axes, shown in Figure 4.10.

4.4.4 Medial proximal tibial angle assessment

The medial proximal tibial angle (MPTA) was described by the angle between the tibial surface at the joint line and the anatomic axes running to the mid-cortical points at 7 and 10cm from the tibial surface, shown in Figure 4.10.

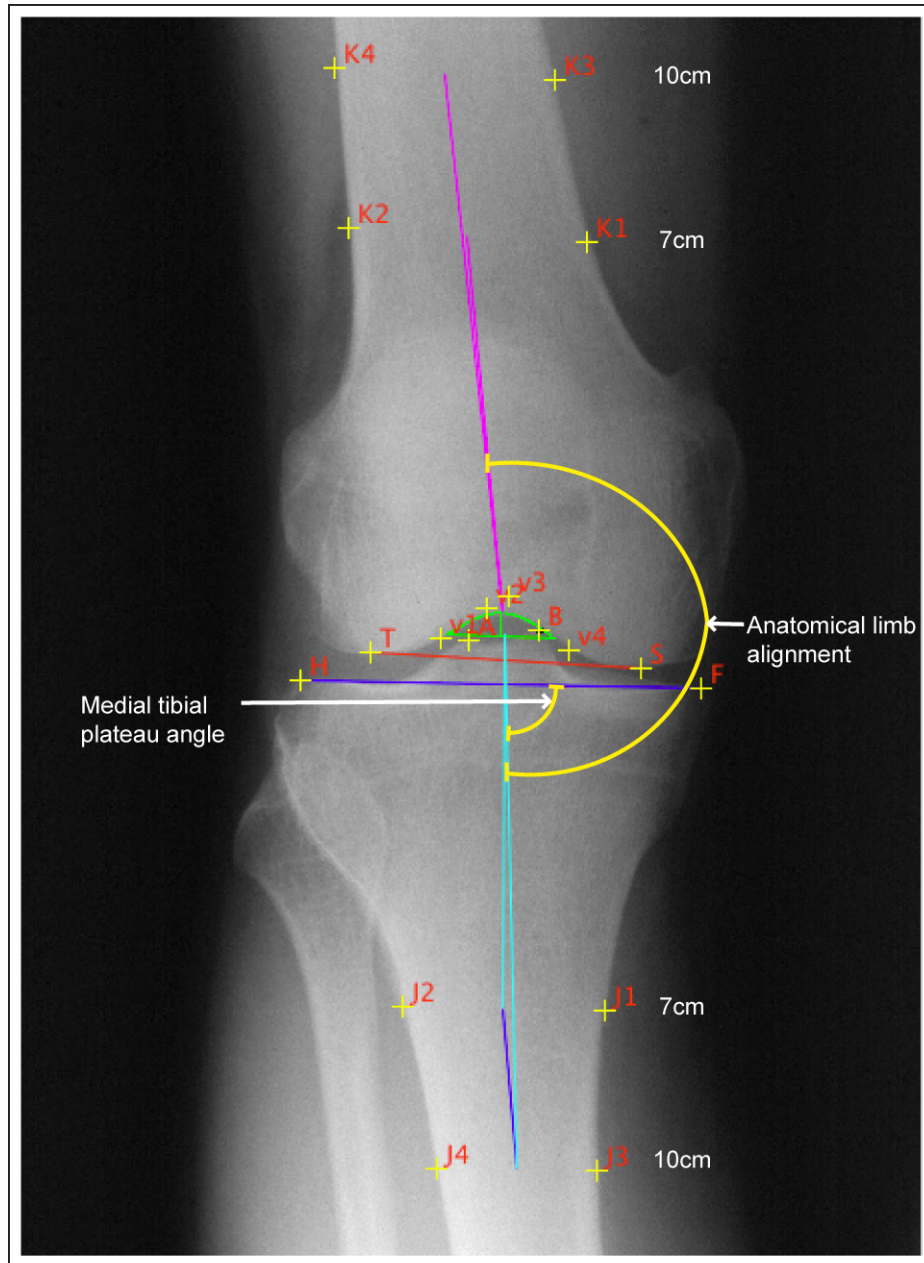


Figure 4.10 – A screenshot to show the femoral anatomic axes at 7cm and 10cm (purple), the tibial anatomic axes at 7cm and 10 cm (cyan) and an annotation to show the anatomical limb axis and medial tibial plateau axis (yellow).

4.5 The initial testing of KneeMorf: The validity of KneeMorf assessment in comparison to known measurement data

4.5.1 Introduction and Aims

The KneeMorf software had been designed to measure anatomical limb alignment and the medial tibial plateau angle. However, before KneeMorf could be used to assess limb alignment from a radiograph it was necessary to assess the validity of the software in two main ways.

The first aim was to investigate the repeatability of the measurements when assessing specific points. The second aim was to validate the measurements generated by the software against known angles and distances. In other words, it needed to be shown that when KneeMorf was used to assess an angle or distance of a known value that it returned the same value. Therefore, KneeMorf was tested against a range of measurements.

4.5.2 Method

Using calibrated graphpaper a diagrammatic outline of a knee was drawn. At defined points on this paper were placed markers to represent the selection points for the KneeMorf programme. The graphpaper allowed the calibration programme of the KneeMorf software to be set. The knee outline was marked with the specific points that the KneeMorf programme should

select, shown in Figure 4.11. To allow a range of angles to be generated accurately, the template was scanned electronically to Photoshop CS4 (Adobe, USA), an image manipulation software. The distal femur and the proximal tibia were segmented and rotated in 5° increments with relation to the femoral and tibial shaft respectively. This provided seven different angle values to assess, to allow investigation of any change in measurement error as the value measured changed. The angles created for each measurement are outlined in Table 4-2.

	<i>Anatomical limb alignment (°)</i>	<i>MTPA at 100mm (°)</i>
Angles for measurement	165	75
	170	80
	175	85
	180	90
	185	95
	190	100
	195	105

Table 4-2 – Angles to be assessed in the graphpaper validation of KneeMorf.

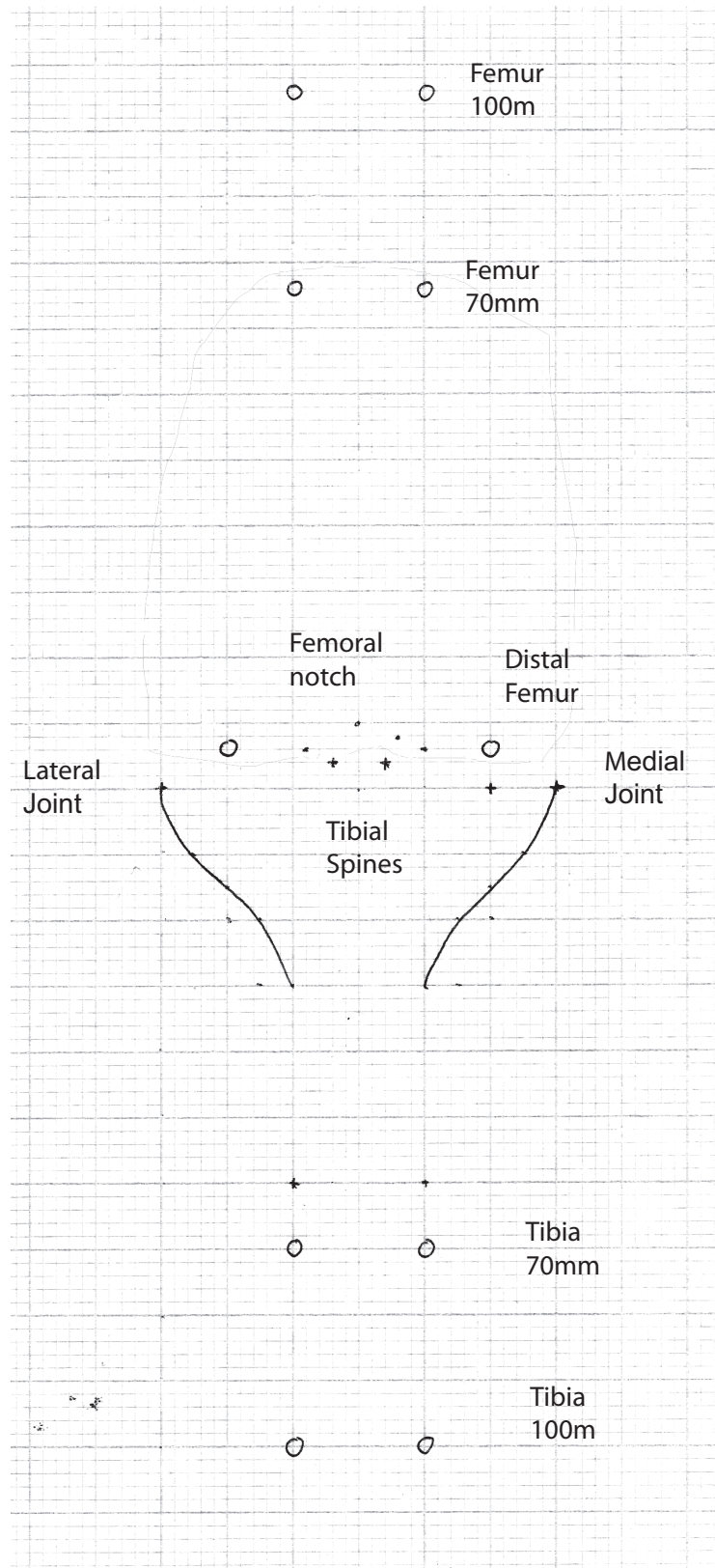


Figure 4.11 – The test template against which KneeMorf was validated. The markers that acted as the selection points for the KneeMorf programme are annotated. The curve of the tibial plateau has been drawn in to aid interpretation but was unnecessary for the point selection.

The images were imported to KneeMorf, calibrated and the points selected as per the software protocol. For the reproducibility study each measure was repeated three times each at a weekly interval to protect against measurement bias.

To assess the accuracy of KneeMorf against the graphpaper gold standard, mean measurement from the three weekly measurements were calculated and compared to the known graphpaper measurements using intra-class correlation coefficients (ICC), co-efficient of variation and the standard deviation of the difference between the measurements. The co-efficient of variation reports the percentage variation between the values of a “gold standard” measurement technique and a new method; in this case the measurements from KneeMorf. It is calculated by dividing the within subject SD by the sample mean. A variation of less than 10% is considered to be acceptable. Whilst a weakness of this assessment is the reliance on the sample mean, in this case the test measurements are on the same sample, so the means will be very similar. The advantage of the co-efficient is that it provides an easy comparison between techniques. The method is summarised on the data assessing KneeMorf measurement of anatomical limb alignment in Table 4-7.

This was performed for the medial tibial plateau angle (MTPA) and the anatomical limb alignment.

4.5.3 Results

The raw data from the measurements are summarised below in Table 4-3.

Scatter graphs summarising the data and Bland Altman plots showing the mean of the values plotted against the difference between the measurements are shown in Appendix A.

<i>Variable</i>	<i>Gold Standard (°)</i>	<i>KneeMorf 1 (°)</i>	<i>KneeMorf 2 (°)</i>	<i>KneeMorf 3 (°)</i>
MPTA	90	89.9	89.9	89.9
	95	94.1	94.3	94.5
	85	85.6	85.6	85.5
	100	98.8	98.8	98.8
	80	81.2	81.3	81.2
	105	103.9	103.5	103.7
	75	76.4	76.2	76.4
Anatomical Limb Alignment	180	179.9	179.9	179.7
	175	175.2	174.5	175.2
	185	185.1	185.2	184.8
	170	170.0	170.3	169.5
	190	190.2	190.0	190.0
	165	165.2	164.9	165.2
	195	194.7	194.9	194.9

Table 4-3 Validation measurements of anatomical limb alignment and MPTA in degrees, showing the gold standard measurement from the validation image and the repeated measurements from KneeMorf.

4.5.3.1 Results - Repeatability

The intra-class correlation between the repeated measurements are summarised in Table 4-4. The correlation between the repeated measures for the MPTA was 1.0 and the anatomical alignment was 0.99, which are both rated as excellent.

The coefficient of variation calculations are summarised below in Table 4-5. The coefficient of variation for alignment was 0.13% and for MPTA was 0.14%. The within subject standard deviation was 0.12° for the MPTA assessment and 0.25° for the alignment assessment. The 95% limits of agreement between the repeatability measurements were therefore $\pm 0.24^\circ$ and $\pm 0.5^\circ$ for the MPTA and the alignment respectively.

<i>Measurement</i>	<i>Intra class correlation coefficient</i>
Mean proximal tibial angle	1.0
Limb alignment	0.99

Table 4-4 Intra class correlation of repeated measures

<i>Measurement</i>	<i>Coefficient of variation (%)</i>	<i>Within subject standard deviation (°)</i>
Mean proximal tibial angle	0.13	0.12
Limb alignment	0.14	0.25

Table 4-5 Coefficient of variation of repeated measures

4.5.3.2 Results – Comparison to gold standard

To compare the KneeMorf measurements to the gold standard measurements from the graphpaper, the three repeated KneeMorf measurements for each case were aggregated and intra-class correlations were calculated. These are summarised in Table 4-6, which shows that all measures were rated as being an excellent correlation.

<i>Measurement</i>	<i>Intra Class correlation Coefficient</i>
Medial proximal tibial angle	0.994
Limb alignment	1.0

Table 4-6 Intra-class correlation of gold standard graphpaper measurement to KneeMorf assessment of the anatomical alignment and the medial proximal tibial angle (MPTA).

To quantify the difference between the gold standard and the KneeMorf measurement, the co-efficient of variation and within-subject SD were calculated. The calculations of the co-efficient of variation and within subject SD for the MPTA are shown in Table 4-7 and the table of results is shown in Table 4-8. The results show a variation of 0.75% for MTPA assessment and 0.04% for anatomical limb alignment assessment, which are both very low. The within subject standard deviation provides a measure, in degrees, of the variation between the techniques. The variation between methods for the MTPA was 0.67° and the variation for the limb alignment was less than 0.3° .

<i>Cas e</i>	<i>Graphpaper Gold Standard (°)</i>	<i>KneeMorf Measurement (°)</i>	<i>Mean (°)</i>	<i>Standard Deviation</i>	<i>Varianc e</i>
1	90	89.87	89.94	0.09	0.01
2	90	90.13	90.06	0.09	0.01
3	95	94.29	94.65	0.50	0.25
4	85	85.55	85.28	0.39	0.15
5	100	98.80	99.40	0.85	0.72
6	80	81.23	80.62	0.87	0.76
7	105	103.72	104.3 6	0.91	0.82
8	75	76.34	75.67	0.95	0.90
9	90	89.85	89.93	0.10	0.01
10	90	90.18	90.09	0.13	0.02
11	95	94.33	94.66	0.48	0.23
12	85	85.63	85.31	0.44	0.20
13	100	98.83	99.41	0.83	0.69
14	80	81.32	80.66	0.93	0.87
15	105	103.53	104.2 6	1.04	1.09
16	75	76.16	75.58	0.82	0.68
17	90	89.87	89.93	0.09	0.01
18	90	90.17	90.09	0.12	0.01
19	95	94.11	94.55	0.63	0.40
20	85	85.58	85.29	0.41	0.17
21	100	98.79	99.39	0.86	0.74
22	80	81.15	80.58	0.81	0.66
23	105	103.90	104.4 5	0.78	0.61
24	75	76.44	75.72	1.02	1.04
Calculation			Result		
Mean of all sample means			90.00°		
Variance within cases			0.46		
Common within Subject standard deviation ($\sqrt{\text{variance}}$)			0.68		
COEFFICIENT VARIATION			0.75 %		
+/-2 SD			88.67-91.32		

Table 4-7 Calculation of coefficient of variation for MTPA 100mm

<i>Measurement</i>	<i>Coefficient of variation (%)</i>	<i>Within subject standard deviation (°)</i>
MTPA 100mm	0.75	0.67
Limb alignment	0.04	0.07

Table 4-8 Summary of coefficient of variation between methods

4.5.4 Summary of results

The reproducibility study showed excellent agreement between repeated measures. The ICC for the MPTA and anatomical alignment were 1.0 and 0.99 respectively, which are all excellent agreements. The coefficient of variation results were all less than 0.15% with standard deviations of less than 0.4°, which show very small variation between the repeated measures.

The assessment of KneeMorf against known measurements reported very high ICC results across all measures; 0.99 and 1.0 for the MPTA and anatomical alignment respectively.

The co-efficient of variation was 0.75% and 0.04% for the MPTA and alignment respectively, which were very low coefficients meaning very little variation between the gold standard measurement and that provided by KneeMorf. The within subject standard deviation was less than 1° for all measures and the measure for limb alignment is very small at less than 0.1°.

The results showed that KneeMorf provides both an accurate and precise measure of the anatomical limb alignment, medial tibial proximal angle, distal femoral angle and condylar plateau angle when the measurement points were based on a diagrammatic image.

4.6 Validation of KneeMorf on plain radiographs

4.6.1 Introduction and aim

Section 4.5 showed that the KneeMorf software calculation of angles was accurate and precise when measuring known angles and distances from a diagrammatic representation of a knee. In that method the regions to be selected were clearly highlighted. However, when assessing plain radiographs the region to be selected is not already highlighted and the KneeMorf methodology to select the region of interest needed to be validated.

The aim of this section was to investigate the validity of the KneeMorf software assessment of the limb alignment measures when assessed on a plain radiograph. The software against which KneeMorf was assessed was OsiriX, which has been used previously in this chapter to assess the difference between long leg and short leg radiographs (Section 4.3).

4.6.2 Method

The anatomical limb alignment and medial proximal tibial angle (MPTA) were assessed on twenty short leg knee radiographs performed with the same protocol as the Chingford Study. The radiographs were assessed with both OsiriX (described in Section 4.3.2) and KneeMorf. The results were tabulated and the measurements obtained with OsiriX and KneeMorf were compared with intra-class correlation, within-subject SD and co-efficient of variation.

4.6.3 Results

The raw data is shown graphically in Appendix A. The intra class correlations between the measures made with OsiriX and KneeMorf are shown in Table 4-9. These show that there was a good correlation between the OsiriX and KneeMorf techniques when assessing the MPTA and an excellent correlation between the different measurement techniques for the anatomical limb alignment

<i>Measurement</i>	<i>Intra Class Correlation Coefficient</i>
Medial proximal tibial angle	0.737
Anatomical limb alignment 100mm	0.989

Table 4-9 – Intra class correlation between OsiriX and KneeMorf for limb alignment measures.

The co-efficient of variation (Table 4-10) for the MPTA was 0.98% and the within subject SD was 0.86°. The Co-efficient of variation between the measures for the anatomical alignment was 8.4% and the within subject SD was 0.35°.

Measurement	Coefficient of variation (%)	Within subject standard deviation (°)
Medial proximal tibial angle	0.98	0.86
Anatomical Limb alignment	8.4	0.35

Table 4-10 – Coefficient of variation and within subject standard deviation between OsiriX and KneeMorf methods for anatomical limb alignment and medial proximal tibial angle assessment.

4.6.4 Summary of results

This study showed excellent correlation between the OsiriX and KneeMorf measurement of anatomical limb alignment and good correlation of the MPTA. This correlation was better than previously reported reliability studies in the literature, which reported correlation of 0.87 [197] and 0.79 [130].

The co-efficient of variation between OsiriX and the KneeMorf assessment of MPTA and anatomical alignment were less than 10% and the within-subject SD was 0.35° and 0.86° respectively.

These results show that any KneeMorf is an acceptable tool to assess limb alignment on a plain radiograph.

4.7 Reproducibility of KneeMorf on the Chingford dataset

4.7.1 Introduction and aims

Sections 4.5 and 4.6 above showed that the KneeMorf software application was an accurate measure of limb alignment assessed from diagrammatic

outlines of a knee joint and from a set of validation radiographs. This section investigated the inter and intra-observer reliability of the KneeMorf measurements when used to assess radiographs from the actual Chingford dataset. The data generated from this study would also provide raw data on the Chingford population to enable a power calculation for a nested case-control study in chapter 5

4.7.2 Method

Two observers performed reproducibility studies on twenty randomly selected radiographs from the baseline (year 0) Chingford visit. This was the first use of KneeMorf on the Chingford cohort radiographs. Each observer worked from a training booklet providing information on position of markers in relation to osteophytes and other anatomical variations. A training set of a further twenty radiographs was conducted together to ensure reproducibility of selection. For this study, each observer performed three readings on each radiograph, each at a week interval to the previous reading. The results were exported from KneeMorf, tabulated and assessed using SPSS (Version 22). Intra-class correlations and co-efficient of variation were calculated to investigate the inter-observer and intra-observer variation.

4.7.3 Results – Inter-Observer

The inter-class correlation is shown in Table 4-11. The measures for anatomical alignment and MPTA both show excellent correlation between the two observers. The co-efficient of variation analysis is shown in Table 4-12. The variation for anatomical alignment was 0.12% and the within-

subject SD was 0.17° . The results for the MPTA assessment showed a variation of 0.5% and SD of 0.44°

Measurement	Inter-Class correlation Coefficient
Medial proximal tibial alignment	0.803
Limb alignment	0.991

Table 4-11 – Summary of the Intra-Class correlation for the inter observer study

Measurement	Coefficient of variation (%)	Within subject standard deviation ($^{\circ}$)
Medial proximal tibial alignment	0.5	0.44
Limb alignment	0.12	0.17

Table 4-12 – Summary of the coefficient of variation and within subject standard deviation for the inter observer study

4.7.4 Results – Intra-observer

The results for the intra-observer analysis are shown below. The intra-class correlation (Table 4-13) shows excellent agreement for both measures. The co-efficient of variation (Table 4-14) was 0.31% and 0.12 for the MPTA and the anatomical alignment respectively. The within-subject SD was less than 0.3° for both measures.

Measurement	Intra-class correlation Coefficient
Medial proximal tibial alignment	0.913
Limb alignment	0.991

Table 4-13 - Summary of the Intra-Class correlation for the intra observer study

Measurement	Coefficient of variation (%)	Within subject standard deviation (°)
Medial proximal tibial alignment	0.31	0.28
Limb alignment	0.12	0.17

Table 4-14 - Summary of the coefficient of variation and within subject standard deviation for the intra observer study

4.7.5 Summary of results

The results for the reproducibility studies of KneeMorf on the Chingford Study radiographs show excellent inter and intra-observer agreement.

4.8 The proportion of Chingford radiographs that are suitable for a short leg radiographic alignment study

4.8.1 Introduction and Aim

The literature review in Section 1.5.2 showed that the mean distance below the tibial plateau in previous studies using short leg radiographs [128] [120] was 10cm. KneeMorf was therefore designed to assess limb alignment from the joint to a point 10cm down the femur or tibia. However, the amount of tibia and femur included in the radiograph was not part of the standardisation of protocol for the initial Chingford radiographs. Therefore it was necessary to ensure that a reasonable proportion of the Chingford radiographs would include both the femur and tibia at 10cm from the joint line. Were the radiographs not to include 10cm of both the femur and tibia, KneeMorf would not be able to assess alignment in that case. An understanding of the number of cases likely to be unreadable was

necessary so that the total number of cases in any future study could be adjusted to allow for these excluded cases.

The aim of this section was to determine what proportion of radiographs in the Chingford study would allow measurement of the anatomical limb alignment at 10cm from the joint line.

4.8.2 Method

A random number generator was used (SPSS, Version 22), limited from 0001 to 1000, to select 57 subjects from the Chingford study group at baseline. A DICOM viewer, OsiriX, was used to assess the radiographs. The radiographs were loaded in to OsiriX, calibrated and the maximum amount of diaphysis visible on the radiograph were measured and stored in SPSS for assessment. The distance of femoral and tibial diaphysis visible for measurement were tabulated and shown in histograms and the proportion of radiographs available for assessment at each distance from the joint line was calculated.

4.8.3 Results

The histograms showing the results for maximal femoral and tibial shaft distance visible on the radiograph are shown in Figure 4.12 and Figure 4.13. The proportion of femora and tibia suitable for measurement at centimetre increments is shown in Table 4-15.

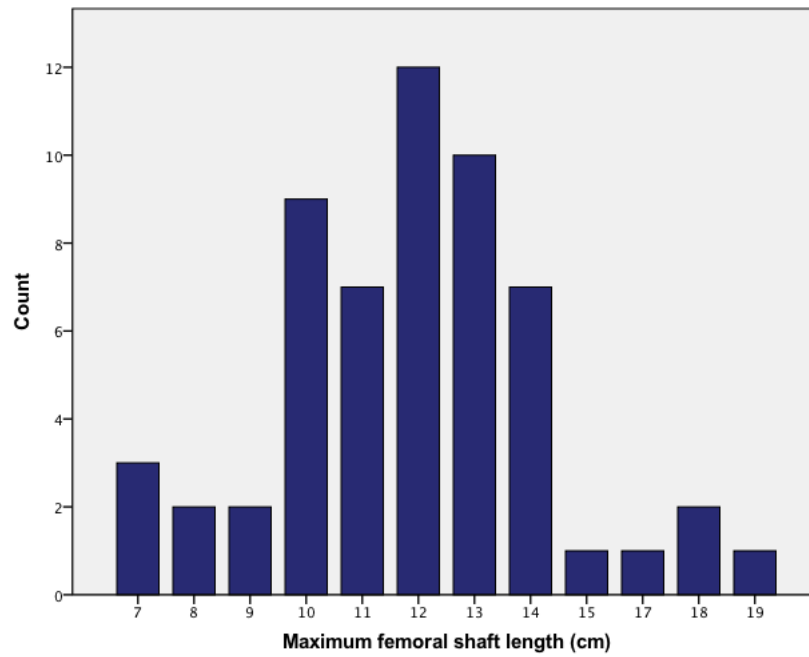


Figure 4.12 – Histogram showing the maximum measurable distance of the femoral shaft from the joint line in a group of Chingford cohort radiographs.

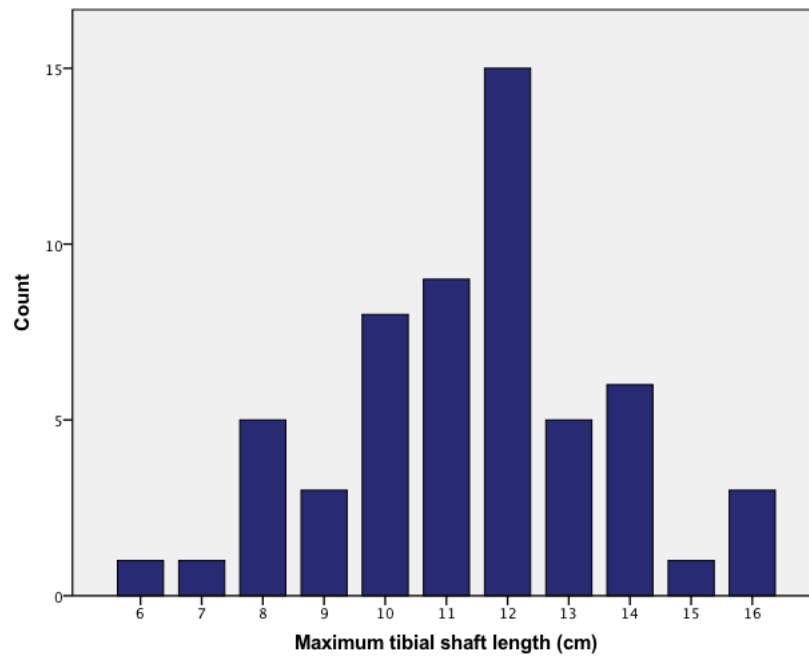


Figure 4.13 - Histogram showing the maximum measurable distance of the tibial shaft from the joint line in a group of Chingford cohort radiographs.

<i>Distance below joint line</i>	<i>Percentage Femurs allowing measurement (%)</i>	<i>Percentage Tibias included (%)</i>
7 cm	100	98
8 cm	95	96
9 cm	91	88
10 cm	88	82

Table 4-15 – Proportion of Chingford radiographs available for measurement at increasing distance from the joint line.

Table 4-15 shows that approximately 88% of femora and 82 % of tibiae would be suitable to assess alignment at a 10cm distance from the joint line. This would need to be accounted for in any future power calculation for study of alignment in the Chingford Cohort.

4.9 Summary of results

This chapter has described the design of the limb alignment component of KneeMorf, a software package to measure alignment, joint space and bone shape of the knee joint on a plain radiograph. Data storage is integral to the design and radiographic quantitative scores such as the Kellgren and Lawrence score are also able to be stored within the dataset.

The Chingford radiographs are short leg antero-posterior knee radiographs and the validity of their use to assess anatomical limb alignment was assessed by a study to compare limb alignment measured from short leg radiographs to long leg standing views. Overall the results showed excellent correlation, however in cases where extra-articular mal-union of previous

fracture existed there was discrepancy between the measurements. When all measurements over a population were assessed, this did not affect the overall correlation but careful interpretation of future results would be necessary and ideally, known cases of tibial or femoral fracture would be excluded.

The accuracy and precision of the measurement of the anatomical limb alignment and medial tibial plateau angle were investigated. The measurements were accurate when compared to a test sheet of known angles. KneeMorf was tested against a “gold-standard” radiographic assessment method and was shown to be valid and reproducible.

The reproducibility of KneeMorf on radiographs from the Chingford dataset was assessed. The inter and intra-observer assessments showed excellent agreement and very low co-efficient of variation.

The distance from the joint line at which the femoral and tibial shaft alignment could be measured in the Chingford cohort was assessed. Study revealed that an expected 80% of tibiae and 90% femora would be suitable for assessment of alignment at 10cm from the joint line. This would need to be accounted for in any future power calculation for the study of alignment in the Chingford study.

In summary, this Chapter has shown that KneeMorf is both accurate and precise when used to measure bony alignment in the Chingford dataset.

5 A nested case-control study to investigate the 20 year risk of varus knee alignment in the development of AMOA

5.1 Aim

The aims of the work presented in this Chapter were to investigate the 20-year risk of limb alignment and proximal tibial alignment in the development of anteromedial osteoarthritis.

5.2 Introduction

As outlined in detail in Section 1.4, there are no long-term radiological studies investigating the role of anatomical limb alignment and proximal tibial alignment in the development of medial arthritis. The medium term studies investigating the role of limb alignment in the development of arthritis have conflicting results, with a study reporting increased risk of OA with mal-alignment [74] and others showing no increased risk [75].

It is well reported that mal-alignment predicts progression of established OA but once OA is established [60] [63], damage to the joint contributes to malalignment. This would mean that measurement of alignment may be just a measure of existing joint space damage such as cartilage loss or meniscal tear or extrusion [68] [71] [69] [198].

The Chingford study provides a 20-year longitudinal radiographic study in which to assess the role of mal-alignment prior to the development of

arthritis and risk of mal-alignment in the development of medial arthritis has not been described in a 20-year longitudinal study previously.

This chapter uses KneeMorf, a software application validated in chapter 4, to assess anatomical limb alignment and proximal tibial angle in a nested case-control study in the Chingford Study to investigate the role of alignment in the development of anteromedial osteoarthritis.

5.3 Null Hypothesis

1. There is no difference in the anatomical limb alignment at baseline between a group who develop anteromedial osteoarthritis (AMOA) at 20 years and a control group who do not develop radiographic AMOA at 20 years.
2. There is no difference in the medial tibial plateau angle at baseline between a group who develop anteromedial osteoarthritis at 20 years and a control group who do not develop radiographic AMOA at 20 years.

5.4 Method

A nested case control study was designed to investigate the 20-year risk of anatomical limb alignment and proximal tibial vara in the development of medial arthritis. The Chingford Study of 1000 women provided the dataset to

study and the study design is outlined Figure 5.1. Baseline was defined as the Year 0 visit in the Chingford Study of 1000 women. Both cases and controls exhibited no arthritis at baseline; the radiographic KL score was less than 2 and no joint space narrowing was present. The case group developed medial arthritis during the 20-year study. Medial arthritis was defined as radiographic KL score of greater than 2 with joint space narrowing only on the medial side, excluding lateral arthritis from the case group. The controls exhibited no radiographic arthritis either at baseline or at the 20 year follow up. All subjects with history of tibial or femoral fracture were excluded so that extra-articular malunions would not change the mechanical alignment, as shown in section 4.3.

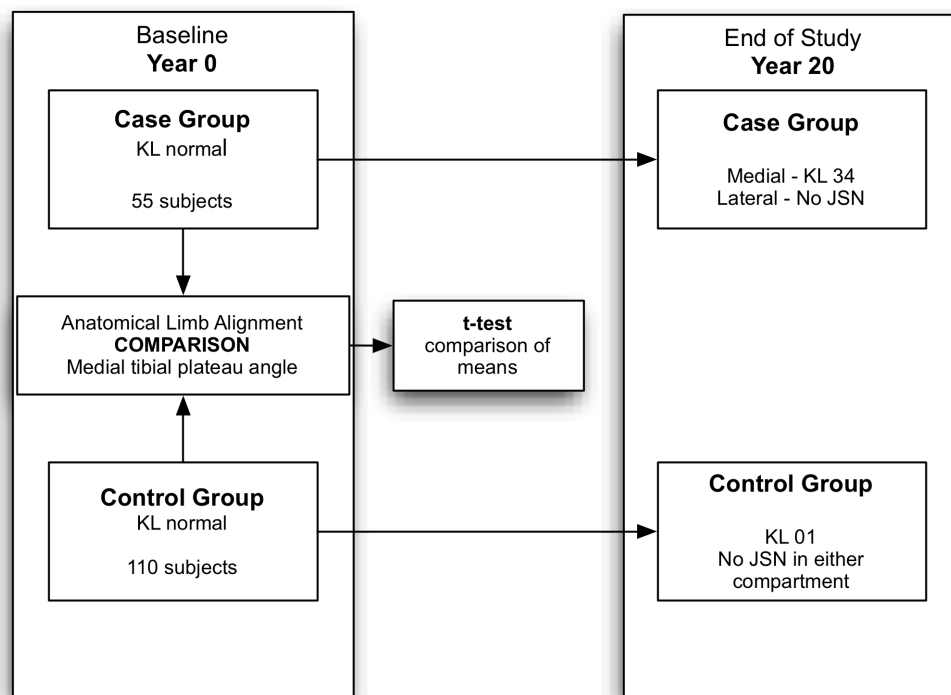


Figure 5.1 - Overview of study design, showing the comparison of anatomical limb alignment and medial tibial plateau angle between the case and control group at baseline, prior to the development of arthritis.

An anatomical limb alignment of 180° means that the anatomical axes of the femur and tibia are co-linear. This does not mean that the mechanical axis of the limb is also in a straight line since the femoral neck offset adds valgus to the anatomical alignment measured. Kraus *et al* [120] showed that on average the difference between anatomical and mechanical axis is 4.3° . From this information an anatomical axis of 184° would equate to a neutral mechanical axis of 180° .

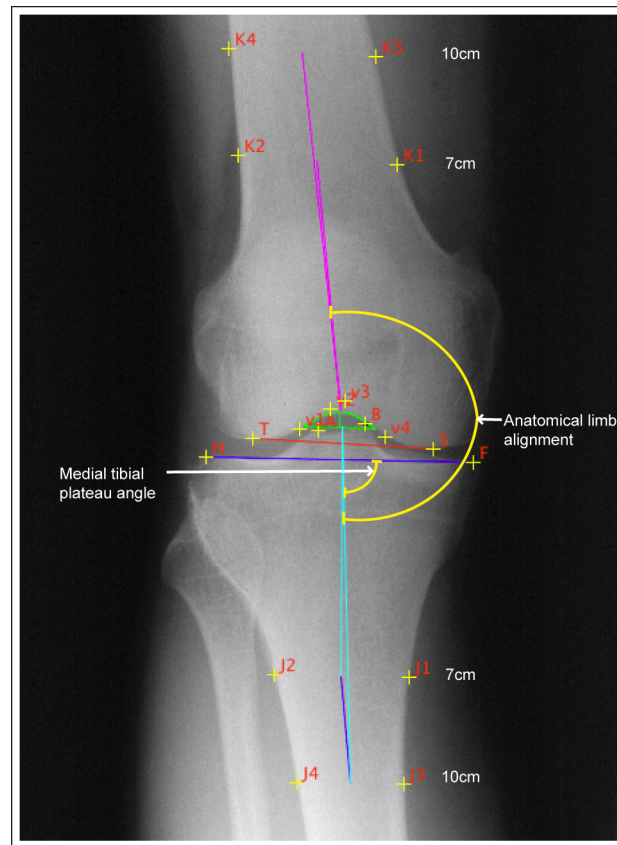


Figure 5.2 – Representation of the measurement of the anatomical limb alignment and medial proximal tibial angle using KneeMorf.

5.4.1 Power Calculation

The power calculation was performed using the Altman nomogram method. Data from the reproducibility study was used as pilot data to define the standard deviation of the dataset and this was used in the power calculation to define the standardised difference.

$$\text{Standardised difference} = \frac{\text{required difference}}{\text{standard deviation}}$$

Therefore :

$$\text{Anatomical alignment} = \frac{2^{\circ}}{1.95^{\circ}} = 1.03$$

$$\text{Medial proximal tibial angle} = \frac{1^{\circ}}{0.921^{\circ}} = 1.09$$

Reading from Altmans nomogram at a power of 0.9 and a significance level of 0.05 resulted in 40 case. The power of 40 cases was then corrected to allow for the expected number of radiographs that would not allow measurement at 10cm from the joint, as described in Section 4.8.

$$\text{Femoral inadequate radiograph risk} = 0.88$$

$$\text{Tibial inadequate risk} = 0.82$$

$$\text{Corrected power} = \frac{\text{power}}{\text{femoral risk} \times \text{tibial risk}}$$

$$\text{Corrected power} = \frac{40}{0.82 \times 0.88} = \frac{40}{0.72} = 55$$

Therefore 55 cases were selected from the Chingford cases and a group of twice this number of controls was selected. The cases were matched for BMI, a confounder of arthritis development [199], [200] [120].

5.4.2 Statistical analysis

The anatomical limb alignment and the medial tibial plateau angle were assessed at baseline using KneeMorf and the statistical difference in mean angles between the case group and the control group was investigated using a t-test. The range of angles measured was represented with histograms and box and whisker plots summarised the median values.

5.5 Results

5.5.1 Anatomical limb alignment results

Radiographs were assessed in 55 subjects in the case group and 110 subjects in the control group. Eleven subjects in the case group and 30 in the control group were excluded since there was not enough femoral or tibial shaft visible to assess alignment at 10cm from the joint line. This left 41 and 80 subjects remaining in the case and control group respectively, which was acceptable with regard to the power calculation in section 5.4.1.

The mean anatomical limb alignment at baseline for the case and control group is shown in Table 5-1 and t-test comparing the means in the case and control group is shown in Table 5-2. The mean alignment in the case group was 181.8° and the mean alignment in the control group was 183.2°, a difference of 1.4°. The lowest anatomical alignment in the case group was 174.1° whereas the lowest angle in the control group was more than 4° higher. The greatest angle in the case group was 185.1°, more than 3° less than the greatest angle in the control group.

The difference in means was 1.4° , which was statistically significant ($p=0.002$). The range of angles measured is shown side-by-side as a histogram in Figure 5.3 and Figure 5.4 shows a box and whisker plot comparing the anatomical alignment in the case and control group. These show the median angle for the control group is higher than that for the case group, although the ranges are similar. There were no extreme outliers in either group.

	Case	Control
N	41	80
Mean	181.83°	183.19°
Median	182.51°	183.20°
Std. Deviation	2.50°	2.03°
Minimum	174.1°	178.7°
Maximum	185.1°	188.5°

Table 5-1 – Summary of the anatomical limb alignment in the case and control groups.

Mean Difference ($^{\circ}$)	Std. Error Difference	Sig.
1.4	0.42	0.002

Table 5-2 – t-test result comparing the means of anatomical limb alignment at baseline in the case and control group.

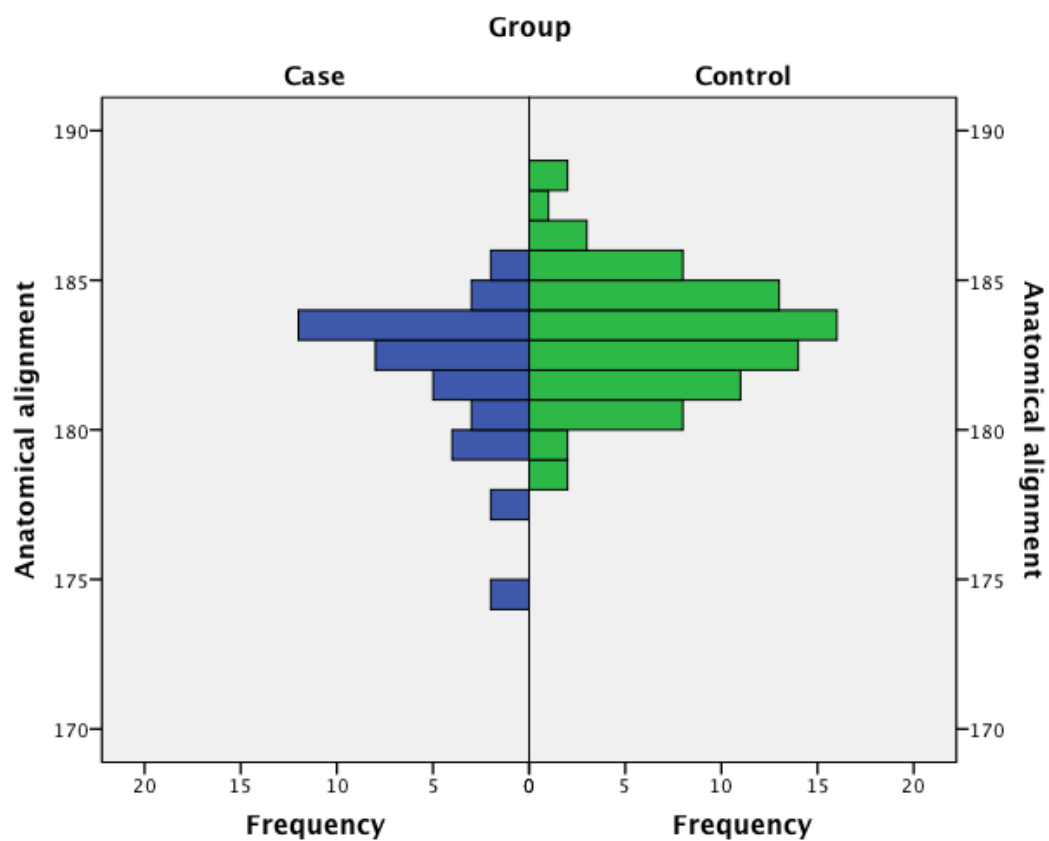


Figure 5.3 – Histograms to show the anatomical limb alignment results for the case and control groups at baseline.

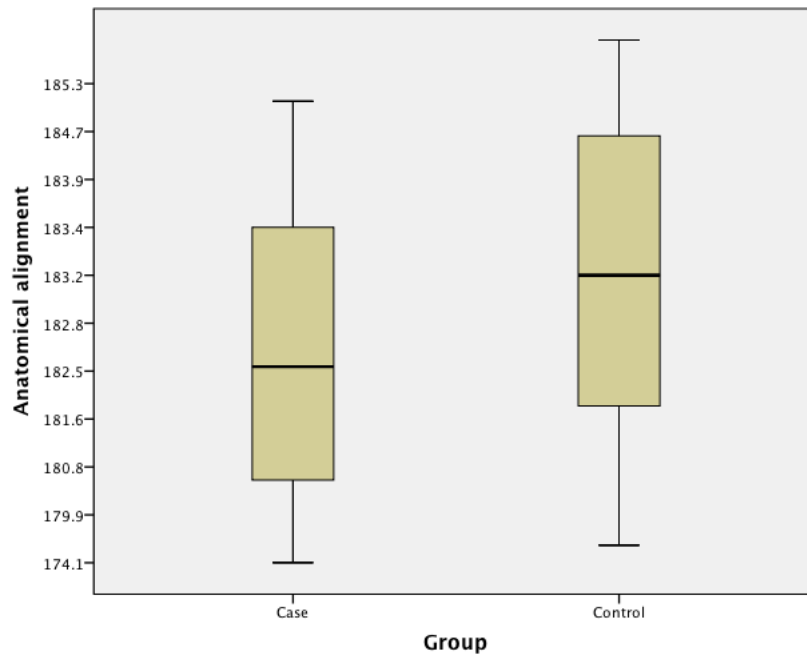


Figure 5.4 – Box and whisker plot to show the difference in anatomical alignment between the case and control group at baseline.

5.5.2 Medial tibial plateau angle results

The mean medial tibial plateau angle at baseline for the case and control group is shown in Table 5-3 and t-test comparing the means in the case and control group is shown in Table 5-4. The mean MTPA in the case group was 87.4° and in the control group was 88.6°. The difference in means was 1.21°, which was statistically significant ($p < 0.001$). The range of angles measured is shown side-by-side as a histogram in Figure 5.5 and Figure 5.6 shows a box and whisker plot comparing the anatomical alignment in the case and control group.

	Case	Control
N	55	110
Mean	87.38	88.59
Median	87.58	88.50
Std. Deviation	1.04	1.27
Minimum	85.1	85.6
Maximum	89.3	92.1

Table 5-3 - Summary of the medial tibial plateau angle in the case and control groups.

Mean Difference	Std. Error Difference	Sig.
1.21	0.20	<0.001

Table 5-4 – t-test result comparing the means of medial tibial plateau angle at baseline in the case and control group.

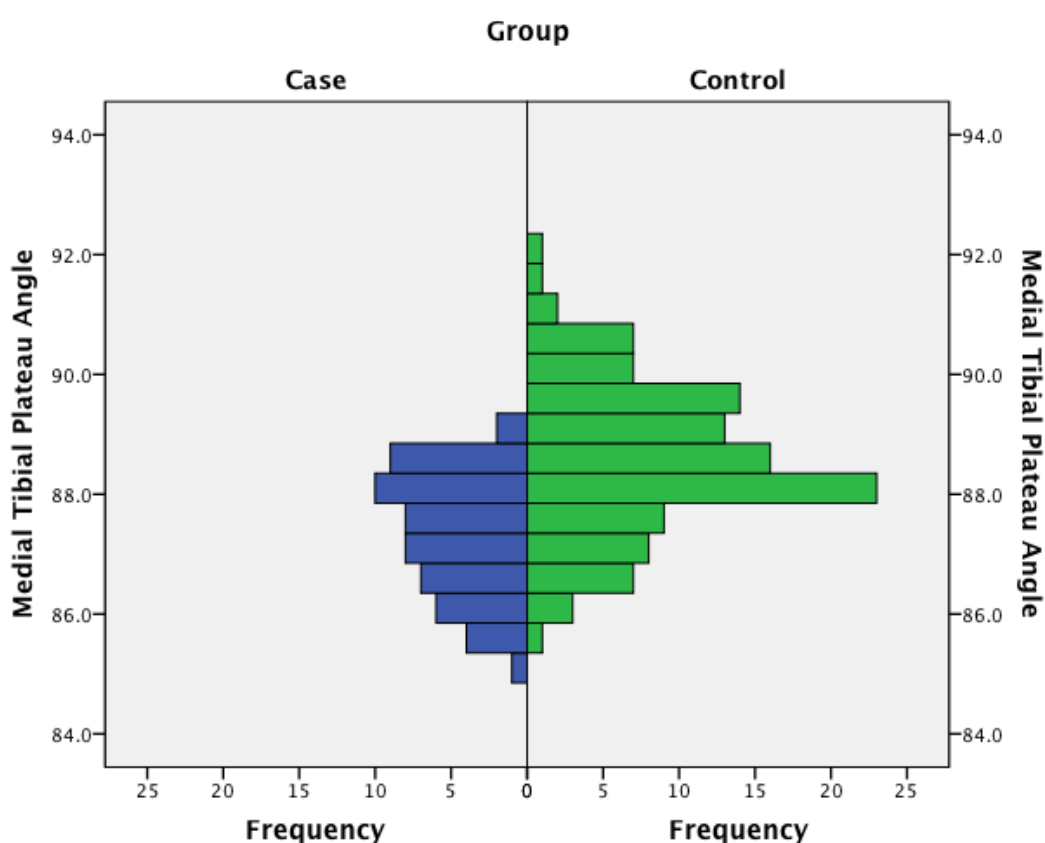


Figure 5.5 – Histograms to show the medial tibial plateau angle results for the case and control groups at baseline.

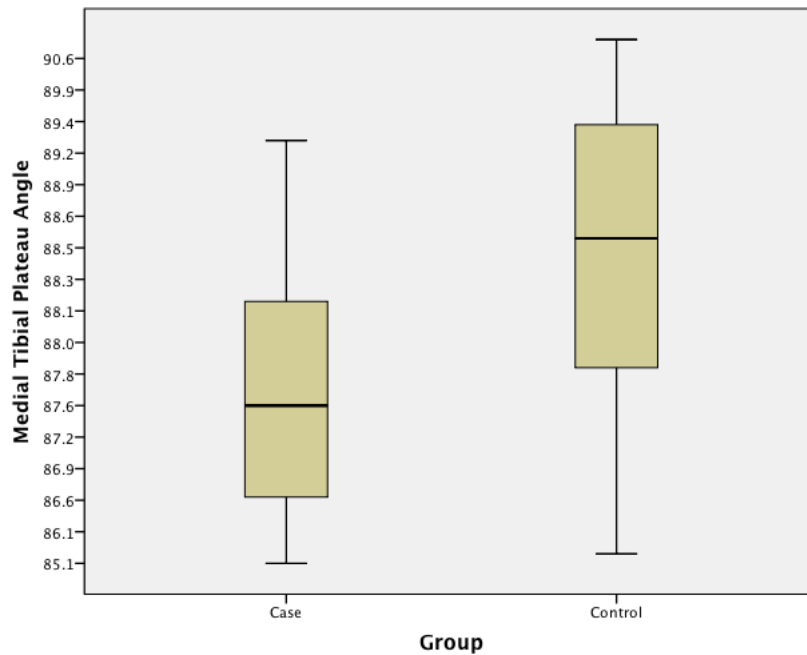


Figure 5.6 – Box and whisker plot to show the difference in medial tibial plateau angle between the case and control group at baseline.

5.6 Summary of results

The results showed a significant difference of 1.4° in the anatomical limb alignment between the case group who developed arthritis by the 20-year follow-up and the control group who did not develop arthritis meaning that the first null hypothesis could be rejected. The range in both groups was similar but the minimum and maximum in the case group were both lower than those in the control group. The mean alignment in the case group was lower than that in the control group, meaning that those who developed medial arthritis tended more towards varus at baseline than the control group.

Since the measurement is of the anatomical alignment, a precise baseline mechanical alignment cannot be calculated. Kraus *et al* [120] described an

average 4.3° difference between the mechanical and anatomical alignment. If this correction is made to the results obtained here, the case group alignment would be 177.5° , which is 2.5° of overall limb varus but this measurement is not validated in the Chingford population. However, what can be concluded is that those who developed medial arthritis by 20 years tended more towards a varus alignment than those who did not develop medial arthritis.

The assessment of the medial tibial plateau angle showed that the case group who subsequently developed medial arthritis was significantly more in varus, by 1.21° than the control group.

This is the first study to show an increased 20-year risk of developing medial OA with increased varus anatomical alignment and an increased varus medial tibial plateau angle. The difference between the groups is small but is within the measurement error of the methodology. Whilst the difference is statistically significant, it is small, at less than 1.5° and the clinical relevance of this is not clear. As the varus angle increases the risk of AMOA may also increase but this cannot be stated from this work.

6 The development of a method to assess medial tibial plateau morphology

6.1 Aims

This chapter describes and validates a methodology to assess the morphology of the anterior region of the medial tibial plateau, the medial tibial upslope. Once validated the methodology was then used in Chapter 7 to investigate the risk of abnormal tibial plateau morphology in the development of anteromedial osteoarthritis (AMOA).

The specific aims of this chapter were:

1. To validate the selection of the MRI coronal and sagittal image on which to base the assessment of the tibial upslope.
2. To validate the medial tibial upslope measurement method.
3. To validate the use of MRI to assess sub-chondral anatomy.
4. To determine the optimum position on the medial tibial plateau to assess the tibial upslope.

6.2 Introduction

The anatomy of the medial tibial plateau is summarised in Section 1.4.4. Only one previous study has investigated risk of developing anteromedial osteoarthritis related to the anatomy of the tibial upslope [201]. This was a small retrospective MRI study of 20 patients already diagnosed with AMOA and compared to a control group who had undergone MRI for ACL rupture.

Whilst the angle of the tibial upslope was increased in the AMOA group in comparison to the ACL group, it is clear from the literature outlined above that a shallow tibial plateau is a risk factor for ACL rupture. This may mean that the control group present with an abnormally low angle rather than the angle increased in AMOA. However, measurement of the angle of the tibial upslope provides a simple surrogate marker to describe the morphology of the concave medial tibial plateau, an increase in which may cause increased cartilage stress leading to arthritis.

This chapter describes the validation of a method to assess the bony anatomy of the medial tibial plateau and Chapter 7 uses this method to investigate the role of medial tibial plateau anatomy in the development of anteromedial osteoarthritis.

6.3 The accuracy and precision of OsiriX

6.3.1 Introduction

OsiriX is a DICOM viewing software application with in-built measurement tools, which has been described in detail in Section 1.7. These tools include angle measurement software, to measure the angle between two straight lines and distance measurement tools. In order to utilise these tools to investigate the bony anatomy of the medial tibial plateau, they needed to be validated against known measurements. Therefore, plain radiographs were obtained of a metallic set square and goniometer of a known (control)

dimensions and of an object with a known (control) angle. The radiographs were assessed with OsiriX and the known measurements were assessed.

6.3.2 Aim

To validate the digital measurement tools provided with the OsiriX application. The subsequent assessment of the anatomy of the medial tibial plateau in Chapter 7 is dependent on reliable and valid measures of angle and distance provided by the measurement tools contained within OsiriX and this section validates these tools.

6.3.3 Method

To assess the accuracy and precision of the measurement tools in OsiriX plain radiographs were taken of a metallic set square ruler, with a handle at 90° to the ruler and a metal goniometer using a standard digital capture plain radiograph. To assess the effect of size of angle on the angle measurements, radiographs were taken of the goniometer at 4 different angles. The angles were 20°, 45°, 80° and 120°. The metallic end of the metallic ruler was measured with a caliper and was 40mm in length. The angle between the metallic handle was assessed with a digital goniometer and was 90°. An example of the radiograph is shown in Figure 6.1. In this example the angle set on the goniometer is 20°.

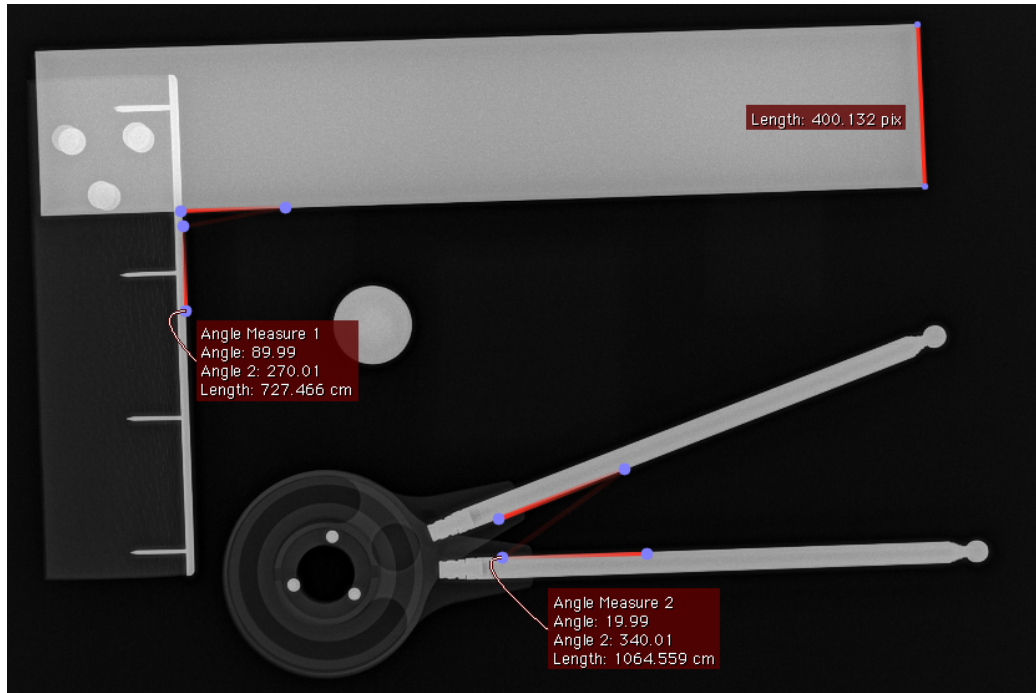


Figure 6.1 – Plain radiograph of the metallic set square ruler and goniometer with the measurements from OsiriX overlaid.

The results were tabulated in SPSS (V.22, IBM) and the difference between the measures were assessed with co-efficient of variation and a Bland Altman plot was constructed to assess if the measurement error changed as the size of angle measured changed.

6.3.4 Results

The co-efficient of variation for the distance measurements was 0.09%, which is very low. The common within subject deviation (CWSD) was 0.03°, which is also very low. The co-efficient of variation for the angle

measurements was 0.11% and the CWSD was 0.09°, both of which are very low.

The Bland Altman plot is shown below in Figure 6.6. This shows that there is no change in measurement error as the size of the angle measured changed, all measure were within two standard deviations of the mean of the difference.

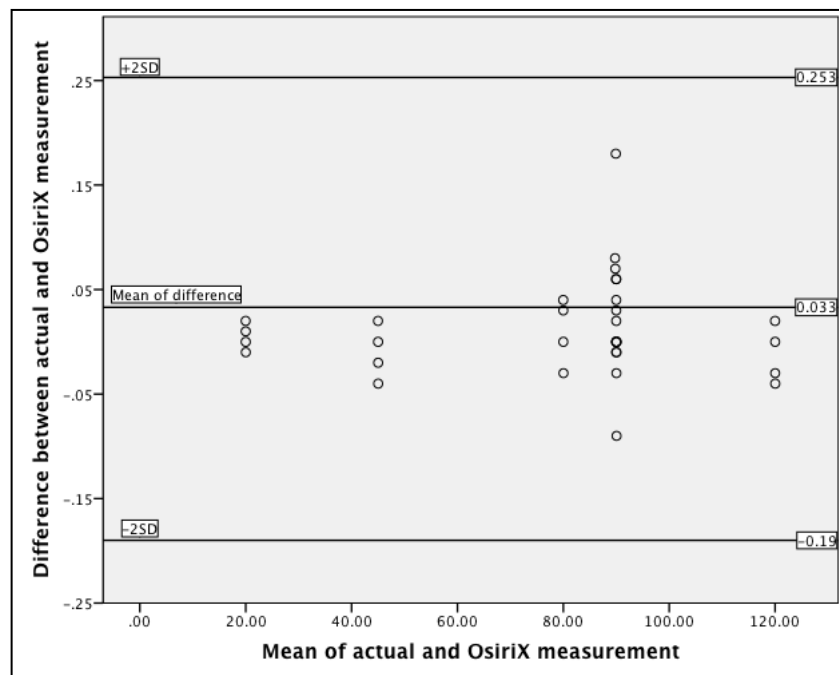


Figure 6.2 – Bland-Altman plot to show the change in measurement difference as the angle measured changed.

6.3.5 Summary of results

This section has shown that the measurement tools of OsiriX and accurate at measuring length and angles on a radiograph.

6.4 Description of method to assess tibial upslope

A teaching atlas was developed, showing all the steps of the method, which is shown in Appendix B. The coronal image was selected as the image with the most prominent (specifically highest) medial tibial spine. If there was no difference in medial tibial spine height in more than one coronal image, then the image with additionally the highest lateral tibial spine was selected. The width of the medial tibial plateau on the selected coronal image was measured from the tip of the medial spine to the medial joint line, not including any osteophytes if present. Two sagittal images were then selected. The first was the image closest to the mid point of this line (50% of the distance from the medial joint line to the medial tibial spine) and the second was the next sagittal image toward the medial tibial spine. This process is shown in Figure 6.3.

The angle of the medial tibial upslope was measured as the angle between two lines, which were manually segmented onto the sagittal MRI image. The first line followed the medial tibial upslope, which was defined as the upward facing bony region in the anterior half of the tibial plateau on the sagittal image. The line commenced at the apex of the upslope and stopped at the inflection point of the upslope as it merged into the flatter region just posterior to it. The second line followed the bony surface of the region posterior to the upslope, from the inflection point to another point on the bony surface, at least 1cm further posterior.

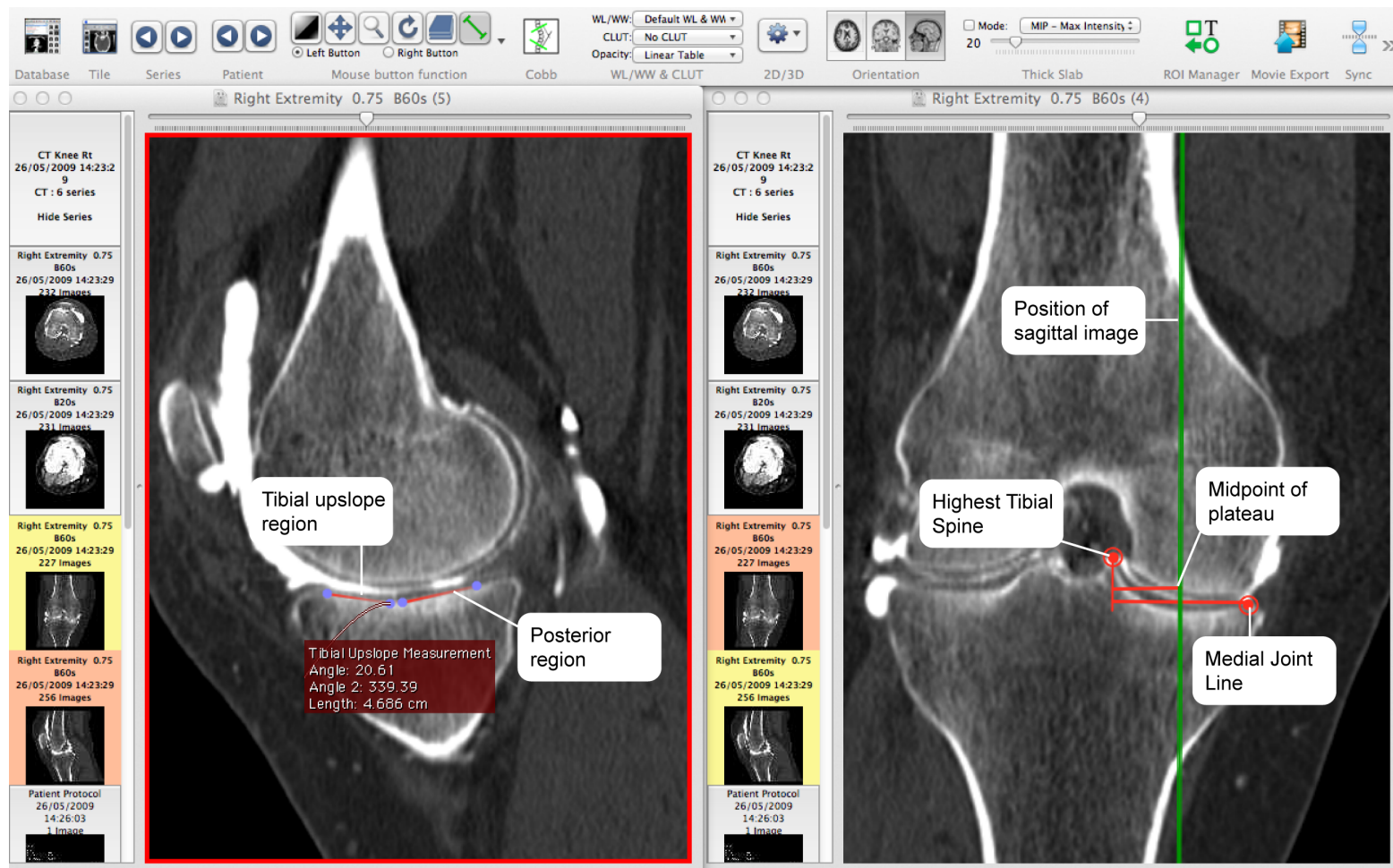


Figure 6.3 – An annotated screenshot of OsiriX showing the measurement points on the sagittal (left) and coronal (right) images

6.5 Validation of the method to assess the tibial upslope

6.5.1 Introduction

The medial tibial plateau is concave from anterior to posterior. It is also concave from medial to lateral, with the medial joint line medially and the medial tibial spine laterally each higher than the central surface. The effect of this concavity in the coronal plane on the measurement of the tibial upslope is unknown. If the angle measured centrally in the medial compartment differs from that measured at the medial or lateral edges of the compartment, the coronal position of the point of measurement would need to be controlled for in any future experiments. An example of a tibial plateau in the coronal plane and the different morphology of the medial tibial plateau at different positions in the sagittal plane are shown below in Figure 6.4. The change in angle of the tibial upslope at different positions across the plateau was assessed later in this chapter, section 6.6, since it could be formally assessed only once this methodology to select the coronal and sagittal image had been finalised. This section investigates if the method to measure the tibial upslope can reliably select the same coronal and sagittal slice on the MRI on which to measure the tibial upslope and assessed the reproducibility of the method to assess the tibial upslope.

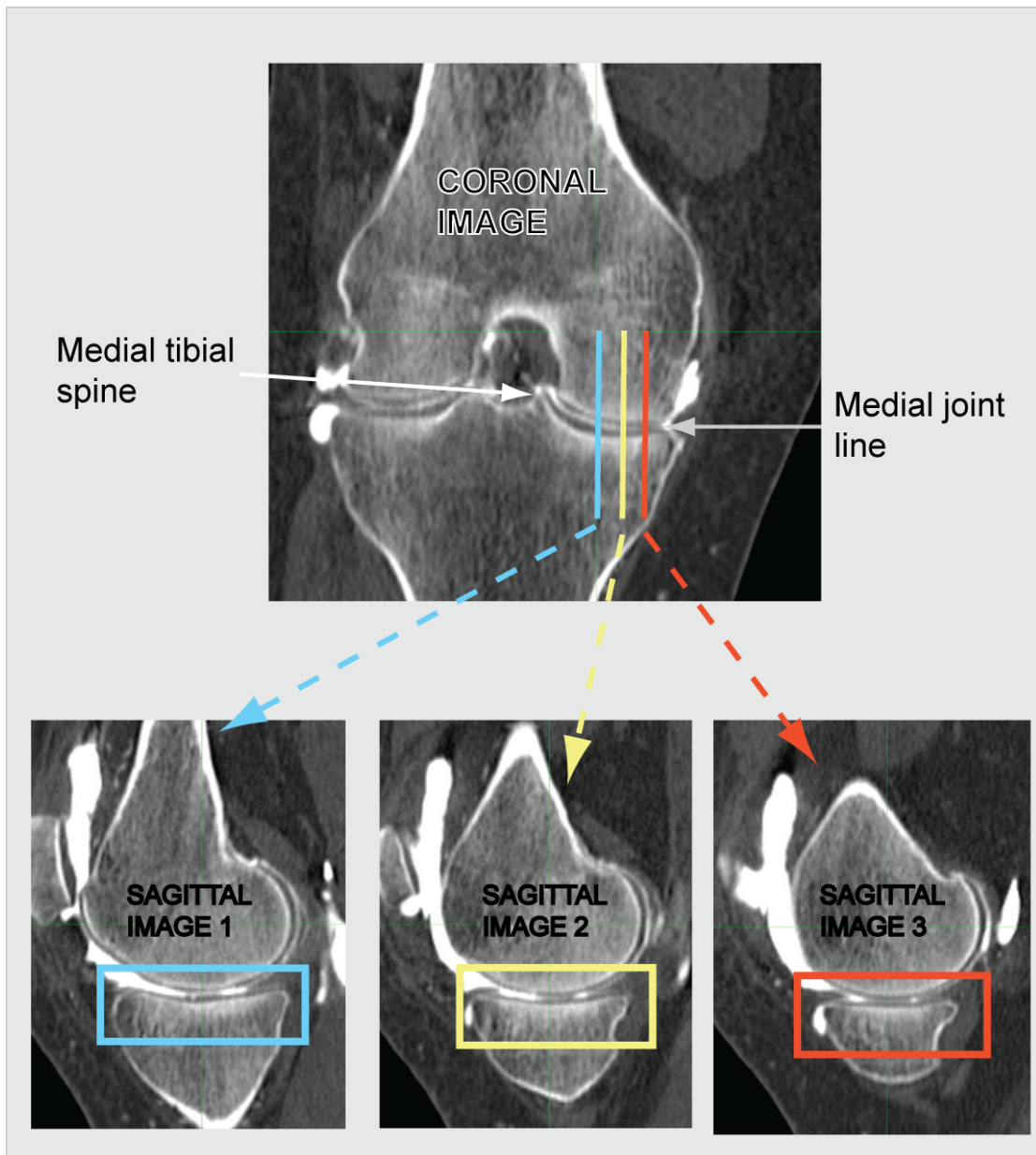


Figure 6.4 – A coronal CT image of a knee joint (above) with the medial tibial spine and the medial joint line labeled. Different positions across the plateau are marked in blue, yellow and red. The sagittal image at the corresponding position is shown below, with the coloured box highlighting the area of the tibial plateau upslope. Note the difference in shape of the plateau dependent on the coronal positioning.

6.5.2 Aim

A reproducible measurement technique to assess the tibial upslope needed to be based on reliable selection of the specific coronal and sagittal MRI image on which to assess the morphology. The aims of this section were:

1. To assess the reproducibility of the selection of the coronal and sagittal image on which to assess the tibial upslope
2. To assess the reproducibility of the measurement methodology to assess the tibial upslope.

6.5.3 Method

Four orthopaedic clinical research fellows were recruited as observers. Each observer was taught the method outlined above (section 6.4) and worked from the teaching aid shown in Appendix B on a teaching set of 10 MRIs and then each observer assessed the same 15 knee MRIs. The observers recorded the coronal image selected and the sagittal image selected and the measurement of the tibial upslope. This enabled calculation of the intra-observer assessment of both the MRI image selection and the tibial upslope measurement. In order to assess the inter-observer reliability of the tibial upslope measurement, this author assessed the same 15 MRI scans three times at one-week intervals.

The results were tabulated. The coronal and sagittal images selected by observers were compared using the intra-class correlation coefficient for categorical variables. The inter-observer variability of the tibial upslope

measurement was assessed by calculating the intra-class correlation and the co-efficient of variance as described by Bland and Altman. This method of inter-observer assessment was used because it provides an actual measure in degrees of the mean standard deviation across all of the measurements. This standard deviation may then define a confidence interval of the variability in measurement.

6.5.4 Results

The coronal image selection is shown below in Table 6-1. The intra-class correlation coefficient was 0.99, showing an excellent correlation in the coronal image selected between observers. In almost every case the observers selected the same coronal image.

Coronal Slice Selection				
Case	Observer 1	Observer 2	Observer 3	Observer 4
1	14	14	14	14
2	16	16	16	16
3	16	16	16	16
4	16	16	16	16
5	17	17	17	17
6	13	13	13	13
7	15	15	15	15
8	15	15	15	15
9	16	16	16	15
10	14	14	14	14
11	14	14	14	13
12	16	16	16	16
13	16	16	16	16
14	16	16	16	16
15	17	17	17	17
Intra-class correlation coefficient – 0.99				

Table 6-1 A table showing the raw data of the reproducibility of MRI coronal image selection

The sagittal image selection is shown in Table 6-2. The intra-class correlation coefficient was 0.99, again showing excellent agreement between observers. These results showed that the method of selecting the sagittal image on which the tibial upslope would be measured was reproducible.

	<i>Sagittal Slice Selection</i>			
Case	Observer 1	Observer 2	Observer 3	Observer 4
1	45	45	45	45
2	17	18	18	18
3	16	16	16	16
4	16	16	16	16
5	45	45	45	45
6	16	17	17	16
7	44	44	44	43
8	45	45	44	44
9	18	18	18	18
10	44	44	44	44
11	45	46	45	44
12	16	16	16	16
13	45	45	45	45
14	45	45	45	45
15	16	17	16	16
	Intra-class correlation coefficient – 0.99			

Table 6-2 A table showing the raw data of the reproducibility of MRI sagittal image selection

The intra-class correlation of the inter-observer assessment of the tibial upslope was 0.843, which is rated as excellent. The measurements of the tibial upslope on the sagittal images were tabulated and the co-efficient of variation was calculated (Table 6-3). The coefficient of variation was 6.3% and the common within subject standard deviation was 0.64° , which showed low variation between the observers.

Case	Observer 1	Observer 2	Observer 3	Observer 4	MEAN	SD	VARIANCE
1	6.75	5.95	6.2	6	6.23	0.37	0.13
2	8.85	8.6	8.85	9	8.83	0.17	0.03
3	4.2	4.6	3.95	5	4.44	0.46	0.21
4	18.45	17.1	18.1	18.2	17.96	0.59	0.35
5	8.37	7.15	8.1	9.05	8.17	0.79	0.62
6	11.4	12.1	11.55	11.9	11.74	0.32	0.10
7	6.95	8.15	6.1	7.4	7.15	0.86	0.73
8	14.45	14.8	15.95	14.1	14.83	0.80	0.64
9	11.95	12.2	12.85	11.4	12.10	0.60	0.36
10	9.8	9.35	8.05	9.65	9.21	0.80	0.64
11	8.5	8.35	7.9	8.6	8.34	0.31	0.10
12	9.35	8.9	7.7	10.2	9.04	1.04	1.09
13	10.5	10.85	10.4	10.8	10.64	0.22	0.05
14	9.7	11.1	9.25	10.2	10.06	0.79	0.63
15	13.35	11.8	12.5	12.1	12.44	0.67	0.45

Sample Mean (SM)	Within subject variance	Common within subject standard deviation (CWSD)	Coefficient of Variance
Mean of all MRI means	Mean of all MRI variance	SQRT of within subject variance	CWSD/SM*100
10.1	0.41	0.64	6.34

Table 6-3 Tables showing the raw data of the reproducibility of the measurement of extension facet angle and the variance calculations.

The intra-observer assessment showed an intra-class correlation between the three repeated measurements of 0.913, which is rated as excellent. The co-efficient of variation was 9.6%, which is a low variation between the three repeated measurements.

6.5.5 Summary of reproducibility results

The selection of the coronal and sagittal images was highly reproducible, with an intra-class correlation of 0.99 for both measures.

The co-efficient of variation for the measurement of the tibial upslope was low and the standard deviation of the measurement of the tibial upslope showed that 95% of the error of measurement (standard deviation of error x 1.96) would be less than 1.25°.

6.6 Assessment of the change in EFA across the medial tibial plateau

6.6.1 Introduction

The medial tibial plateau is concave in both the coronal and sagittal planes. In the coronal plane the plateau is highest at the medial tibial spine and as the outline is traced more medially there is a deepest region before rising to a higher point at the most medial aspect at the joint line. This concavity was likely to affect the measurement of the tibial upslope (as outlined in Figure 6.4), yet the change in the tibial upslope measurement at different points across the medial tibial plateau has not been described. The work described in this section was designed to assess the difference in the tibial upslope at different points across the medial tibial plateau.

CT scans depict the subchondral surface of a joint well and additionally the average distance between images on CT scan is 1/10th of that between images on an MRI scan. Therefore CT scans provide approximately 60-70 separate sagittal images across the medial tibial plateau and assessment of all of these would provide the change in the tibial upslope across the plateau.

6.6.2 Aim

The aim of this section was:

1. To investigate the change in the tibial upslope at different regions across the medial tibial plateau.

6.6.3 Null Hypothesis

There is no significant difference between the tibial upslope measurements at different regions across the medial tibial plateau.

6.6.4 Method

To assess the change in the tibial upslope across the medial tibial plateau the upslope angle was measured on every sagittal image on the CT scans of 7 subjects who had undergone CT assessment of their knee. For each subject, the plateau was separated into regions, each representing 10% of the plateau width. The mean of all the measurements in each region were tabulated and represented graphically. The differences in the tibial upslope in different regions of the medial tibial plateau were assessed with t-tests.

6.6.5 Results

A summary of the tabulated results by subject is shown in Table 6-4.

Subject	Mean (Std Dev) (°)	Min (°)	Max (°)	Range (°)
1	10.5 (5.5)	1.6	18.7	17.1
2	13.6 (8.5)	1.8	26.9	25.1
3	10.0 (4.6)	1.6	17.7	16.1
4	15.0 (5.8)	2.9	23.6	20.7
5	13.2 (9.1)	0.2	26.4	26.2
6	11.9 (6.3)	0.8	21.2	20.4
7	14.6 (5.8)	1.9	21.0	19.1

Table 6-4 Summary of tibial upslope measurements by subject

The graph of the tibial upslope measurements at different points across the medial tibial plateau is shown in Figure 6.5. Zero percent was the most medial part of the joint and 100% would be the tip of the medial tibial spine. There is a clear change in the tibial upslope measurement dependent on the region across the plateau at which it is measured.

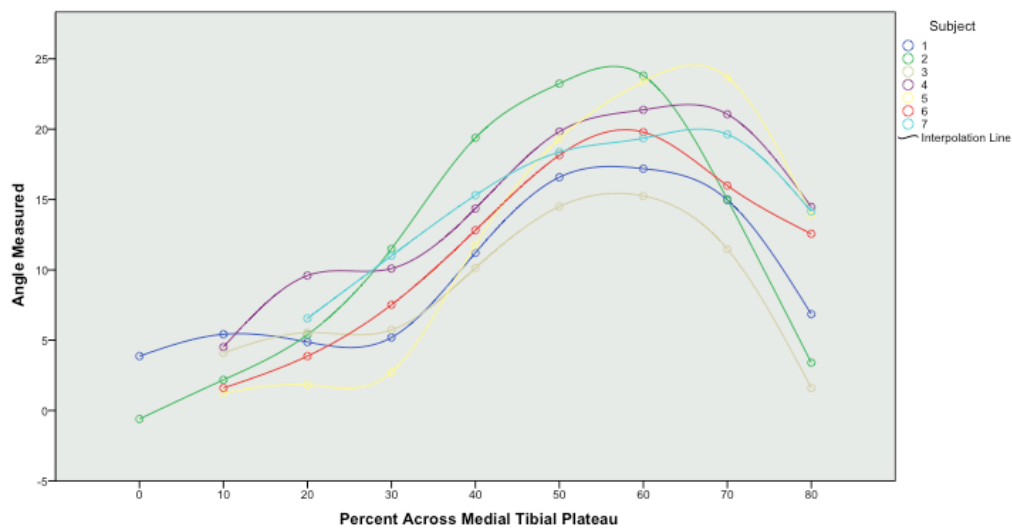


Figure 6.5 - Measurement of the tibial upslope at different regions across the medial tibial plateau for each subject. The x-axis shows the percentage distance across the medial tibial plateau, with 0% the medial joint line and 100% the tip of the medial tibial spine.

There was consistency to the pattern of change in the tibial upslope across the medial tibial plateau. The magnitude of the tibial upslope was least when measured at the medial joint line and the tibial spine and the greatest angles were measured more centrally in the medial plateau.

There was a large range in the angle measured across the medial tibial plateau within subject. The greatest range within the same subject across the medial tibial plateau was 26.2° and the smallest range was 16.1° , which showed that the position at which the tibial upslope was measured affected the actual measurement obtained. Further interpretation of the graph in Figure 6.5 showed that the greatest angle was consistently measured between 50 and 70% across the medial tibial plateau.

This was further investigated by comparing within each subject the angles measured between 50-70% and those measured at positions on the plateau at less than 50% and greater than 70% across the plateau. The values of the tibial upslope in the two different regions were compared with t-tests and this is summarised in Table 6-5.

There was a significant difference in the tibial upslope measurements between 50 and 70% across the medial plateau when compared with measurements taken outside of this area. The smallest difference between the two regions was 5.9° and the greatest was 13.5° .

<i>Subject</i>	<i>Measurement position</i>	<i>Mean Angle (°)</i>	<i>Difference (°)</i>	<i>Significance (°)</i>
1	50-70%	16.9	8.9	p<0.01
	Rest of plateau	8		
2	50-70%	23.5	13.5	p<0.01
	Rest of plateau	10		
3	50-70%	14.9	7.1	p<0.01
	Rest of plateau	7.8		
4	50-70%	20.6	7.8	p<0.01
	Rest of plateau	12.8		
5	50-70%	21.5	11.5	p<0.01
	Rest of plateau	10		
6	50-70%	18.9	9.7	p<0.01
	Rest of plateau	9.2		
7	50-70%	18.8	5.9	p<0.01
	Rest of plateau	12.9		

Table 6-5 – The difference between the tibial upslope measured between 50 and 70% across the medial tibial plateau and the upslope measured outside of this area.

The large difference in the tibial upslope between the regions across the medial tibial plateau emphasises the importance of the reproducibility work on the selection of the sagittal image to measure presented in Section 6.5, since an error of 20% or approximately 1cm may change the angle measured by as much as 15°. Additionally, the region between 50% and 70% across the plateau is an area of relatively little change in consecutive measurements. Therefore, any error of selection in the sagittal image to assess in this portion of the plateau would lead to a smaller error in measurement of the angle.

6.6.6 Summary of results

There was a significant difference in the measurement of the tibial upslope between different regions of the medial tibial plateau. The greatest angles were measured between 50 and 70% across the medial plateau, when the

medial joint line was defined as 0% and the medial tibial spine was defined as 100%.

6.7 Validation of the use of MRI to assess bony anatomy

6.7.1 Aim

1. To validate the use of MRI to assess the bony anatomy of the medial tibial plateau by comparing measurements made from MRI and CT in the same subject.

6.7.2 Introduction

Sections 6.3 and 6.5 proved that the methodology devised to assess the morphology of the medial tibial plateau is reproducible and that the measurement tools are accurate and precise. However, the validity of using MRI scans to assess the bony anatomy of the plateau has not been assessed. For the results of the assessment of MRI to be valid there must be certainty that the interpretation of the bony anatomy from the MRI is correct.

Computer tomography (CT) scans provide a reliable representation of the bony surface of a joint. In this section, the measurements of the tibial upslope from CT scans and MRI scans were assessed.

6.7.3 Method

For this study the tibial plateau morphology of seven subjects who had undergone both CT arthrogram and MRI scans were assessed. None of the patients had cartilage loss in the medial or lateral compartment. The validated method described in Section 6.5 was used and a single observer, (this author, NB), selected the appropriate coronal slice on both the CT and MRI scan for each subject. The tibial upslope was then measured on each available sagittal image on the MRI scan and at matched positions on the CT scan. The results were tabulated and the tibial upslope at the matched points on the MRI and CT scans across the plateau were compared with intra-class correlations and the difference in measurement with change of magnitude of the angle measured was assessed with a Bland-Altman plot.

6.7.4 Results

The intra-class correlation between the CT and the MRI measurements was 0.988, which is rated as excellent. The CT and MRI measurements are summarised in Table 6-6.

<i>Modality</i>	<i>N</i>	<i>Mean (°)</i>	<i>Std Dev</i>	<i>Std Error of the Mean Difference (°)</i>
MRI	49	12.4	7.30	0.16
CT	49	12.1	7.26	

Table 6-6 Summary of matched CT and MRI measurements of the EFA

A Bland Altman plot was constructed to assess the effect of measurement size on the error between the two imaging modalities. If the difference

between the MRI and CT measurements changes as the angle measured also changes then this may introduce a size related error. The Bland Altman plot in Figure 6.6 showed that there was no change in the difference between the CT and MRI measurements as the magnitude of the angle measured increased.

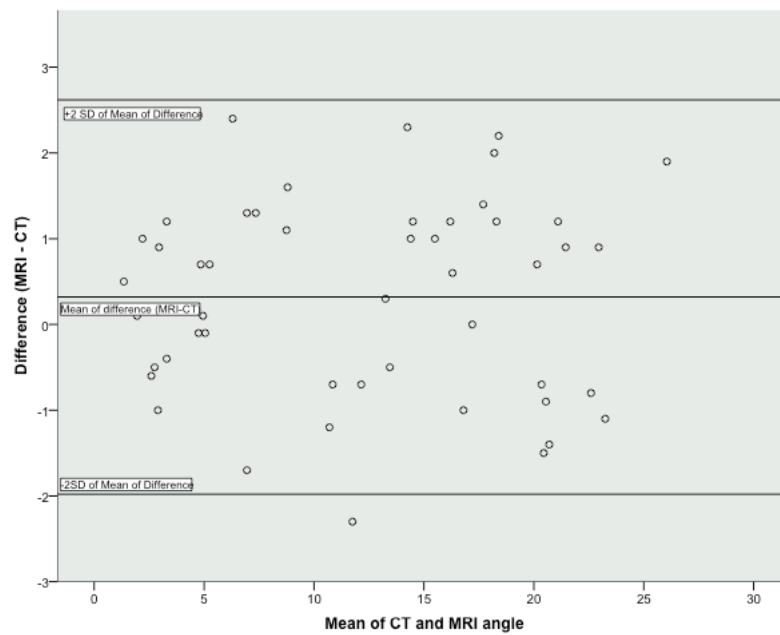


Figure 6.6- Bland Altman plot to show the difference between CT and MRI measures of EFA as the magnitude of the angle changes.

6.7.5 Summary of results

The results validated the use of MRI to assess the bony anatomy of the medial tibial plateau. The intra-class correlation between the two methods was excellent and there was no effect on the error with change in the measurement size.

6.8 Pilot study of the role of the medial tibial upslope in anteromedial osteoarthritis.

6.8.1 Introduction and aims

The work above described a reproducible and valid measurement method to assess the medial tibial upslope. The image selection to measure the upslope was reproducible and the MRI measurements correlated well to CT assessment of the sub-chondral bony anatomy. The medial upslope was shown to vary across the plateau, however it was unknown on which sagittal image the tibial upslope should be measured when comparing two groups in a study of risk. There was no data in the literature to inform which sagittal image should be used to measure the upslope or which region of the plateau would show the greatest difference between groups. A pilot study was designed with two aims:

1. To determine the optimum position on the medial tibial plateau at which to measure the tibial upslope to when comparing two groups.
2. To determine if there was a difference in tibial upslope between a group with anteromedial arthritis and a group without.

6.8.2 Null hypothesis

There is no difference in the medial tibial upslope at matched regions across the medial tibial plateau between a group with early anteromedial arthritis and a control group.

6.8.3 Method

Thirty-eight subjects had undergone MRI for knee pain and were diagnosed with early AMOA; partial thickness cartilage loss in the anteromedial tibial plateau and an intact ACL. Twenty-two subjects underwent knee MRI for acute ACL rupture with no cartilage loss and acted as a control group. Subjects with full thickness tibial cartilage lesions were excluded since this may be accompanied by tibial plateau bone attrition so affecting the tibial upslope. The tibial upslope was measured on all slices through the medial tibial plateau in the mid-coronal plane using the method outlined above in 6.7.3. The measurements were separated into 10% regions, providing 10 regions for comparison across the plateau. A t-test was used to compare the means in each region between the ACL control group and the study group with AMG.

6.8.4 Results

Figure 6.7 shows the comparison of the mean angle between the control group of ACL rupture and the study group with AMG. Table 6-7 shows the mean difference between groups and the t-test to investigate statistical difference between groups.

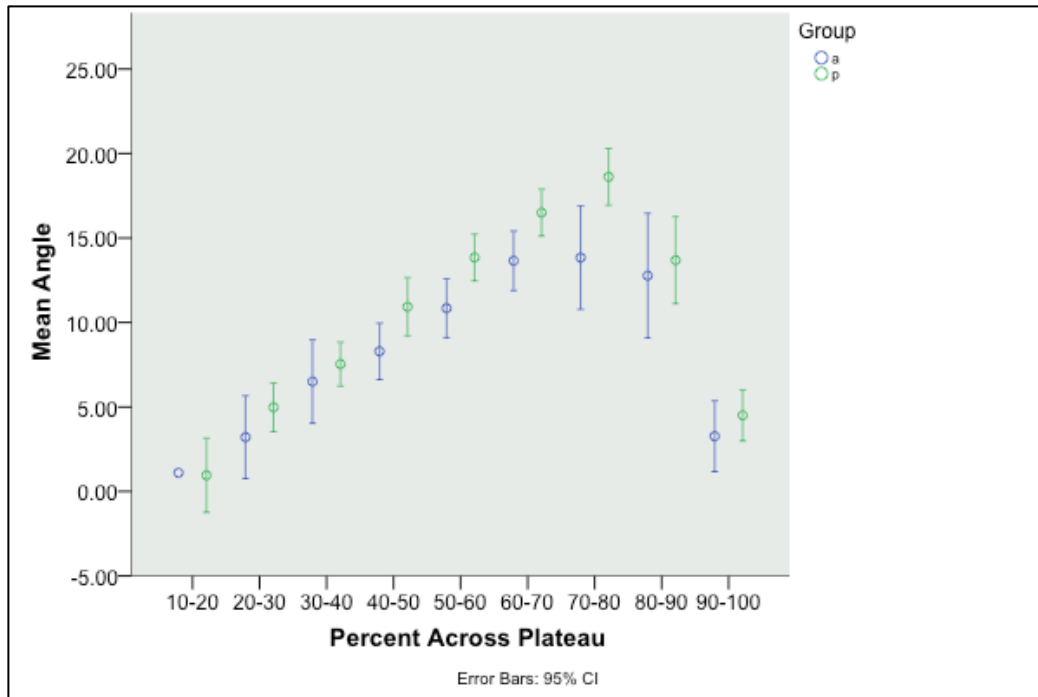


Figure 6.7 – Graph comparing mean angle across the medial tibial plateau between groups. (a=ACL control group, p=AMOA case group)

<i>Region of medial tibial plateau (%)</i>	<i>Group</i>	<i>Number</i>	<i>Mean (°)</i>	<i>Difference Mean (°)</i>	<i>T-Test p-value</i>
0-10	Control	2	5.3	2.1	0.8
	AMOA	1	3.2		
10-20	Control	1	1.1	0.145	0.97
	AMOA	11	1.0		
20-30	Control	14	3.2	1.76	0.18
	AMOA	31	5.0		
30-40	Control	16	6.5	1.04	0.41
	AMOA	41	7.5		
40-50	Control	22	8.3	2.64	0.05
	AMOA	40	10.9		
50-60	Control	20	10.8	3.00	0.01
	AMOA	43	13.8		
60-70	Control	23	13.7	2.85	0.01
	AMOA	38	16.5		
70-80	Control	23	13.8	4.78	0.003
	AMOA	39	18.6		
80-90	Control	20	12.8	0.92	0.68
	AMOA	40	13.7		
90-100	Control	6	3.3	1.24	0.47
	AMOA	29	4.5		

Table 6-7 – Mean angle by group and t-test to show difference between groups (a=ACL control group. p=partial thickness study group)

In the sagittal regions between 40% and 80% across the medial tibial plateau there was statistical difference between the control group with ACL rupture and the study group with early AMOA. The differences between the mean angles in these regions ranged between 2.6° and 4.8° . The null hypothesis was rejected. The greatest differences were between the regions between 50 and 80% across the plateau.

Future measurements of the medial tibial upslope need to be controlled for the position on the plateau at which the measurements are taken. Measurements obtained at matched regions between 50 and 80% would provide the greatest difference between groups. Additionally, the results from section 6.6 have shown that the regions with the least difference between adjacent measurements were between 50 and 70%.

6.9 Summary of validation work

A reproducible method to assess the medial tibial upslope has been presented. It was shown that the region on the tibial plateau at which the medial tibial upslope is measured significantly affects the value returned, so this would need to be controlled for in any future experiment. The region with least change in the upslope was the region between 50 and 70% across the plateau from the medial joint line to the tibial spine. The use of MRI to assess the upslope was validated using CT.

The pilot study showed that there was a significant difference in the tibial upslope between subjects with early AMOA and a control group and that

this difference was greatest in the region between 50 and 80% across the plateau. This matched well with the region with the least change in the upslope measurements.

The weaknesses of the pilot study were that the control group was known to already have knee pathology, ACL rupture, which may be related to abnormal knee morphology and so may not act as a true control group. Additionally, the case group with early AMOA had already developed cartilage loss and so the difference in upslope may have reflected a process of the disease rather than a pre-existing risk factor for the development of arthritis.

The ideal study group would be a matched group who were all normal at baseline. An incident group would then develop AMOA and a control group would not develop AMOA. The medial tibial upslope would then be compared at baseline.

7 The role of tibial plateau morphology in the development of anteromedial osteoarthritis – A nested case control study.

7.1 Aims

Chapter 6 described the development of a valid technique to measure the medial tibial upslope on an MRI scan. Whilst the pilot study described in section 6.8 proved a significant difference in the tibial upslope between two groups, the selection of each of the groups had weaknesses. The first was that the case group had already developed anteromedial arthritis and so it was unknown if the difference in the upslope preceded the development of was a result of the arthritis. The second main weakness was that the control group was known to have another knee pathology, which may have been related to abnormal knee morphology. The work described in this chapter addressed those weaknesses by investigating the medial tibial upslope in groups prior to the development of anteromedial osteoarthritis.

The aims were:

1. To investigate the role of an increased medial tibial upslope in the development of arthritis.
2. To investigate the change in the medial tibial upslope during the development of anteromedial arthritis.

7.2 Introduction

The ideal methodology to address the weaknesses of the pilot study in section 6.8 would be a longitudinal MRI study of subjects who develop arthritis with an MRI both prior and subsequent to developing anteromedial arthritis. The Multicenter Osteoarthritis Study (MOST) was able to provide a cohort of subjects with MRI scans at a 30-month interval of a group who developed AMOA and a group who did not develop AMOA during the time period.

The Multicenter Osteoarthritis Study (MOST) is a longitudinal, prospective, observational study of knee arthritis [202]. It is based in the University of California, San Francisco (UCSF) and is supported financially by the United States Government by way of the National Institute of Health and National Institute for Ageing.

The MOST principal investigators describe the overall aims of the study as “To identify novel and modifiable biomechanical factors (including physical activity-related factors), bone and joint structural factors (including those assessed by MRI of the knee), and nutritional factors that affect the occurrence and progression of OA-related knee symptoms and radiographic knee OA.”

At baseline, 3026 participants between the ages of 50 and 79 years were recruited; 60% women and 15% African American. At 30 month follow up the MOST group report 99% follow-up, 1492 are white females. Each underwent clinical and radiological assessments at baseline, 30 months and

70 months. At the time of this Thesis, the baseline and 30 month radiology was available for assessment and these provided a longitudinal dataset for MRI assessment. Whilst the MOST dataset is not open access, research proposals are accepted from external Investigators and data may be released for assessment.

It is unknown if the medial tibial upslope changes over time. Certainly when bone attrition [203] is present as part of the end stage of an arthritic process, macroscopic assessment of the tibial plateau at surgery and assessment of plain radiographs shows that the shape of the proximal medial tibial plateau is changed. This change of end stage disease, with overlying full thickness cartilage loss, is not of relevance to this study. However, this study does allow the short-term change in the tibial upslope to be assessed.

In the validation work and pilot study assessments outlined above it was unknown if the subtle changes in the depth of cartilage caused change to the shape of the underlying sub-chondral plate. Similarly, if there was seen to be a rapid change in the upslope over time then any difference in the upslope at baseline may reflect an early part of the arthritic process not detected radiologically rather than a true difference at baseline. The design of this study allowed a longitudinal assessment of any potential change in the upslope whilst a joint develops early arthritis.

If there was no significant change in the upslope over this time then it is unlikely that there would have been significant change prior to the development of AMG. This would therefore provide confidence that the

upslope measured at baseline was the subjects own anatomy rather than the result of a pathological process.

7.3 Null hypotheses

- **Study 1** - There is no difference in the medial tibial upslope at baseline between an incident group who are radiologically normal at baseline but progress to anteromedial osteoarthritis at the 30-month follow-up and a control group who are radiologically normal at both the baseline and 30-month follow-up.

- **Study 2** - There is no difference in the incident group medial tibial upslope measurements between baseline and the 30-month follow-up.

7.4 Method

The MOST principal investigators were contacted directly and research proposals submitted. The research proposal was accepted and this work is covered by the ethics approval attached to the main MOST study.

7.4.1 Study Structure

7.4.1.1 Study One

The study is a nested case control study and is outlined in Figure 7.1. The incident group was defined as a group who had no radiological signs of arthritis at baseline (Kellgren and Lawrence score 0 or 1) but subsequently developed radiological arthritis at the 30-month follow-up (Kellgren and Lawrence score 2-4). The MRI scans were then assessed to ensure that the pattern of arthritis was anteromedial, full thickness cartilage loss in the medial compartment with an intact ACL. The control group was an age and gender matched group who had no radiological signs of arthritis at either the baseline or 30-month follow-up.

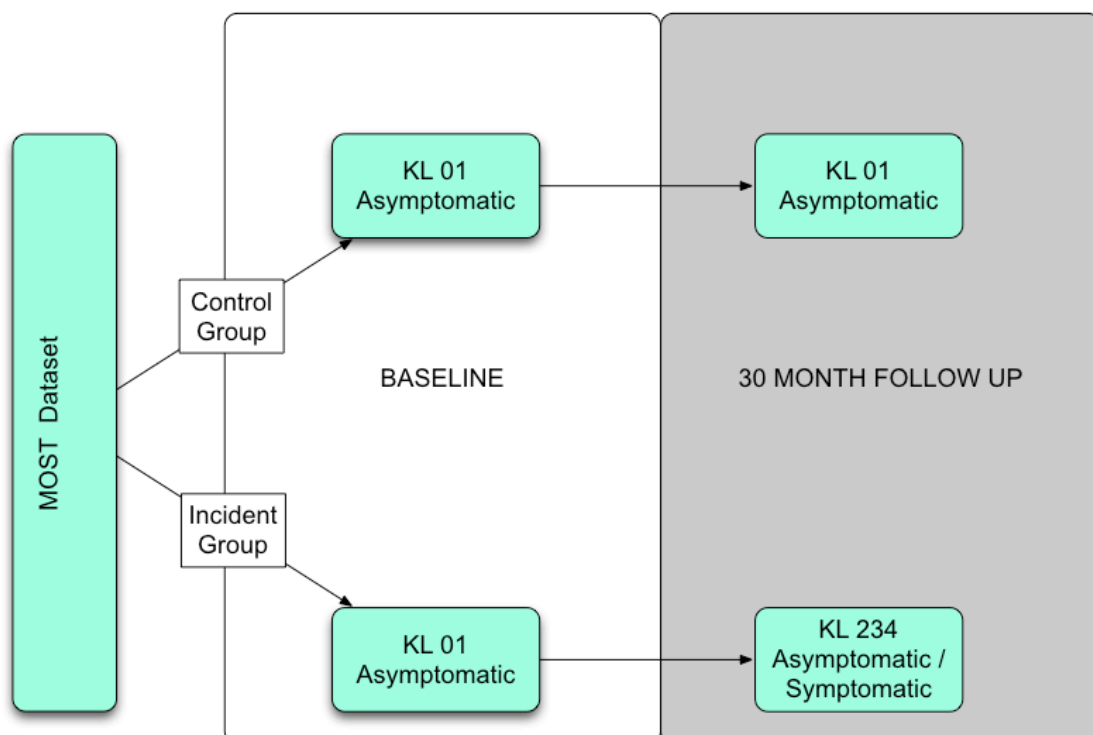


Figure 7.1 - Flowchart of MOST study structure. (KL – Kellgren and Lawrence Score)

7.4.1.2 Study Two

The medial tibial upslope was assessed at baseline in Study One. To enable the investigation of possible change in the medial tibial upslope after AMOA had developed, the upslope was assessed in the incident group at the 30-month follow up and compared to the paired measurement at baseline using a paired t-test.

7.4.2 Method of medial tibial upslope measurement

Using the validation work in Chapter 6, it was decided that the sagittal image assessed must lie between 60-70% across the plateau from the medial joint line to the medial tibial spine. If no sagittal image was in this range, the image closest to 60% was used for the upslope assessment. To ensure that the percentage across the medial plateau was known for each subject, the percentage from 0% at the medial joint line to 100% at the medial tibial spine was calculated for each sagittal image for each subject. The coronal image on which the sagittal percentage across the plateau was calculated was selected using the highest tibial spine method validated in section 6.5. Once the sagittal image had been selected, the upslope was assessed using the validated method described in section 0.

7.4.3 Power calculation

The power calculation was performed using Altmans nomogram [172]. The required difference was set at 1.5° between the incident and control group. This value was selected since it was greater than the measurement error of the technique and was less than the difference between groups in the pilot

study. The standard deviation of the data was taken from the pilot study in section 6.8 and was 3.4° . This provided a standardised difference of 0.44 and the power was set at 0.8. Reading from the nomogram provided a required sample size of 145 subjects in the incident group who developed arthritis. The MOST study group asked that twice this number were assessed in the control group.

7.4.4 Case Selection

The MOST study group coordinator provided age, gender and ethnic origin matched samples for 145 incident cases and 290 controls. Five patients of the control group were excluded after assessment of the MRI scans showed an absent anterior cruciate ligament. The MOST group coordinator provided all of the MRI scans in a blinded fashion and sent a separate file with the code to provide the specific group the subject belonged to which was only assessed after all readings had been performed. This ensured that the reader was unaware of group allocation for each patient (blinded).

7.5 Results

7.5.1 Comparison of the region of medial tibial plateau assessed in each group.

The sagittal measurement point, which needed to be controlled to ensure consistency, was normally distributed and the histogram describing the data

is shown in Figure 7.2. The measurement point between groups was then compared with an independent sample t-test and Table 7-1 shows that the mean difference between groups was 0.4%, which is neither clinically nor statistically significant. This means that any difference between the two groups is unlikely to be due to difference in position of measurement.

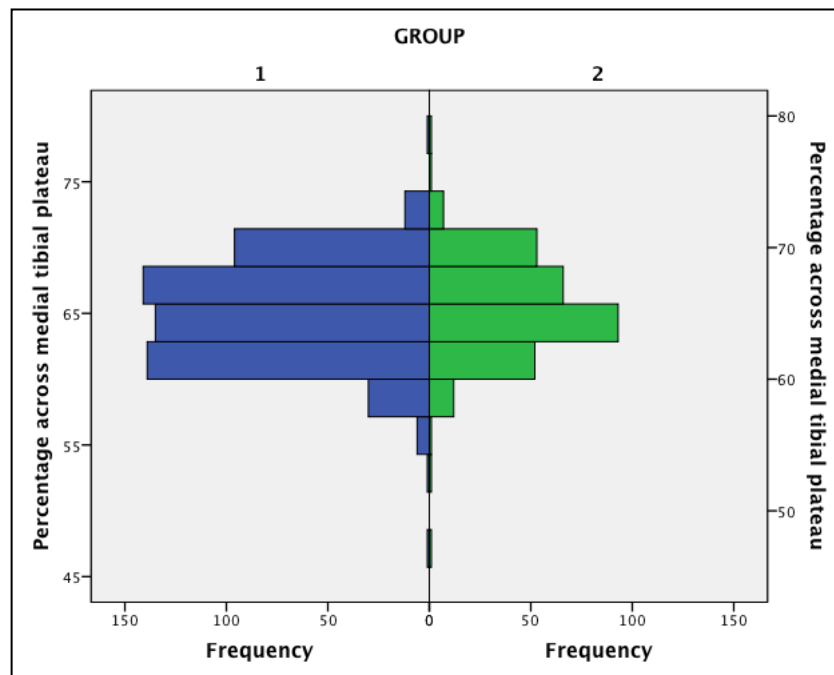


Figure 7.2 - Histogram to show sagittal position of measurement position in the two groups. (Group 1 – Control group. Group 2 – Incident group)

Group	N	Mean position of measurement	Std. Deviation	Std. Error Mean	Mean Difference (%)	p-value
Control	285	65.0	3.6	0.21	0.4	0.31
Case	145	65.4	3.6	0.30		

Table 7-1 Comparison of sagittal position of medial tibial upslope measurement in the incident and control groups.

7.5.2 Study One - Comparison of medial tibial upslope between groups

Table 7-2 summarises the data of the medial tibial upslope measured for both the incident and control group.

Group	Number	Mean	Std Deviation	Maximum	Minimum	Range
Control	285	13.21	3.53	28	7	21
Case	145	19.76	3.42	26	5	21

Table 7-2 – Summary of the assessment of medial tibial upslope between the control and incident groups.

The measurements of the medial tibial upslope in each group were normally distributed and the histograms describing these measurements are shown in Figure 7.3 and Figure 7.4.

The mean difference in medial tibial upslope between the groups was 6.54°. This is a statistically significant difference and is much greater than the error in reproducibility of measurement defined in Section 6.5.5. The null hypothesis for study one was rejected, the medial tibial upslope at baseline is significantly greater in the incident group than in the control group.

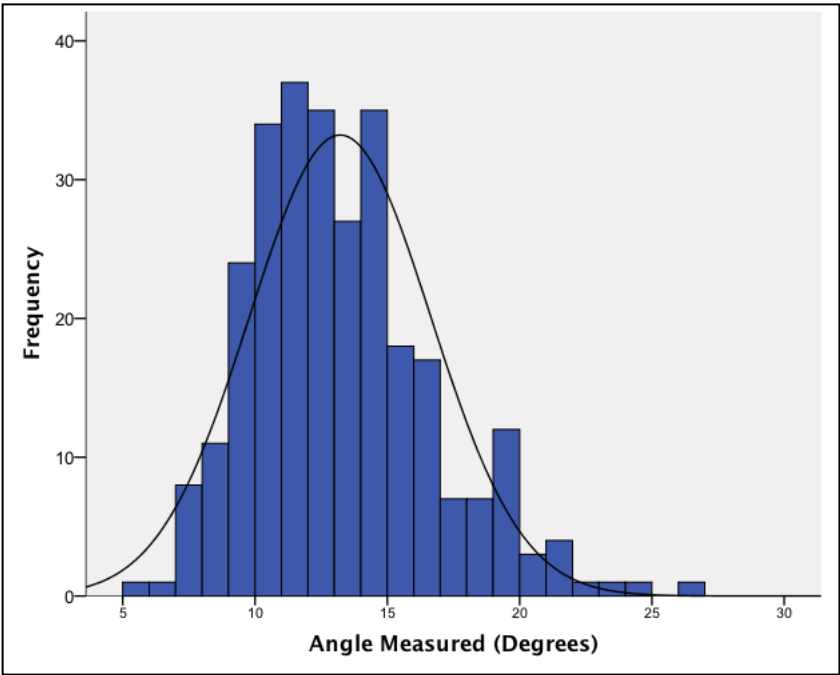


Figure 7.3 – Histogram to show medial tibial upslope measurements in the control group

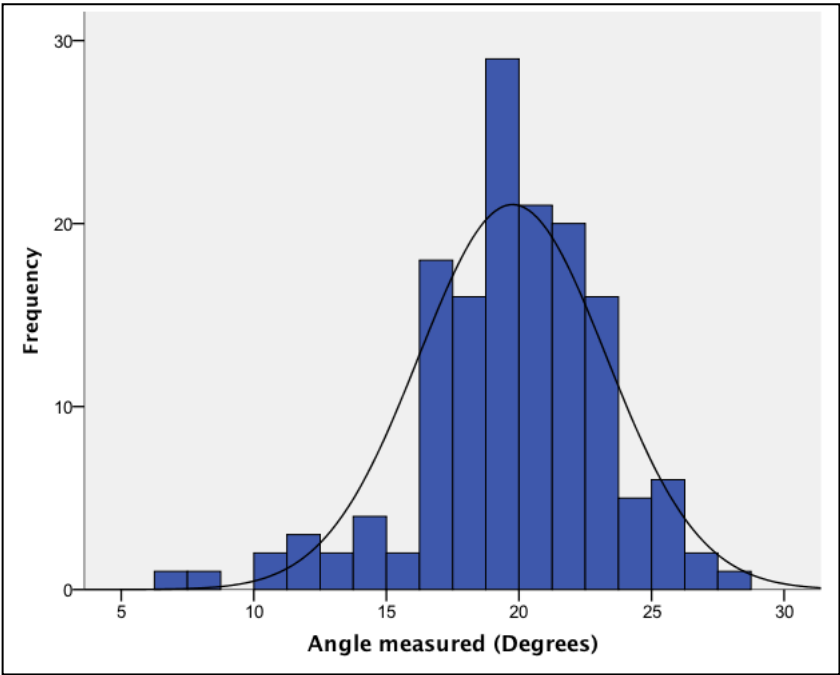


Figure 7.4 - Histogram to show medial tibial upslope measurements in the incident group

<i>Group</i>	<i>N</i>	<i>Mean measurement (°)</i>	<i>Std. Deviation</i>	<i>Std. Error Mean</i>	<i>Mean Difference (°)</i>	<i>p-value</i>
Control	285	13.21	3.53	0.203	6.54	<0.001
Case	145	19.76	3.42	0.289		

Table 7-3 – Independent sample t-test of the difference in medial tibial upslope between the incident and control groups.

7.5.3 Study Two - Assessment of change in medial tibial upslope over time

The medial tibial upslope measurements for each subject at baseline and 30 months were tabulated and assessed using a paired sample t-test. This is shown in Table 7-4. There is a 0.34° difference in the EFA between baseline and 30-month follow-up. This difference is neither statistically nor clinically significant and is smaller than the measurement error. The null hypothesis for Study Two cannot be accepted; the medial tibial upslope does not significantly change during the 30-month period that anteromedial osteoarthritis develops.

<i>Group</i>	<i>N</i>	<i>Mean measurement</i>	<i>Mean Difference (°)</i>	<i>Std. deviation of difference in mean</i>	<i>Std Error of Mean</i>	<i>p-value</i>
Baseline	137	19.68	0.34	1.06	0.09	0.71
30-month	137	19.71				

Table 7-4 – Within subject comparison of medial tibial upslope at baseline and 30-month follow-up.

7.6 Summary of results

The work in this chapter has shown that there is a baseline statistically significant difference of 6.5° in the medial tibial upslope between an incident

group who develop arthritis and a control group who do not. During the development of arthritis there is no significant change in the medial tibial upslope when paired samples are assessed.

8 The role of MRI in anteromedial osteoarthritis

8.1 Introduction

Anteromedial osteoarthritis (AMOA) is a specifically defined sub-set of knee arthritis, described as medial compartment cartilage loss in the presence of a functioning anterior cruciate ligament (ACL) [9]. The study of such a well-defined disease enables specific risk factors of arthritis to be investigated with a smaller risk of confounding factors from other patterns of arthritis than a study of more general arthritic population allows. For example, the work presented in Chapters 5 and 6. If the different types of arthritis are not recognised and investigated separately then subtle risk factors, which may be important to one pattern of OA but not another, may be missed. Indeed, recent publications by the US government FDA have called for better descriptions of the different patterns of knee OA or “phenotype” [204]. They believe that the “closer categorizations” of the different types of disease may help to understand the risk factors for development and progression of each pattern of disease rather than assuming that each is the same.

The original description of AMOA in 1991 [9] provided a description of the disease both at plain radiographic assessment and at intra-operative assessment. This enabled clinicians to recognise the disease and refine treatment options, such as partial knee replacement or high tibial osteotomy. Additionally, the plain radiographic description enabled studies, such as

those presented in Chapters 2 and 3 to assess the epidemiology and progression of a specific sub-group of arthritis.

The previous chapters in this body of work have investigated AMOA using diagnostic criteria based on plain radiographic findings, describing joint space loss and the presence and size of osteophytes. Whilst the methods used for both diagnosis and epidemiological studies are validated for both diagnostic and research purposes [22, 24, 205], they provide little information regarding the status of the intra-articular structures of the knee, such as the cartilage surfaces, meniscus and ligaments.

Magnetic resonance imaging (MRI) assessment of a knee joint enables detailed assessment of these intra-articular structures [162, 206-208]. As a consequence of this, contemporary epidemiological studies such as the Osteoarthritis Initiative (OAI) and the Multicentre Osteoarthritis Study (MOST) [202], have been using MRI in parallel with plain radiographs to investigate the progression of arthritis and risk factors for development and progression of disease. Indeed MRI data from MOST has been used in Chapter 7 to investigate the role of the morphology of the medial tibial plateau in the development of AMOA

Since the study of AMOA provides a specific study group and the largest epidemiological investigations into knee arthritis now use MRI as the main imaging tool, there was a need to be able to recognise AMOA in MRI studies. It was therefore necessary to define the MRI description of AMOA,

so that these large epidemiological studies based on MRI findings can recognise and investigate AMOA.

There has to date been only one investigation into the role of MRI in the clinical assessment of AMOA [161], and the clinical relevance of the use of MRI was questioned. However, there have been advancements in MRI technology since that publication and there are important clinical questions that MRI may be able to be answered.

This chapter had two main aims. The first was to provide an MRI description of AMOA to enable the disease to be recognised and studied in large epidemiological studies. The second aim was to investigate the relevance of modern 3 Tesla MRI in the clinical and peri-operative assessment of AMOA. Specifically, the role of MRI in the pre-operative assessment of the anterior cruciate ligament, the relation of lateral osteophytes to lateral cartilage loss

8.2 Description of the MRI AMOA scoring system

To achieve the first aim of defining the MRI description of AMOA, an MRI scoring system needed to be designed and validated. Whilst there were already MRI scoring systems in use, such as the whole organ MRI scoring system (WORMS) [160] described in Section 1.6.3, these do not allow for a general description of the pattern of disease. The WORMS system focuses on defining and mapping the change in “biomarkers” of osteoarthritis, such as chondral damage, meniscal damage, osteophytes and sub-chondral

bone marrow lesions. The scoring system is summarised in Table 8-1. The WORMS system was too complicated to define a simple description of AMOA but it was important to describe the markers included within the WORMS score, so that the description from this thesis might be translated to the knees that had already been assessed with the WORMS system.

Articular Feature	Score
Cartilage signal and morphology	0-6
Subarticular bone marrow abnormality	0-3
Subarticular cysts	0-3
Subarticular bone attrition	0-3
Marginal osteophytes	0-7
Medial and lateral meniscal abnormality	0-6
Anterior and posterior cruciate integrity	0-1 each
Medial and lateral collateral integrity	0-1 each
Synovitis	0-3
Loose bodies	0-3
Periarticular cysts/bursae	0-3

Table 8-1 – A summary of the WORMS scoring system [160]

In collaboration with a consultant musculo-skeletal radiologist, a simplification of the WORMS was devised and this is described here. The scoring system is validated in section 8.3.

8.2.1 Regions of the knee

The patellofemoral compartment was defined on a sagittal MRI as that part anterior to a line drawn from the centre of the femoral condyle to the most anterior portion of the medial meniscus, Figure 8.1. The medial and lateral compartments were defined as in Figure 8.2. This was based on the regions described in the validated WORMS, BLOKS and MOAKS [149, 152, 160] scores.

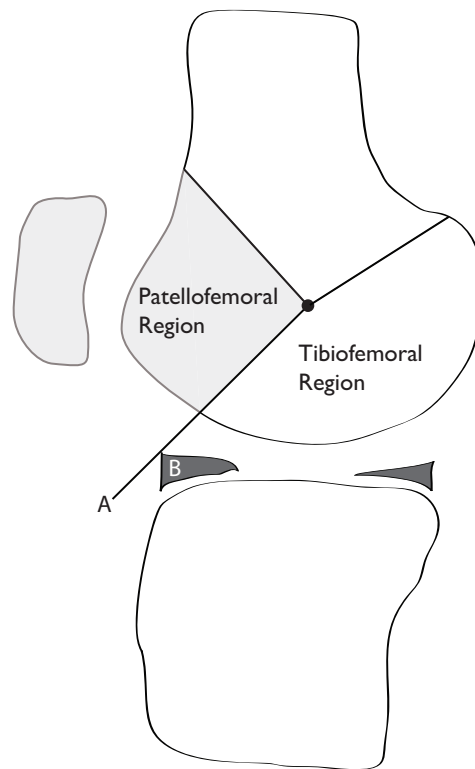


Figure 8.1 Schematic to show demarcation of patellofemoral and tibiofemoral regions – Sagittal view. The femur is depicted at the top and tibia below, with the meniscus shown in between.

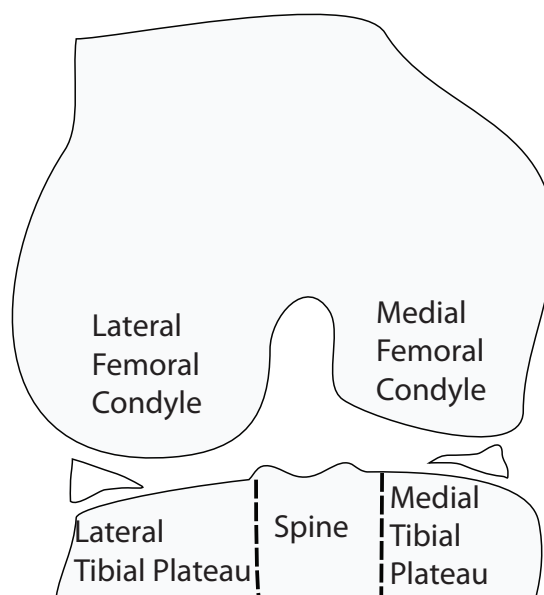


Figure 8.2 Schematic to show demarcation of tibiofemoral regions – Coronal view

8.2.2 Osteophytes

Osteophytes are a common finding in osteoarthritis and have been used to define the presence of disease [209]. They are outgrowths from the joint margins, beginning initially as cartilage and then undergoing enchondral ossification [17]. Osteophytes were scored on a scale of 0 to 3, based on the four category score in the OARSI assessment of osteophytes [24]. A score of 0 was a normal smoothly curved margin from the subchondral plate to the tibial or femoral rim with only one change in angle and with no overlap over a line drawn vertically from the tibial or femoral rim; in other words, no osteophyte was present (Figure 8.3). A score of 1 was a minor deviation from the above, 2 an obvious and 3 a large irregularity.

Osteophytes were assessed in eight locations; the joint line in each of the four tibiofemoral compartment margins on each side of the intercondylar notch and the posterior margin of each femoral condyle (Figure 8.5). The posterior femoral osteophytes are found at the medial and lateral margins of each posterior femoral condyle and have been termed the “mouse ear” osteophyte. They are most visible on the axial view (Figure 8.5) and are considered important clinically because inadequate clearance may lead to technical difficulties with prosthetic joint placement. Notch osteophytes were assessed on the coronal view.

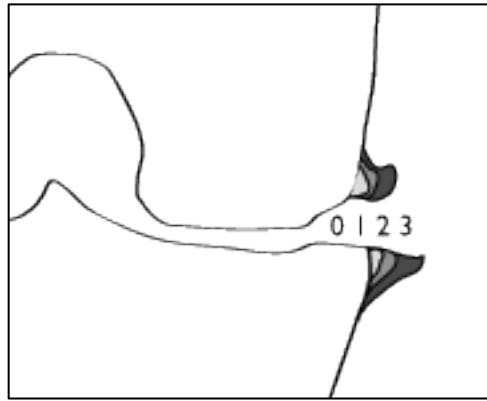


Figure 8.3 A diagrammatic representation of the grading of osteophytes



Figure 8.4 – Coronal T2 weighted MRI showing position of osteophytes and representation of bone marrow lesions and meniscal extrusion. 1, 2 and 3– bone marrow lesions, 4 – extruded medial meniscus, 5 – medial femoral osteophyte, 6 – lateral femoral osteophyte, 7 – medial tibial osteophyte, 8 – lateral femoral notch osteophyte, 9 – medial femoral notch osteophyte.

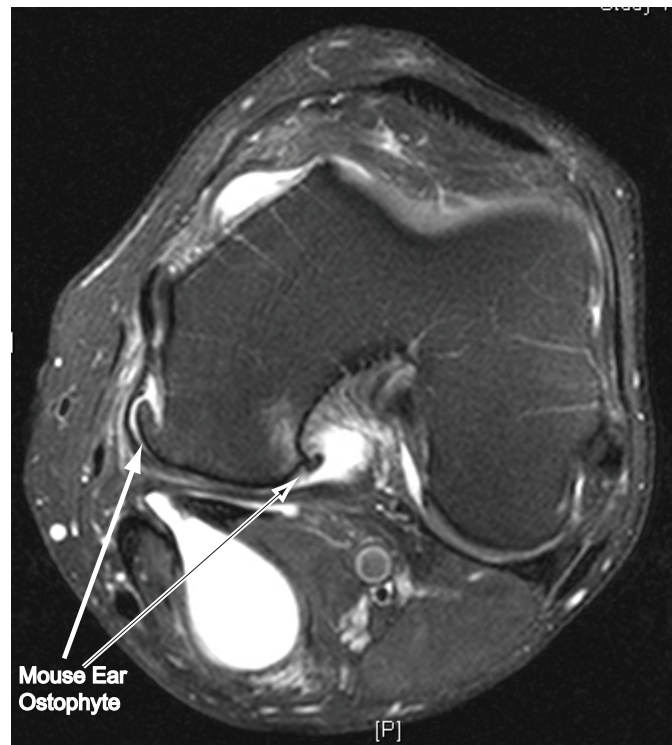


Figure 8.5 Axial T2 weighted MRI showing position of posterior femoral osteophytes – “Mouse ear osteophytes”. Note is made of a large Baker's cysts in the posterior aspect of the knee.

8.2.3 Bone marrow lesions

A bone marrow lesion (BML) is a “unique MRI-determined abnormality” [162], of ill-defined margins and high signal intensity on fat-suppressed or STIR images. It has been suggested that these may represent bone marrow necrosis or micro-trabecular remodeling [210]. A subchondral bone marrow lesion was defined as an area of high signal abutting the subchondral plate on any one of the FSPD images [141]. Bone marrow lesions were scored as present or absent, and therefore not differentiated on size. All tibiofemoral regions were assessed for the presence of BMLs (Figure 8.4).

8.2.4 Anterior cruciate ligament

The anterior cruciate ligament (ACL) was scored from 0-3, with 0 being normal; 1 when minor signal changes were present in an intact ligament; 2 with more significant splaying, kinking or ganglion formation but with preserved orientation of fibres; and 3 indicating rupture. This system was based on the work of Crema *et al* [207] and also reflects the intra-operative clinical scoring system used locally (Nuffield Orthopaedic Centre, Oxford) to grade damage to the ACL during knee arthroplasty. This system is summarised in Figure 8.6.

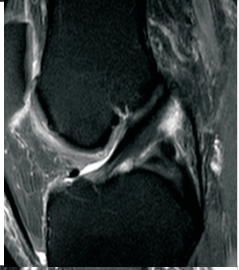
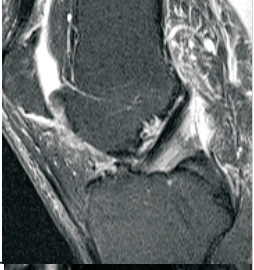
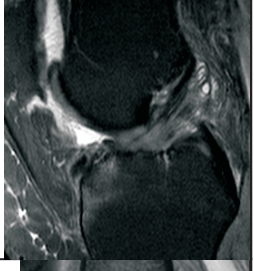
ACL- 0	Normal		
ACL - 1	Broadly intact. Minor splaying of fibres, perhaps by ganglionic material, but otherwise intact		
ACL - 2	Significant disruption of structure or laxity but with preservation of integrity between origin and insertion		
ACL - 3	Ruptured		

Figure 8.6 Summary of the ACL grading system. The column on the left shows the grade of the scoring system, the middle column describes the MRI definition with a pictorial representation of the ACL and the right hand column shows an MRI scan example.

8.2.5 Cartilage lesions

The tibial and femoral joint surfaces of the medial and lateral compartments and the patellofemoral compartments of the knee were assessed for presence of full thickness cartilage lesions. The definition of a cartilage lesion was a full thickness loss of cartilage, down to the subchondral plate and greater than 0.5cm in size [160]. The tibial and femoral sides of each

compartment were scored separately but were not further sub-divided. The medial and lateral aspects of the patellofemoral joint were also scored for cartilage loss. The trochlea (femoral side of patellofemoral joint) was defined as the area of femoral articular surface anterior to a line passing from the femoral mid-condylar point to the most anterior aspect of the meniscus in the sagittal plane (Figure 8.1). The articular surface posterior to this line was considered part of the tibio-femoral joint.

8.2.6 Meniscal damage

Meniscal damage was scored using the guidelines for semi-quantitative assessment outlined in the BLOKS, WOMS and MOAKS scores [152]. A tear was defined as 'high signal intensity in the meniscus extending to an articular surface seen in at least two consecutive slices' [160]. The score was binary, the meniscus was either torn or not. The quality of the meniscal tissue was also assessed as in the MOAKS score [152] and was rated as macerated if largely absent.

8.2.7 Meniscal Extrusion

Meniscal extrusion is known to be a risk factor for the subsequent development of osteoarthritis [211, 212]. Extrusion was measured using a previously validated method [211]. The assessment was made on the specific coronal MRI image where the medial tibial spine was maximal, the

selection of which was validated in section 6.5. The edge of the joint was defined as the most medial part of the medial tibial plateau not including osteophytes. A line parallel to the tibial shaft was drawn upward from the tibial rim to bisect the meniscus. The portion within the joint was classified as supported and that without the joint was classified as unsupported. The meniscus was classified as extruded when more than 30% of the meniscal body was unsupported. This is shown diagrammatically in Figure 8.5.

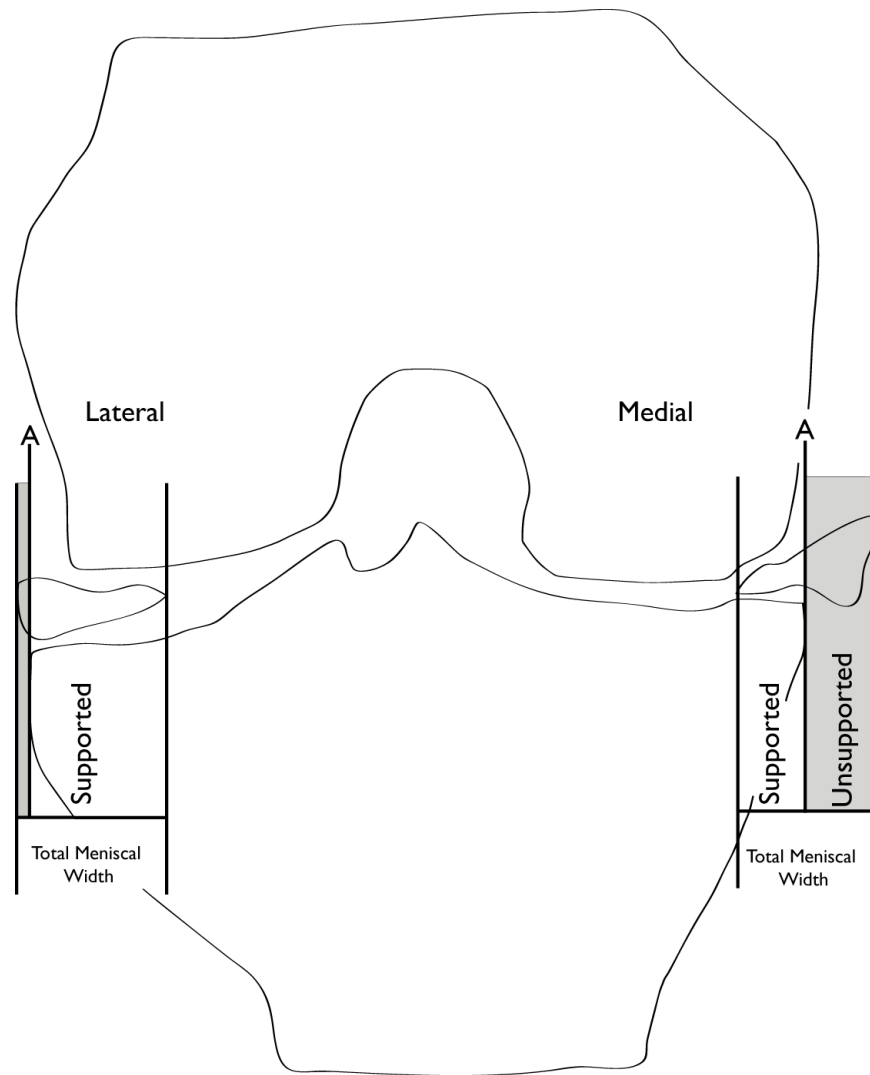


Figure 8.7 - Method of measurement of meniscal extrusion. Line 'A' is drawn vertically upward from the tibial rim, dividing the meniscus. The portion within the joint is supported and without unsupported. The meniscus is classified as extruded when the unsupported portion is $>30\%$ of the total meniscal width. In this example the medial meniscus is extruded, the lateral meniscus is not.

8.2.8 Posterior cartilage preservation

This related to an assessment of the posterior cartilage of the medial tibial plateau on the sagittal plane MRI. An intact rim of posterior cartilage behind the area of full thickness cartilage loss was scored as 1. If the posterior cartilage rim had been eroded, this was scored as 0.

8.2.9 Recoding the categorical scores

The scores for bone marrow lesions, full thickness cartilage lesions, meniscal tear and meniscal tears were binary in nature, they were either present or not. However the scores for osteophytes and ACL status were categorised into four possible outcomes; normal and then three increasing grades of size or degeneration for osteophytes and ACL status respectively. At the time of the design of the score it was unknown if the reproducibility of the 4 category scores would be suitable for use in the score. Therefore, it was decided that they would also be scored or “recoded” into simpler versions of the score, which could be used if the reproducibility of the 4 category scores was poor. The recoding of the osteophyte score was to a binary score; no osteophyte present or osteophyte present. The ACL score was recoded to a three category score; normal, abnormal and ruptured.

8.3 Reproducibility and validity studies

To assess the reproducibility and validity of the scoring system described above, a reproducibility of inter-observer and intra-observer variability and an investigation of the criterion validity was undertaken. Since the scoring system generated categorical data, a Kappa statistic was used. The Kappa statistic is a measure of inter-rater agreement for categorical data calculated by the observed agreement related to the expected agreement [172]. The formula is shown below:

$$\kappa = \frac{P_o - P_e}{1 - P_e}$$

Where κ = Kappa

P_o = Observed frequency of agreement

P_e = Expected frequency of agreement

The interpretation of these values is shown below in Table 8-2.

<i>Value of κ</i>	<i>Strength of Agreement</i>
<0.2	Poor
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Good
0.81-1.00	Excellent

Table 8-2 – Summary of the interpretation of the inter-rater agreement score for the Kappa statistic [172].

8.3.1 Intraobserver study

8.3.1.1 Method

A scoring atlas was developed as a teaching aid, which described the scoring system outlined above. The aim of the teaching aid was to standardise the grade selected for each marker. This was especially important for those MRI “biomarkers” graded from 0-3 since these were the markers in which the greatest variation was expected. The aid focused on pictorial representations of each of the grades for each of the biomarkers. This is shown in Appendix C.

The MRI scans of fifteen knees were each assessed twice, with a one-week gap between readings to decrease measurement bias. The results were tabulated (SPSS v22, IBM, USA) and Kappa statistic calculated to describe the reproducibility of the scoring for each marker.

8.3.1.2 Results

The results for the intra-observer study are shown in Table 8-3.

<i>Measurement</i>	<i>Full Score Kappa</i>	<i>Recode Score Kappa</i>
Lateral femoral BML	1.0	-
Lateral femoral cartilage loss	1.0	-
Lateral femoral osteophyte	0.1	0.84
Lateral femoral posterior osteophyte	0.1	-
Lateral femoral notch osteophyte	0.44	0.83
Medial femoral BML	1.0	-
Medial femoral cartilage loss	1.0	-
Medial femoral osteophyte	0.36	1.0
Medial femoral posterior osteophyte	0.31	1.0
Medial femoral notch osteophyte	0.21	1.0
Lateral tibial BML	0.81	-
Lateral tibial osteophyte	0.59	1.0
Lateral tibial cartilage loss	1.0	-
Lateral meniscal extrusion	1.0	-
Lateral meniscal tear	1.0	-
Medial tibial BML	1.0	-
Medial tibial osteophyte	0.38	1.0
Medial tibial cartilage loss	1.0	-
Medial posterior tibial cartilage preservation	1.0	-
Medial meniscal extrusion	1.0	-
Medial meniscal tear	1.0	-
ACL	0.1	1.0

Table 8-3 - Intraobserver Kappa assessment of scoring system. The results for the full scores are shown in the central column. The recoded scores for those scores with multiple categories, as described in section 8.2.9, are shown in the right hand column.

The results show excellent intra-observer reproducibility in all regions of the knee for the scores assessing BML, meniscal tear and extrusion, full thickness cartilage loss and posterior cartilage loss. The Kappa value for all

of these scores was 1.0. The intra-observer reproducibility for ACL assessment was poor at just 0.1. When the scores were recoded to normal, abnormal or ruptured, the Kappa value improved greatly to 1.0. This suggests variability in determining the difference between Grade 1 and Grade 2 ACL degeneration on the MRI scan. Overall, the assessment of osteophytes was rated as poor to moderate. When the recoded score was used the intra-observer reproducibility improved to be rated as excellent.

8.3.2 Interobserver study

A similar method was then used to assess the inter-observer reproducibility.

8.3.2.1 Method

Two observers (this author and a specialist musculoskeletal radiology consultant) assessed a further set of different MRI scans. Thirty-two MRI scans were each assessed once by each observer. The results were tabulated and assessed using the Kappa statistic.

8.3.2.2 Results

The results for the inter-observer study are tabulated below in Table 8-4

<i>Measurement</i>	<i>Full Score Kappa</i>	<i>Recode Score Kappa</i>
Lateral femoral BML	1.0	-
Lateral femoral cartilage loss	0.59	-
Lateral femoral osteophyte	0.77	1.0
Lateral femoral posterior osteophyte	0.70	0.78
Lateral femoral notch osteophyte	0.67	1.0
Medial femoral BML	0.84	-
Medial femoral cartilage loss	1.0	-
Medial femoral osteophyte	0.76	0.78
Medial femoral posterior osteophyte	0.79	1.0
Medial femoral notch osteophyte	0.76	1.0
Lateral Tibial BML	0.91	-
Lateral tibial osteophyte	0.82	1.0
Lateral tibial cartilage loss	0.90	-
Lateral meniscal extrusion	1.0	-
Lateral meniscal tear	0.83	-
Medial tibial BML	0.84	-
Medial tibial osteophyte	0.64	1.0
Medial tibial cartilage loss	1.0	-
Medial posterior tibial cartilage preservation	1.0	-
Medial meniscal extrusion	1.0	-
Medial meniscal tear	0.81	-
ACL	0.58	0.64

Table 8-4 – The inter-observer Kappa assessment of scoring system showing the results for the full categorical scores in the middle column and for the simplified recoded scores, where applicable, in the right hand column.

8.3.3 Validity Study

8.3.3.1 Introduction

The work described above showed that assessment of the MRI score to assess AMOA is reproducible but it does not test the criterion validity of the score. Criterion validity is when a well-established assessment method or technique, the criterion, is used to assess or validate the use of a new method. The criterion and the new technique must be related to one another, in other words the criterion validity investigates if the well-established method and the new method are measuring the same thing.

In this section the criterion validity of the new score was assessed using intra-operative assessment of the status of the cartilage surfaces and the status of the ACL as the criterion.

8.3.3.2 Method

Operative data were collected for knees from the 32 scans investigated for the inter-observer study. The status of the cartilage and the integrity and status of the ACL were assessed intra-operatively and the results compared to the MRI assessment.

Three consultant knee surgeons made the intra-operative assessment during the course of a standard unicompartmental knee replacement. This was part of their normal surgical routine [35]. The grading used for the surgical assessment is outlined below in Table 8-5.

Marker	Operative Description	AMOA MRI Score	Recode Score
Cartilage Score	Normal	0	-
	Full thickness lesion	1	-
ACL	Normal	0	0
	Synovial damage	1	1
	Longitudinal splits	2	
	Rupture	3	2

Table 8-5 Description of the surgical grading of cartilage and ACL damage. The operative description of the grade of cartilage and ACL damage is shown with the corresponding MRI score. The recode score, described in section 8.2.9, is shown in the right hand column. There is no recode score for the cartilage assessment.

Results

Table 8-6 shows the results of the Kappa assessment between the intraoperative findings and the MRI results.

Measurement	Full Score Kappa	Recode Score Kappa
ACL	0.56	0.66
Lateral femoral cartilage loss	0.83	0.82
Lateral tibial cartilage loss	0.64	0.63
Medial femoral cartilage loss	1.0	1.0
Lateral tibial cartilage loss	1.0	1.0

Table 8-6 Kappa assessment of intraoperative findings against MRI findings. The Kappa for both the full MRI score and the recoded MRI score are presented.

8.3.3.3 Summary of results

The results above show good agreement between the operative and MRI assessment of both lateral tibial cartilage loss and status of the ACL. The results for the ACL inter-rater, although still good, are not as high as the scores from the assessment of full thickness cartilage lesions, which are rated as excellent. This may be because the operative assessments were based on the surface appearance of the ACL whereas the MRI may report intrasubstance change which is not visible from the surface as discussed in the work of Sharpe *et al* [161] and this is further investigated in section 8.5.. Importantly all cases of ACL rupture or incompetence were scored as the same by both methods.

8.3.4 Summary of reproducibility and validity results

The reproducibility study showed excellent inter-observer and intra-observer results for the assessment of BML, cartilage loss, posterior cartilage preservation and meniscal extrusion of tear. The results for assessment of

the of osteophytes and the ACL were rated as poor to moderate but when recoded to a system with less categories, the reproducibility for both of these was rated as excellent.

Overall the inter-rater agreement between the operative findings and the MRI score and the assessment of the criterion validity of the MRI score, were either good or excellent. The work described in this section has shown the MRI score to be both valid and reproducible and the score is used in the next section to describe the MRI findings of AMOA.

8.4 The MRI description of anteromedial osteoarthritis

8.4.1 Introduction

The work in section 8.3 above showed that the new MRI score was reproducible and provided a valid assessment of the clinically important features of full thickness cartilage lesions and the status of the ACL. MRI assessment of knee arthritis has become an important component in longitudinal studies assessing the risk of arthritis development and progression and although AMOA is a common pattern of knee arthritis, the MRI description of it has not been defined.

The aim of this section is to define the MRI description of AMOA by describing the MRI findings of a cohort of subjects with radiographic end-stage or 'bone-on-bone' AMOA. This will provide a definition of the disease,

which may be used in epidemiological studies. Since AMOA is a specifically defined and common sub-set of knee arthritis the study of this pattern of disease, excluding different patterns of arthritis whose development or progression may be due to different risk factors, may enable a more refined investigation of the risk factors of knee arthritis.

8.4.2 Method

The MRI scans of one hundred (100) knees in 89 subjects with AMOA on plain radiographic assessment; full thickness medial compartment loss and preservation of the lateral compartment joint space, were selected from a specialist knee clinic (Nuffield Orthopaedic Centre, Oxford). As part of the subjects' pre-operative investigations prior to arthroplasty surgery, they had undergone MRI scan assessment of their affected knee. The examinations were performed on a Phillips 3 Tesla scanner. The image set included coronal, axial and sagittal fat saturated proton density (FSPD) images (TR=4000ms, TE=40-50ms, 256*256 matrix, FOV 14cm, NEX 2) and Sagittal T1 weighted repolarised DRIVE sequence (TR=630, TE=20ms, 256*256 matrix, FOV 14cm, NEX 2). These sequences were designed to provide a range of images to optimise visualisation of all tissues, as outlined in the literature review in Section 1.6.

The MRI scans were scored independently by a Consultant musculoskeletal radiologist and this author using the same validated MRI atlas described in section 8.2. The radiologist was the same person who had performed the inter-observer study described above in section 8.3.2. Each MRI reader

assessed all images independently and then any disagreement was reviewed and consensus opinion reached.

Each subject was scored for all of the categories in the scoring system. The results were tabulated to show the proportion of subjects in each grade of each category.

8.4.3 Results

Forty-three of the subjects were male and 46 were female, 11 subjects had bilateral disease, (4 male, 7 female). The mean age was 62.6 years (standard deviation 9.4 years).

The table summarising the proportion of subjects in each category of score is shown in Table 8-7.

Score category	Position / Grade	Medial Compartment (%)	Lateral Compartment (%)
Bone Marrow Lesions	Femoral	81	6
	Tibial	90	12
Tibio-Femoral Cartilage Loss	Femoral	100	3
	Tibial	100	5
Patello-Femoral	Patella	24	24
	Trochlea	20	25
Femoral Osteophyte	0	9	52
	1	30	23
	2	33	14
	3	28	11
Tibial Osteophyte	0	8	55
	1	34	28
	2	38	13
	3	20	4
Mouse Ear Osteophyte	0	7	60
	1	25	31
	2	30	7
	3	38	2
Notch Osteophyte	0	14	47
	1	35	28
	2	33	17
	3	18	8
Meniscal Extrusion	Extruded	100	2
Meniscal Tear	Nil	0	80
	Tear	63	20
	Maceration	37	0
ACL	0	26	
	1	46	
	2	25	
	3	3	
Posterior cartilage preservation	-	97	

Table 8-7 – Table to show the summary of the proportion of subjects in each category of the MRI score

All medial compartments showed full thickness cartilage loss both in the anteromedial tibial cartilage and the femoral cartilage. There were varying amounts of retained cartilage on the posterior rim of the medial

compartment but in all cases where the ACL was intact there was an obvious rim of retained cartilage. Rupture of the ACL (grade 3) was present in 3%; whilst 71% showed intra-substance high signal (46% grade 1 and 25% grade 2) and 26% were normal. Of the three cases with ACL rupture, two had lost the posterior rim of cartilage. Of clinical interest, those with suspected ACL rupture from the MRI were seen to have ruptured ACL at operative inspection. The medial meniscus was either extruded or macerated in every case with concomitant abnormal intra-substance MRI signal.

Seven percent of cases showed lateral compartment full thickness cartilage loss; two percent on the femoral joint surface, 4% on the tibial joint surface and 1% on both the femoral and tibial surfaces. Twenty-five percent of the lateral femoral and 8% of the lateral tibial surfaces had some partial cartilage thinning in the central weight bearing area. Six percent had bone marrow lesions (BML) in the lateral distal femur and twelve percent of the lateral tibiae showed BMLs.

Assessment of the lateral meniscus showed that 20% were torn and 2% were extruded. Four of the 5 cases of tibial full thickness cartilage loss were seen to have a lateral meniscal tear.

Fifty eight percent (58%) of cases were seen to have a lateral tibiofemoral osteophyte. On the medial side there was a common pattern of osteophyte formation; 93% posteromedial and postero-lateral aspect of medial femoral condyle (mouse ear osteophyte); 92% medial tibial; 91% medial femoral and

91% in the intercondylar notch. 89% of cases had osteophytes in the medial femoral and medial tibial compartments and a medial mouse ear osteophyte.

It was observed that 22% of the lateral aspect and 26% of the medial aspect of the PFJ had at least a small area of full-thickness cartilage area in either the patella or trochlea surface. Thirteen percent of all knees had some full thickness loss in both the medial and lateral aspects of the PFJ. The PFJ cartilage was normal in 16% of cases.

8.4.4 Summary of results

This section has described the MRI findings of 100 subjects with end-stage anteromedial osteoarthritis. The MRI assessment of the knee correctly identified all cases of ACL incompetence and in no cases did the MRI assessment incorrectly identify an intact ACL as being deficient. Seven subjects who seemed to have radiographic AMOA after assessment with plain radiographs were seen to have lateral compartment cartilage loss at both MRI and operative assessment. MRI assessment would therefore have a clinical role in assessment of these cases pre-operatively to guide treatment options.

All remaining subjects were seen to have AMOA. The MRI description of end stage AMOA was therefore, full thickness cartilage loss of the medial femur and tibia with an intact ACL and a preserved rim of posterior cartilage. All cases will have either a medial tibial or medial femoral osteophyte and almost 90% of subjects will have osteophytes in three positions; the medial

tibia, medial femur and posteromedial femur (mouse ear osteophyte). The lateral cartilage is seen to be intact although the lateral meniscus may have a tear or be extruded. This MRI description can be used to define the disease in epidemiological studies that use MRI scans to assess the knee.

8.5 The MRI assessment of the anterior cruciate ligament in AMOA

8.5.1 Introduction

Section 8.4 above defined the MRI description of anteromedial osteoarthritis. A previous assessment of the clinical role of MRI in AMOA by Sharpe *et al* [161] reported that MRI assessment might report ACL damage when the ACL was actually found to be intact at operative assessment. The role of MRI to assess the ACL in the peri-operative period was therefore questioned. This section investigates the reliability of the MRI assessment of the ACL to the operative findings. The criterion validity of ACL assessment at MRI was investigated in section 8.3.3 and this section investigates the agreement of the MRI and intra-operative findings of the ACL in more detail.

8.5.2 Method

The MRI and intra-operative description of the ACL from the 100 subjects in section 8.4 were cross tabulated and compared using the Kappa statistic. This was performed both for the full score containing four categories; normal, synovial damage, longitudinal splits and ruptured, and the recoded

score of normal, abnormal and ruptured as described in the validity section (section 8.3.3).

8.5.3 Results

The operative assessment of the ACL showed that rupture of the ACL (grade 3) was present in 3%, 77% showed intrasubstance high signal (43% grade 1 and 34% grade 2) and 20% were normal.

The cross-tables of the MRI and intra-operative findings are shown in Table 8-8. The Kappa value for agreement is rated 0.46, which is moderate. This appeared to be due to crossover between grades 1 and 2; when the ACL was abnormal but not ruptured. When this was recoded as described in section 8.2.9, so that grade 1 and 2 were merged, the Kappa statistic improved to 0.7, which is rated as excellent agreement. This is shown in Table 8-9.

		ACL- MRI findings				Total
		0	1	2	3	
ACL - Operative findings	Normal	17	3	0	0	20
	Synovial damage	6	28	9	0	43
	Longitudinal splits	3	15	16	0	34
	Ruptured	0	0	0	3	3
Total		26	46	25	3	100
Kappa		0.46				

Table 8-8 – Cross-table of the MRI score assessment of the ACL and intra-operative ACL findings. The Kappa score is highlighted below the table.

		ACL - MRI findings			Total
		Normal	Abnormal signal	Ruptured	
ACL - Operative findings	Normal	17	3	0	20
	Superficial damage	9	68	0	77
	Ruptured	0	0	3	3
	Total	26	71	3	100
Kappa		0.70			

Table 8-9 – Cross-table of the recoded MRI assessment of the ACL and the intra-operative ACL assessment. The Kappa score is highlighted below the table.

The results show that a normal ACL at MRI is very likely to be normal at operative inspection. Also, every ACL that was ruptured at operative inspection had also been reported as ruptured on MRI. The findings of this study are in agreement with the study of Sharpe *et al* that the significance of abnormal MRI signal in the ACL on the function of the ACL is unknown. However, MRI is a useful tool to exclude a ruptured ACL and additionally a normal ACL on MRI would predict a normal ACL at operative inspection.

8.6 The interpretation of lateral compartment osteophytes in AMOA

8.6.1 Introduction

Osteophytes are understood to be a global marker of osteoarthritis within a joint and the presence of an osteophyte within a joint is diagnostic of arthritis [22, 173]. However, despite previous MRI studies investigating the relationship between osteophytes and arthritis occurring anywhere in a joint [5], it is presently unknown if osteophytes are specific to the individual joint compartment in which they occur. When assessing a symptomatic patient in

a surgical clinic, the interpretation of the lateral osteophyte may influence the treatment options discussed with the patient. For example, the interpretation of a lateral osteophyte visible on the plain radiograph in a patient with AMOA will affect whether lateral compartment sparing surgery, such as an osteotomy or partial knee replacement, is thought of as a suitable treatment.

8.6.2 Method

The patient group for this study was the same as section 8.4, describing the MRI findings of 100 patients with AMOA. In addition to the MRI and intra-operative findings, this author also assessed the plain radiographs of this group. The osteophytes on the plain radiograph were scored using the osteophyte component of the OARSI score [24], which was described and validated in section 2.3.

The presence of an osteophyte on the plain radiograph in the lateral compartment was scored for both the lateral tibial and lateral femoral joint line. These results were cross-tabulated with the cartilage assessment from the intra-operative and MRI assessment described in section 8.4. The sensitivity, specificity and predictive values of a lateral compartment osteophyte as a marker for lateral compartment full thickness cartilage loss were calculated.

8.6.3 Results

Fifty-eight percent of cases were seen to have a lateral tibiofemoral osteophyte of some description but only 7 of these had full thickness cartilage loss. Table 8-10 describes the sensitivity, specificity and positive and negative predictive values of osteophytes in the lateral compartment as a marker for cartilage damage.

<i>Osteophyte position</i>	<i>Area of cartilage loss</i>	<i>Sensitivity</i>	<i>Specificity</i>	<i>Positive predictive value</i>	<i>Negative predictive value</i>
Lateral femoral osteophyte	Femoral cartilage loss	0.67	0.53	0.04	0.98
Lateral tibial osteophyte	Tibial cartilage loss	0.80	0.57	0.09	0.98
Any lateral osteophyte	Any lateral full thickness cartilage loss	0.86	0.44	0.10	0.98
Osteophyte on both lateral tibia and femur	Any lateral full thickness cartilage loss	0.71	0.68	0.14	0.97

Table 8-10 - Sensitivity, specificity and predictive values of lateral osteophytes as a marker of lateral cartilage damage. The results are shown specifically for femoral osteophytes with femoral cartilage loss and tibial cartilage loss with tibial osteophytes and more generally for any lateral osteophyte with cartilage loss anywhere in the lateral compartment and both tibial and femoral osteophytes with any cartilage loss in the lateral compartment.

The presence of any osteophyte in the lateral compartment showed a sensitivity of 0.86 for a full thickness cartilage lesion and the negative predictive value was 0.98. Therefore, the absence of any lateral osteophyte is a good indication of normal lateral cartilage. However, the positive predictive value for any osteophyte indicating full thickness cartilage loss is only 0.1 and the specificity is also low at 0.44. Even if there is an osteophyte on both the lateral femur and lateral tibia, the positive predictive values for cartilage damage did not improve significantly; it was only 0.14.

8.6.4 Summary of results

In the absence of a lateral compartment osteophyte, full thickness lateral cartilage loss in the lateral compartment is very unlikely. However, the presence of a lateral osteophyte should not be taken as a marker of full thickness lateral compartment cartilage damage.

These findings are important both clinically and for research purposes. In a clinical situation, a lateral osteophyte, even osteophytes on *both* the lateral femoral and tibial joint line, should not be interpreted as a surrogate marker of full thickness lateral compartment loss. In research of the pattern of arthritis, the interpretation of an isolated lateral osteophyte as lateral compartment arthritis must be questioned. This re-inforces the importance of MRI assessment of the knee in future epidemiological studies.

8.7 Summary of findings

This chapter has described and validated a simple MRI scoring system to assess the cartilage, meniscus, ACL, osteophytes and bone marrow lesions in an arthritic knee. When interpreting an MRI scan with this score, the presence of AMOA may be defined as full thickness medial compartment cartilage loss with preserved lateral compartment cartilage. The meniscus is invariably extruded or absent and whilst the ACL may exhibit varying degrees of damage, its fibres are in continuity.

Clinically, both a ruptured and defunctioned ACL and a normal ACL may be reliably assessed pre-operatively with MRI. The grades of damage between these two ends of the spectrum are less reliably assessed.

An osteophyte seen on the plain radiograph in the lateral compartment should not be interpreted as a marker of full thickness cartilage loss in the lateral compartment. In cases of uncertainty where lateral cartilage damage would alter the treatment options offered to a patient, an MRI scan may assess the cartilage reliably. In the absence of a lateral compartment osteophyte it would be highly unlikely for a full thickness cartilage lesion in the lateral compartment to be present.

9 Discussion of results

Knee arthritis is a common, progressive and painful condition, which affects the daily lives of hundreds of thousands of people in this country and millions worldwide. There is no medical treatment presently that stops the progression of knee arthritis and once the structural changes and symptoms worsen to a severe degree, the most reliable treatment of pain is with surgery. Whilst there is an ever-growing research community investigating the epidemiology, risk factors and imaging characteristics of the disease there seemed little in this literature to guide the surgeon either in their clinical understanding of the natural history of disease or the assessment of mechanical risk factors which may act as a target for surgical intervention.

The broad aim of this thesis was to use modern large epidemiological datasets and to link this to clinical insight to provide information for clinicians and surgeons about the natural history, risk factors and assessment of anteromedial osteoarthritis (AMOA), a specific type of knee arthritis.

Five main questions were formulated and addressed by a series of experiments and clinical studies:

- What is the burden of AMOA to secondary care in the NHS
- What is the prevalence and incidence of AMOA in a generalisable population and what is the timescale of progression of early AMOA to an advanced disease that may require surgical intervention?

- What is the role of lower limb alignment in the development of AMOA?
- What is the role of proximal tibial morphology in the development of AMOA?
- What is the role of modern MRI techniques in the assessment of AMOA?

The results of each chapter are discussed in turn.

9.1 The surgical burden of anteromedial osteoarthritis

9.1.1 Discussion

The investigation into the surgical burden of anteromedial osteoarthritis showed that the predominant pattern of knee osteoarthritis was unicompartmental, with 62.2% by KL, 69.7% by Ahlback and 70.2% by OARSI scoring with medial disease and 8.3%, 8.6% and 9.7% respectively with lateral disease. Bi-compartmental disease, either with or without patellofemoral damage, accounts for 26.5%, 19.4% and 20.1% respectively. Isolated patello-femoral disease accounts for 3.1% by KL and 2.3% by Ahlback. This breakdown of the compartmental pattern of knee OA attending a surgical clinic has not been described before. Interestingly, the mean age of each group increases both with the involvement of more than one compartment and increasing severity of disease.

The radiographic score used to assess the radiographs affected the reported patterning of disease. The Ahlback and OARSI scores, which are

based purely on assessment of joint space narrowing, had good agreement. However the Kellgren and Lawrence score differed significantly to both of the other scores. This difference is because the KL score diagnosed a relatively larger proportion of bilateral condylar disease and relatively less isolated disease than the other scores. This is likely to be due to the role of the osteophyte in the KL score where an isolated osteophyte in a compartment without joint space loss would classify that compartment as having disease. This difference needs to be accounted for when interpreting the patterning of arthritis reported in the epidemiological literature.

The overall breakdown of pattern of disease fits well with the epidemiological literature [213, 214] meaning there is no difference in the pattern of disease that attends a surgical clinic than that which is reported in the general population.

As expected, osteophytes were more common in the compartment with joint space loss than that without. Previous work has shown that an increased compartment specific osteophyte score markedly increased the risk of ipsilateral OA progression and was associated with malalignment to the side of the osteophyte [218]. However in this cross-sectional study presence of osteophytes in a compartment did not correlate with joint space loss in that compartment. Whilst osteophytes are a valuable marker in longitudinal studies assessing progression of disease, they may have limited surgical value in diagnosing compartment specific arthritis. In other words, a lateral joint space osteophyte with isolated medial joint space loss may not be a

marker of bi-compartmental disease, which may be of importance in surgical decision making and this was further investigated in section 8.6.

Of great interest to a surgical academic, only 24.6% of patients presented with bone on bone disease. All others presented with partial joint space loss on the radiograph. Whilst it is widely accepted that the treatment of choice for end stage disease is arthroplasty, there is no consensus as to the best treatment for partial thickness disease. Recent OARSI guidelines [219] have highlighted the controversial nature of arthroscopic joint lavage for these patients. Whilst unicompartmental replacement or high tibial osteotomy are recommended for younger patients with a unicompartmental pattern, the results of these in patients without full thickness cartilage loss may be unpredictable [35].

9.1.2 Limitations

Some of the methods require discussion. The age of patient affects both the pattern and severity of knee osteoarthritis that presents to clinic. This was therefore a potential bias in the study, if the local population did not match the nationwide population structure. Data from the Office for National Statistics showed that the population of Oxford was no different to that of the country as a whole, meaning that any bias from population structure is unlikely. The specialist centre where the study was based is a centre of Tertiary referral and therefore may have received a different pattern of referrals to other centres. To overcome this, strict criteria were used to ensure that only primary referrals from the local population were assessed. Referrals from out of the local region, those who had had any previous knee

surgery and those referred as second opinions were excluded. Therefore, findings are likely to reflect the local population rather than a specialist referral pattern.

Whilst the total proportion of patellofemoral disease is similar to the published literature, the proportion of isolated patellofemoral disease was lower than might have been expected given previous studies [215]. It is known that a skyline patellofemoral radiograph can aid in the diagnosis of PFJ osteoarthritis[216] and therefore, the low rate of isolated PFJ osteoarthritis may be related to only 21% of the entire study group having skyline views. However, all patients presenting with predominantly anterior knee pain were investigated with a skyline view and the main studies investigating the prevalence of PFJ OA also did not use a skyline radiograph as part of the diagnostic protocol [48] [217]. Therefore, whilst the lack of skyline view may have altered the proportion of unicondylar disease with PFJ involvement this author believes that any cases with isolated PFJ disease would have been investigated with a skyline radiograph.

It can be argued that those with early disease should not be diagnosed with OA since their pathology may lie elsewhere. However in this group all of those at an early stage of disease, for example KL2, had MRI investigation. These patients were only then included in the study group if the MRI showed areas of significant cartilage degeneration as the major pathology, as outlined in published guidance for the diagnosis of OA using MRI in section 1.6.2 and no other significant cause of pain such as an isolated meniscal tear.

9.1.3 Summary

In summary, this chapter showed that the predominant pattern of knee arthritis presenting to a surgical clinic was unicondylar, either with or without patellofemoral involvement and the medial compartment was most affected. In epidemiological surveys the use of a radiological scoring system based on osteophyte scoring will affect the reported compartmental pattern of OA, with more bicompartmental disease reported. Additionally, the majority of symptomatic patients in a surgical clinic with knee arthritis have only partial joint space loss and this highlights that there is presently no consensus in the surgical management of the majority of patients. As a surgical academic, the importance of the results of the chapter showing that the majority of patients presenting with only radiographic partial thickness disease is that this highlights that there is no data in the literature to help counsel patients how long it might take for the partial thickness disease to progress to a end stage disease. This was investigated in the next chapter.

9.2 The incidence and progression of anteromedial osteoarthritis

9.2.1 Discussion

In this chapter, the prevalence, incidence and progression of anteromedial osteoarthritis were investigated in a 20-year longitudinal cohort. The results showed that amongst all subjects in the study, the prevalence of knee OA was almost 54% and more than 80% of this was medial OA. In those subjects under 50 years of age, only 5% were diagnosed with radiographic OA and not one had end stage disease (KL grade 4 or 5). More than 80% of subjects older than 80 years had radiographic OA and more than 5% of these cases were end-stage disease. The mean age of those with end stage medial OA was 69 years and the mean age of those with knee arthroplasty was 71 years, whereas the mean age of those without radiographic OA was 58 years.

The incidence of AMOA, defined as new cases developing in the 20 year time period divided by all those without OA at the beginning of the study, was 0.4. AMOA accounted for 80% of all the new cases of knee arthritis during the study period. Interestingly, the incidence for each 5-year time period of the study was fairly constant at between 0.1 and 0.17 until the time period between 15 and 20 years when it increased by a large amount to 0.61.

These results fit well with the prevalence and incidence data in the literature reported for general patterns of arthritis. The majority of studies in the literature described an increasing prevalence and incidence with age. The prevalence in general populations is often reported as approximately 0.50 with the prevalence in groups over 80 years of age as high as 0.70 - 0.80. The incidence rate in the literature is generally reported as between 2-4% per year, which is very similar to the five-year incidence of 10-17% for the first 15 years of the study.

The 5-year incidence between year-15 and year-20 was 0.6, which was very high. This equated to an average annual incidence of 15%. Interestingly, the year-20 radiographs were the first radiographs to be digitally captured, in comparison to the plain film technology used in the previous visits at baseline, year 5, year 10 and year 15. This may have affected the interpretation of the markers of osteoarthritis, however there is no evidence in the literature that the change to digital capture of the radiographs should cause this increase in OA. Additionally, the same radiographic positioning protocol was used at year-20 as in all the previous assessments and no additional radiographic views were assessed, since this can increase the diagnosis of arthritis. In addition, the radiographic readings of assessors of the radiographs at year-20 had been validated against the results for the baseline to year-15 radiographs, meaning any difference in interpretation between readers should have been minimal. With the large increase in incidence between year-15 and year-20, the overall incidence and prevalence of arthritis still matched the results from other studies. This increase may therefore, simply represent the expected increase in OA as

the population ages; the prevalence of OA in a population over 80 years of age would be expected to be approximately 70%.

The normal age for a subject with early AMOA was 67 years. The clinical importance of this is that if a patient were to present with AMOA significantly earlier than this, there should be a suspicion that they may have a different aetiology to a standard presentation of AMOA. For example, a patient presenting at age 40 years. This patient would fall without the general population included in this study group and they may be at risk of not following the standard timescale of progression outlined here.

Clinically, the findings of the study into the progression of AMOA are greatly informative for surgical practice and provide information that is not presently in the literature. This is summarised below.

Investigating new cases that developed AMOA during the 20-year study, 50% progressed to KL grade 2, 2% to bone-on-bone disease (KL grade 4) and 4.5% to a knee arthroplasty. Twenty percent of the progression was within 5 years, 45% within 10 years, 64% within 15 years and all cases within the 20 years of the study. These results mean that if a subject does not have radiographic OA at age 60 years, she has a an 18% chance of developing it by the time she is 70 years old (45% of a 20-year incidence of 0.4) and a 40% chance of developing it by the time she is 80. Within this incident group, 6.5% developed end stage or 'bone on bone' AMOA during the 20-year study. When this is extrapolated to the general population, a

total of 2.6% of 60-year old women with normal radiographs will develop end stage AMOA by the time they are 80 years old.

Investigating those subjects with early radiographic OA (KL grade 2 and 3), 11% progressed to end stage disease by 10 years and 37% progressed to end stage disease within the 20 years of the study. This means that the majority (63%) of subjects with early or partial thickness radiographic disease (KL grade 2 or 3) did not progress to bone-on-bone medial arthritis during the 20-year study. In a clinical setting, patients with radiographic partial thickness may now be counseled that they have an almost 40% chance of developing 'bone-on-bone' disease over the next 20 years.

9.2.2 Limitations

The methodology of the chapter does have limitations. There is incomplete follow-up of the cohort, with the 20-year follow up including 77% of the total population. Whilst this is an excellent follow up ratio for a 20-year study, there is potential for population bias. For example, perhaps those subjects with knee pain or known knee arthritis may have preferentially attended over those with no knee symptoms. This could account for the high incidence of the cohort between the 15 and 20-year follow up.

The Chingford Study participants were all female, meaning that any extrapolation of these findings to a male population must only be done with

caution. However, it is known that knee OA is more common in women so the results here will be valid for the large proportion of cases of AMOA.

Importantly, this was a radiographic study and so provides no information regarding the *symptoms* of the subjects. Studies of symptomatic OA usually report a lower incidence of OA than pure radiographic studies so the incidence of in this study may report more cases than had symptoms. Therefore, as a clinician the incidence of AMOA reported here is likely to be higher than the incidence of symptomatic OA who may attend a knee clinic for treatment. However, the proportion of AMOA to lateral disease is very similar to that reported in Chapter 2, meaning that whilst the overall number of people with symptoms may be lower than the radiographic incidence reported here, the pattern of disease is likely to remain the same.

9.2.3 Summary

This chapter, in conjunction with Chapter 2 showed that AMOA was common both in a symptomatic population of patients in a specialist NHS clinic, where it accounted for over 60% of cases and in a general population, where the prevalence was 43% and the incidence was 0.4 over 20 years. The normal age range for developing AMOA was presented and the progression of AMOA in this group was described.

As a surgeon, not only wanting to treat symptomatic patients with end stage AMOA but also wanting to understand and perhaps influence the

development and progression of the disease, it was important to attempt to understand if there were any factors that would place a subject at increased risk of developing AMOA. Surgically, many interventions are based on altering the mechanical environment of the joint and alterations in limb alignment, such as osteotomy, are an accepted surgical treatment of knee OA [156]. However, there was no data in the literature describing the mechanical risk factors for AMOA. Investigation of the role of mechanical factors in the development may identify risk factors suitable for surgical intervention.

9.3 The role lower limb alignment in the development of anteromedial osteoarthritis

9.3.1 Discussion

This chapter investigated the role of anatomical limb alignment and the medial proximal tibial angle in the development of AMOA. There was a significant difference of 1.4° at baseline in the anatomical limb alignment between the group who developed AMOA by 20 years and the group who did not develop AMOA. The limb alignment in the AMOA was more varus than the non-AMOA group. There was a significant difference of 1.2° in the medial proximal tibial angle at baseline between the group who subsequently developed AMOA by the 20-year follow-up and the group who did not.

This was the first study to show an increased 20-year risk of developing any pattern of medial OA with an abnormality of alignment that was only in the tibia, the medial tibial plateau angle. This was also the first study to show an increased varus anatomical alignment at baseline in a 20-year longitudinal study. Whilst previous studies have reported varus alignment as risk factor for the development of OA [74], no difference in angle was reported. The knees were categorised as either varus or valgus the difference in degrees was not provided. The literature, outlined in detail in Section 1.4.2, reports conflicting results of the risk of alignment and development of arthritis. Many of the studies in the literature investigate the difference in alignment after the knee joint has already developed OA [71, 72]. Since the arthritis process

also affects alignment through processes such as cartilage, bone or meniscal loss, the significance of these studies is difficult to interpret because it is unknown if the difference in alignment in these studies is due to the arthritis disease process or whether it pre-existed the arthritis. Since the work in this chapter investigated the alignment *before* the development of arthritis, this uncertainty regarding the timing of the development of the difference in alignment is removed.

The results of this chapter are in agreement with the literature, which shows strongly that varus alignment is related to the *progression* of medial knee OA. However, many studies have not been able to show the role in *development* of arthritis due to two main factors. The first of these is the time that the population at risk was studied. This study benefitted from a long 20-year follow-up, which provided a long period of time AMOA to develop. Secondly, the pattern of arthritis, AMOA, was specifically defined. This is likely to have refined the population at risk and enabled subtle risk factors to be identified, which may have been missed in the study of a more general population. For example, the other main study to show alignment as a significant risk factor for development of knee arthritis was specifically investigating a pattern of *lateral* knee OA.

9.3.2 Limitations

The methods require some discussion. The ideal alignment parameter to assess the risk of arthritis development would have been the mechanical alignment. The only radiographs to allow reliable assessment of mechanical alignment would have been a standing long leg assessment showing the

centre of the hip joint, the knee and the talus. These were not part of the Chingford Study radiographic protocol and were therefore not available for study. The use of short leg radiographs to assess the *anatomical* alignment has been validated in the literature but the validation work in this thesis, in Section 4.3, showed that extra-articular malformation, such as fracture malunion, affected the anatomical alignment measures. The method therefore used information in the Chingford Study database to exclude subjects with previous lower limb trauma but it cannot be guaranteed that all cases of this were excluded. Whilst there was published data providing conversion factors from anatomical to mechanical alignment, these were unreliable and were not used. This chapter therefore, provides only the risk of anatomical alignment in the development of AMOA. The absolute angle of the anatomical alignment is less important than the difference between the groups and the fact that the group that developed AMOA was more varus at baseline than the group that did not develop AMOA.

The differences between the groups in both the study of anatomical limb alignment and medial proximal tibial angle were small. Whilst these differences were statistically significant it is uncertain if the difference of less than 2° would be clinically significant. However, over 20 years, these small differences may exert a significant clinical effect. These results do provide evidence to promote further study in this area. An example of future mechanical investigation would be the use of finite element analysis to assess the difference in magnitude and position of force in the medial plateau with increasing varus alignment, in the presence of an intact anterior cruciate ligament. The anatomy of the proximal tibia is complex and during

the assessment of the radiographs for this chapter, it was noted that there seemed to be different shapes to the proximal tibia in different subjects. The overall shape of the proximal tibia may change the loading characteristics of the joint and this would be an avenue of further work.

9.3.3 Summary

Clinically, these results are interesting since they show the importance of limb alignment in the development of AMOA. Limb alignment can be altered by a surgical procedure called an osteotomy. An osteotomy may be either an opening or closing wedge osteotomy and relatively lengthens one side of the femur or tibia to alter the overall limb alignment. Since this chapter showed that both overall alignment and the alignment of the proximal tibia to the tibial shaft are both risk factors for the development of AMOA the role of tibial osteotomy, which may change both of these factors in one procedure, in patients with large overall varus alignment and a varus MPTA needs further investigation. This would be of particular interest in a group with significant pain but no radiographic signs of arthritis.

This chapter showed that the limb alignment and the anatomy of the proximal tibia were a risk factor for the development and provided evidence that these might provide a target for surgical intervention. Therefore, the bony anatomy of the medial tibial plateau was investigated in more detail and this is discussed in the next section.

9.4 The role of proximal tibial morphology in the development of anteromedial osteoarthritis

This chapter defined the change in the medial tibial upslope across the plateau for the first time. The angle of the upslope was shallow most medially, steepening to a maximal angle between 50-75% across the plateau before decreasing as the plateau gradually merges into the medial tibial spine. The slope in the region of 50-65% across the plateau was relatively constant and it was in this area that differences between groups were most marked.

This Chapter was the first work to investigate the role of the medial tibial upslope in the development of AMOA in a longitudinal study, with a significant difference of more than 6° between groups. The upslope in the region between 60-70% across the plateau was significantly increased in comparison to a matched control group at baseline. There was no significant within subject longitudinal change in the tibial upslope. This suggests that the difference at baseline was not due to any previous change in the upslope before arthritis is detected.

As outlined in Section 1.4.4, whilst there is compelling evidence to the role of tibial morphology in knee ligament damage, there is limited published evidence showing that specific morphological differences in the tibial plateau area as a risk factor for the development of knee arthritis. To the author's knowledge, this is the first longitudinal study to show that a specific feature of the medial tibial plateau is implicated in the development of AMOA. One

previous study [201] has investigated the upslope of the tibial plateau but the selection of cases and control groups; with AMOA and post ACL rupture respectively, makes interpretation of the findings difficult. However, the values of the tibial upslope measured in both the control and case group of this study are similar to the angles in the previous study, supporting the findings in the Chapter.

Other studies have shown the relationship of the posterior slope and tibial plateau depth with the risk of ACL rupture. Those studies suggest that the increase in the tibial slope allows the tibia to assume a relatively more anterior position to the femur. Similarly, a decrease in the tibial depth is postulated to allow the tibia to assume an even more anterior position. In other words, the bony restraint to anterior movement of the tibia is reduced, thereby placing an extra stress on the ACL when anterior subluxation of the tibia occurs and increasing the risk of injury. Change in the coronal slope of the tibial plateau has also been shown to affect knee mechanics. An increase in the coronal tibial slope is linked to an increase in the hip adduction moment, causing a relative increase in valgus force at the knee, again implicated in increased risk of ACL rupture. If it is accepted that the morphology of the tibial plateau may affect both the stress in the structures of the knee and the angle of forces across the knee joint then it is reasonable to assume that it may have some role in the pathogenesis of osteoarthritis.

The precise description of the measurement of tibial depth in the literature is the longest measure of a line tangent to the posterior tibial slope measured

to the articular cartilage perpendicular to the tibial long axis. If the three elements of this measure; the posterior tibial slope, tibial upslope and central region are solved as a triangle, then any change in the tibial depth must be accompanied by a change in the tibial upslope. An increase in tibial depth will increase the tibial upslope and a decrease in the depth will also cause a decrease in the tibial upslope. Therefore, a decrease in the tibial depth or tibial upslope may decrease the bony capture of the knee joint as described by Freeman [111]. The significance to this study is that if the tibial upslope is increased then the bony capture of the knee joint may be relatively increased. The work of Freeman *et al* suggests that a more prominent extension facet will contact the extension facet of the femur earlier in extension, loading the articular cartilage in this area for a greater period of the gait cycle. In addition finite element analysis work (FEA) work has shown an increase in tibial cartilage stress as the tibial upslope increases [112]. Therefore, an increased tibial upslope may create increased cartilage stress for a greater period of time, leading to cartilage damage.

This Chapter addressed the weaknesses of previous studies. The design was a nested case control cohort study, whereas previous studies were cross-sectional, measuring cases already with AMOA. Therefore, if the presence of disease causes the tibial upslope to be increased, either through tibial attrition or by bony remodeling due to increase in sub-chondral stress, the angle may be falsely increased. In this study, the MRIs at baseline in each the case and control groups were prior to any arthritis detected, which should have eliminated a falsely raised tibial upslope at

baseline. However, the diagnosis of arthritis was by plain radiography. To recap, both cases and controls were radiologically Kellgren and Lawrence score 0 or 1 at baseline. The cases progressed to KL 2 or greater over 3 years while the controls did not progress. It was possible that early disease not detectable on plain radiography caused an increase in the tibial upslope. However, none of the cases had cartilage loss on the baseline MRI. In addition, there is no significant within subject progression of the tibial upslope during the study. This suggests that it was unlikely that there had been significant change in the upslope prior to radiological arthritis developing.

The range of the tibial upslope is the same in both groups, 21°. In the case group the minimum measured tibial upslope is 5° and the maximum 26°. In the control group the minimum is 7° and the maximum is 28°. However, the mean upslope is significantly increased in the case group in comparison to the control group, 19.8° and 13.2° respectively. Whilst it may seem surprising that the range is the same in each group, this author believes that this reflects the multifactorial nature of risk factors for AMOA development. The tibial upslope is unlikely to be a risk factor with full penetrance; not all with increased tibial upslope will develop AMOA and a shallow tibial upslope will not protect all from the development of AMOA. Additionally, this study is based on a 30-month risk of development of AMOA, not lifetime risk. Clearly some of the controls in this study may subsequently develop AMOA and the cases with a shallow tibial upslope are likely to have other risk factors for the development of disease.

9.4.1 Limitations

The method of the study requires discussion. The measurement of the angle between the tibial upslope and the region posterior to it was reproducible and validated, however it was a basic representation of the three-dimensional anatomy of the tibial plateau. Since this study has shown a significant difference in the upslope between groups the next avenue of study would be to investigate the difference in shape of the entire three-dimensional structure of the tibial plateau.

9.4.2 Summary

This Chapter showed that there were anatomical factors within the knee that were a risk to the development of AMOA. Further work into the shape of the proximal tibia may identify further factors that relate to the development of AMOA. Additionally, the shape of the proximal tibia may be a target for surgical intervention in the treatment of early AMOA.

9.5 The role of MRI in anteromedial osteoarthritis

The findings of the 3-Tesla assessment of knees with end-stage anteromedial osteoarthritis showed full thickness cartilage loss on both the medial femur and tibia with an intact posterior rim of tibial cartilage when the anterior cruciate ligament (ACL) is intact. A repeatable pattern of osteophyte formation was seen with intercondylar notch, posterior femoral, “mouse ear”, and lateral osteophytes all commonly seen. The medial meniscus was always damaged and extruded and in many cases the damage was so advanced that its anatomy could not be defined (macerated). A small number of cases had full thickness cartilage loss in the lateral compartment of the knee and a significant proportion of patients had bone marrow lesions (BML) and lateral meniscal tears.

The MRI description of the end-stage of AMOA provided in this chapter enables the pattern of disease to be recognised in those epidemiological that are based on MRI assessment. The description of the end stage of disease provided in this thesis may also now act as baseline against which to describe ever earlier stages of the disease.

The description of the end-stage of disease also has clinical benefits, providing a more detailed insight to the intra-articular pathology of AMG. Medial partial knee replacement is contraindicated if the ACL is deficient or significant lateral cartilage is identified, but the effect on outcome of more subtle changes in these structures is unknown.

The ACL was normal at MRI in 26% of cases and three of the subjects showed a ruptured ACL at MRI as confirmed at operation. At MRI 71% showed intra-substance high signal (46% grade 1 and 25% grade 2) and 26% assessed as normal by MRI. However, at operative assessment all ACLs with MRI high signal were functionally intact. These findings suggest that clear continuity of fibres of the ACL between origin and insertion at MRI, even if disrupted by ganglionic material, in association with intact posterior tibial cartilage on the medial side on the MRI is a robust radiological method of determining the ACL integrity and function. The MRI scan is therefore potentially useful preoperatively in determining the state of the ACL and can help in preoperative planning as to whether total or partial joint replacement is applicable. Deficiency of the ACL has been shown to be a contraindication to partial knee replacement [220], but further work is needed to assess if MRI ACL intra-substance high signal affects the longer-term outcome of partial knee replacement.

In the medial compartment the meniscus was always extruded or macerated. It is known that both meniscal tears and maceration are associated with increased cartilage loss in the same compartment [221] and our findings in the medial compartment reinforce this. There continues to be debate as to the timing of the meniscal extrusion in the development of AMG; it may be an initiating event or part of the response of the joint to cartilage loss. Studies on earlier presentations of AMG may address this question and the role of surgical meniscal augmentation in the treatment of AMG.

Twenty percent of lateral menisci were torn and there was a significant relationship between this meniscal damage and lateral compartment cartilage thinning. As in the medial joint, the temporal relationship between meniscal tear and cartilage volume loss is unknown. Bone marrow lesions in the lateral compartment should not be taken as a surrogate marker of full thickness cartilage loss since 6% of lateral femora and 12% of lateral tibiae had a BML, none of which were associated with full thickness cartilage loss. Recent work by Willis-Owen et al[222] has shown that as many as 48% of arthritic knees could be treated with UKA and that this could offer a significant economical saving in addition to a potentially superior outcome. However, one of the commonest modes of failure of a unicompartmental knee replacement is lateral progression[223] and if unicompartmental arthroplasty is to become more common an improved understanding of the risk factors for lateral progression is important. Whilst there were no cases of full thickness cartilage loss in the lateral compartment, this study identifies a sub-group of patients with abnormal radiological findings in the lateral compartment. Despite operative assessment not precluding partial replacement, 30% of cases did have lateral compartment changes such as cartilage thinning and BML on MRI and there was a significant relationship between these two findings. However the significance of these MRI findings to long term surgical outcome is unknown. A dedicated prospective study is needed to assess if the findings described here may predict lateral compartment progression.

This study confirms that varying amounts of patellofemoral cartilage damage, from normal to full thickness loss in both facets, are seen in

patients with AMG. Chapter 3 highlighted the lack of precision of using radiographs to assess the patellofemoral joint [224] and here we show that MRI offers a greater level of detail, allowing a better pre-operative assessment of cartilage in the PFJ. Whilst there is evidence that moderate cartilage damage in the PFJ does not affect outcome of partial knee replacement[225], it remains an important factor for many surgeons in assessing the joint prior to arthroplasty [226].

There is a common pattern of osteophytes in the intercondylar notch, medial tibio-femoral joint and a “mouse ear” osteophyte, which to our knowledge is described here for the first time. Eighty nine percent of all subjects had medial femoral and tibial osteophytes along the joint margin along with the “mouse ear” osteophyte. Increasing ACL damage is associated with increasing size of the intercondylar notch osteophytes. The identification of the regular pattern of osteophyte formation is important for PKR surgical technique as the posterior osteophytes are not directly seen at surgery and can be inadvertently left. If not removed, they can misdirect the seating of femoral implantation instrumentation and component, distorting the process of balancing the knee and potentially affecting long-term outcome. In the lateral compartment, tibio-femoral osteophytes were a common finding (58% of all subjects) yet in no cases was there co-existing full thickness lateral compartment cartilage loss. Therefore, lateral osteophytes should not be taken as a surrogate marker for full thickness cartilage loss and should not be a contraindication to treatment of AMOA that spares the lateral compartment.

9.5.1 Limitations

Some aspects of the methodology used require discussion. The study provides a detailed description of the MRI findings of the AMG phenotype and is not intended to be an investigation of pre-operative symptoms or post-operative outcome and these have therefore not been assessed. The MRI acquisition sequences were chosen to provide a balance that would identify most OA changes, but some detail of knee pathology may be lost due to our chosen slice thickness. Decreasing slice size will increase the accuracy of finding changes, but may decrease the cost-effectiveness of the investigation. This author believes that this protocol is a satisfactory compromise.

Whilst the kappa assessment is valuable for assessing reproducibility of categorical data, when used to assess agreement over so many variables, as is the case in this paper, the value is often low. In this light we believe our reported value of 0.63 was satisfactory. Additionally, all cases were scored only after consensus opinion. The intraoperative assessment of the ACL determined whether it was either intact and functioning or not functioning and we have shown that this functional assessment is also possible with MRI. However, this study was not designed to enable a detailed correlation of the MRI grades of ACL damage and the histopathological properties of the ACL. The significance of an increased MRI signal in the ACL on the specific structural properties of the ACL is therefore not answered and is an avenue of further work.

9.5.2 Summary

This study provided important clinical and surgically relevant information to be used in assessing patients suitability for PKR, guiding intra-operative technique and identifying patients who may be at risk of longer-term failure of PKR. Pre-operatively, isolated high signal in the ACL is seen in some patients where ACL integrity is found at intra-operative assessment. Although not a contraindication the effect of these changes on long-term outcome are not understood. This study has shown that lateral osteophytes do not necessarily imply full thickness lateral compartment cartilage lesions and are therefore not a contra-indication to unicompartmental replacement. Intra-operatively, the “mouse ear” osteophyte should be actively sought and removed to ensure proper seating of the femoral prosthesis and bearing if performing a PKR [223]. Post-operatively, the outcome of patients with MRI lateral compartment bone-marrow changes and cartilage thinning should be carefully followed.

Magnetic resonance imaging is the method of choice in the academic study of osteoarthritis, especially in monitoring structural change over time in epidemiological studies. For the first time a detailed MRI description of anteromedial osteoarthritis, the commonest pattern of knee OA seen surgically is described. The work offers important information regarding the management of patients who are candidates for partial knee replacement. In addition the recognition of different patterns of knee OA is a key aim of OARSI and FDA and this will further the understanding and identification of AMG in MRI based studies.

10 The clinical significance of this thesis and discussion of future work

This thesis has tried to link the huge resource of modern epidemiological datasets to the clinical experience of surgeons and other healthcare professionals treating patients with knee arthritis. There is increasing literature available regarding the progression of various MRI 'biomarkers' of disease but little of that seemed relevant to understanding the disease process suffered by patients whom we as clinicians meet each day. Additionally there was little information flowing the other way, from clinicians back to scientists, about the patterns of disease that we recognise clinically and why an understanding of these different patterns may help them in the investigation of disease.

There was a need to define better the pattern of symptomatic knee arthritis that presented to a surgical clinic, to confirm that what seemed to be a common pattern of disease was indeed causing a burden to the NHS or other healthcare providers. The work in Chapter 2 showed that AMOA was the most common pattern of knee OA that presented to secondary care, accounting for between 60 and 70% of all new referrals with knee arthritis, depending on the radiological scoring system used to assess the radiographs. The work in Chapter 3 also showed that AMOA was the most common pattern of knee OA in the community. The prevalence was high, affecting 43% of subjects in the study and the incidence during the study was 0.4. This work showed that AMOA was a common problem, both in the clinical and community setting.

Surprisingly, most of the patients in clinic did not have end-stage disease and they although they were symptomatic, radiologically they were too early in the disease process to discuss joint arthroplasty as a reasonable treatment option. In a clinical situation, patients with early radiological arthritis will often enquire about the time it may take for their disease to progress. There was no data in the literature to inform this discussion with patients. Chapter 3 showed that of all subjects with early AMOA, 11% progressed to 'bone-on-bone' disease within 10 years and 37% by 20 years. A 60-year old lady with no radiographic signs of OA had a 40% chance of developing AMOA in the 20-year study and 6.5% was bone-on-bone disease. This is valuable information to provide to patients when discussing management of their early knee OA.

Anteromedial osteoarthritis is a tightly defined functional and anatomical pattern of knee arthritis. The study of AMOA therefore provides an excellent cohort in which to study risk factors for knee arthritis. When focusing just on AMOA other patterns of knee OA, which may act as confounders when investigating subtle risk factors, are excluded. There is little mention of AMOA in the study of risk in knee OA and indeed in discussion with the coordinators of major international epidemiological studies during collaborative work for this thesis, they had not heard of AMOA. Understanding AMOA meant that a tightly defined group of subjects with knee OA could be investigated using large epidemiological datasets in a way that they had not been before. These datasets were then used to investigate risk factors for the development of AMOA, focusing on those that may be amenable to surgical intervention.

The work in Chapter 5 showed for the first time that an increase in medial proximal tibial angle (MPTA) of the tibia was a risk factor for the subsequent development of AMOA. The anatomical limb alignment in those who developed AMOA was also significantly more in varus than those who did not develop AMOA. Further work outlined in Chapter 6 into the shape of the medial plateau showed for the first time that the shape of the medial tibial plateau was also a risk factor for developing AMOA.

As a surgeon these findings are exciting since they provide information on factors, which lead to the development of OA. These factors are mechanical in nature and it might be that alteration of the mechanical environment of the limb may modify these risk factors and affect the development or progression of AMOA. To understand this better, further work needs to be undertaken in to the specific role of these factors in the development. Investigation of the shape of the proximal tibial metaphysis on plain radiograph may provide more information regarding the risk of knee OA than the measurement of the MPTA can provide. Similarly, a three-dimensional assessment of the tibial plateau may enable better understanding of the role of the tibial upslope in the development of AMOA. Finite element analysis of the tibial plateau and the effect of altering the tibial upslope and alignment of the limb would further clarify the nature of risk conferred by the factors identified in this thesis. In terms of surgical management strategies, anatomical assessment of the effect of osteotomy on the loading of the tibial upslope might provide further insight into the mechanism of this acting as a risk factor for AMOA development.

As both a clinical and research community, we need to understand better the process of OA development and progression. To enable this we need to move on from the radiological classification of disease and to define and diagnose AMOA at an earlier stage. This is why the MRI description defined in Chapter 8 is so important. Now that the end-stage of the disease has been defined here, ever-earlier stages of disease can be described. This will enable much more refined investigation of longitudinal change in knee arthritis and will enable even tighter inclusion criteria into studies of knee OA risk factors. The advantages of using specific patterns of knee OA have been shown by the results of Chapters 5 and 7.

Clinically, Chapter 8 assessing the clinical role of MRI showed some important findings. Whilst modern MRI techniques are still unable to define stages of ACL degeneration, MRI can determine a functioning ACL from an incompetent ACL. The work showed that cartilage lesions in the lateral compartment might be reliably assessed, which is important if compartment-sparing surgery is planned for the treatment of end-stage AMOA. Of great importance to clinical decision-making, lateral osteophytes are not a specific marker of lateral compartment cartilage loss and should not be taken as a surrogate marker for full thickness lateral compartment cartilage loss.

The work in this thesis has provided valuable information both to the clinician and scientist trying to understand the natural history and risk factors of AMOA. There is however, much still to do to try and improve our understanding of this disease.

Appendix A – KneeMorf validation data

Case	Long Leg (°)	Short Leg (°)	Difference (°)
1	3.7	3.8	-0.1
2	2.78	2.8	-0.02
3	2.16	2.1	0.06
4	0.95	5.4	-4.45
5	1.1	0.94	0.16
6	9.2	1.5	7.7
7	15.6	15.27	0.33
8	5.3	5.2	0.1
9	1.6	1.8	-0.2
10	8.7	8.6	0.1
11	2.3	2.2	0.1
12	3.8	3.23	0.57
13	5.2	4.98	0.22
14	6.8	5.84	0.96
15	0.2	0.1	0.1
16	5.12	3.56	1.56
17	7.8	7.7	0.1
18	5.7	5.5	0.2
19	2.4	2.8	-0.4
20	3.5	2.6	0.9
Mean	4.70	4.30	0.40
SD	3.64	3.39	2.06
Mean (Fracture excluded)	4.65	4.39	0.26
SD (Fracture excluded)	3.58	3.51	0.47

Table A-1 – A table to show the raw data for the short leg validation study for KneeMorf. The raw data for each method is shown with the mean and standard deviation shown below.

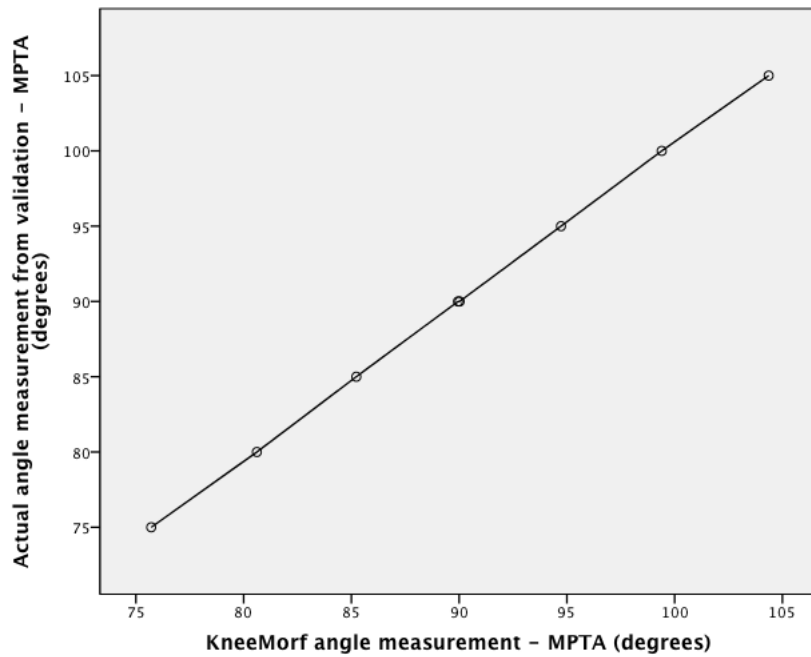


Figure A-1 - Scatter graph with line of best fit plotting the validation value of MPTA against the KneeMorf measurement. This shows good agreement between the values.

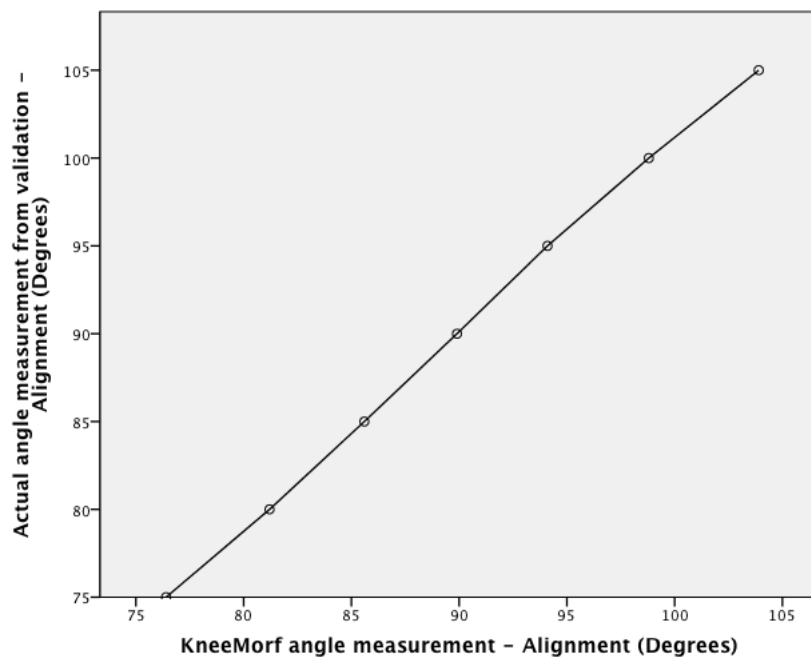


Figure A-2 - Scatter graph with line of best fit plotting the validation value of anatomical alignment against the KneeMorf measurement. This shows good agreement between the values.

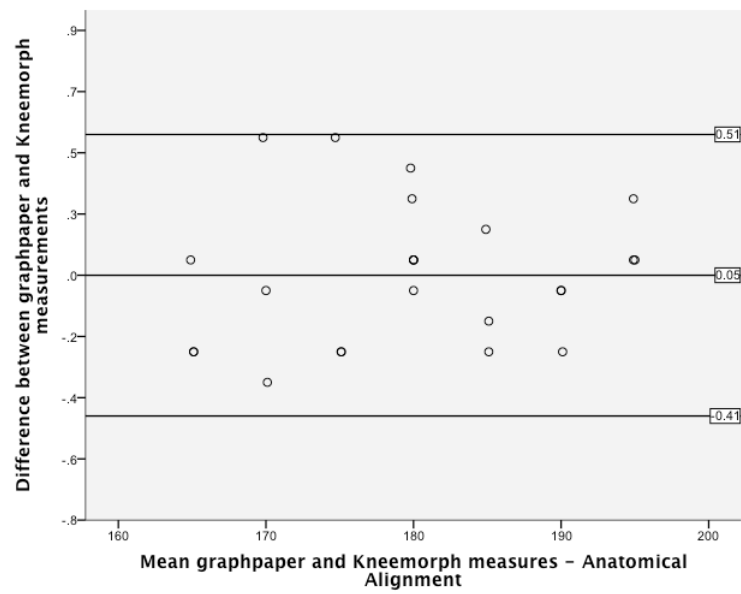


Figure A-3 - Bland-Altman plot comparing measurement of the anatomical alignment with KneeMorph to the graphpaper gold standard.

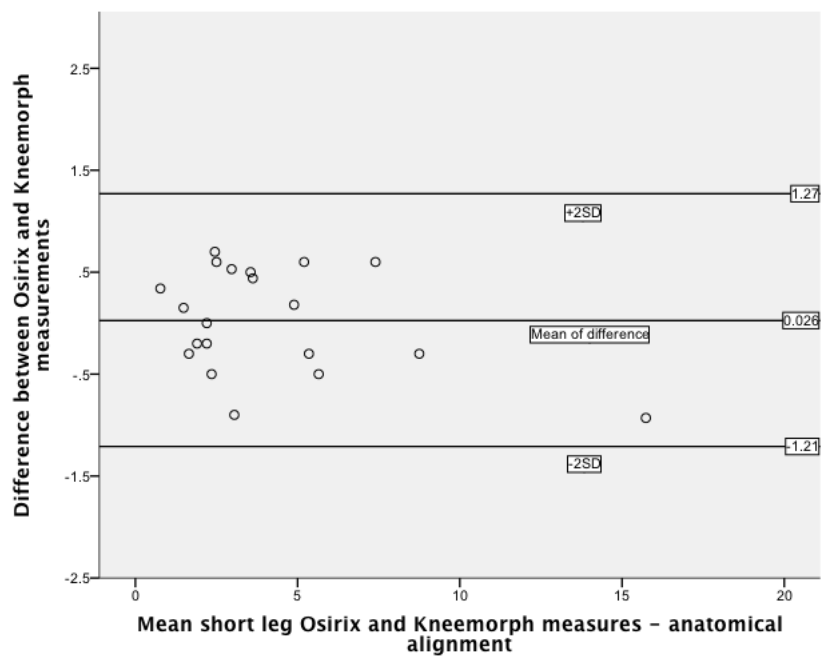


Figure A-4 - Bland-Altman plot comparing measurement of the anatomical alignment with KneeMorph to the OsiriX gold standard – From plain radiographs

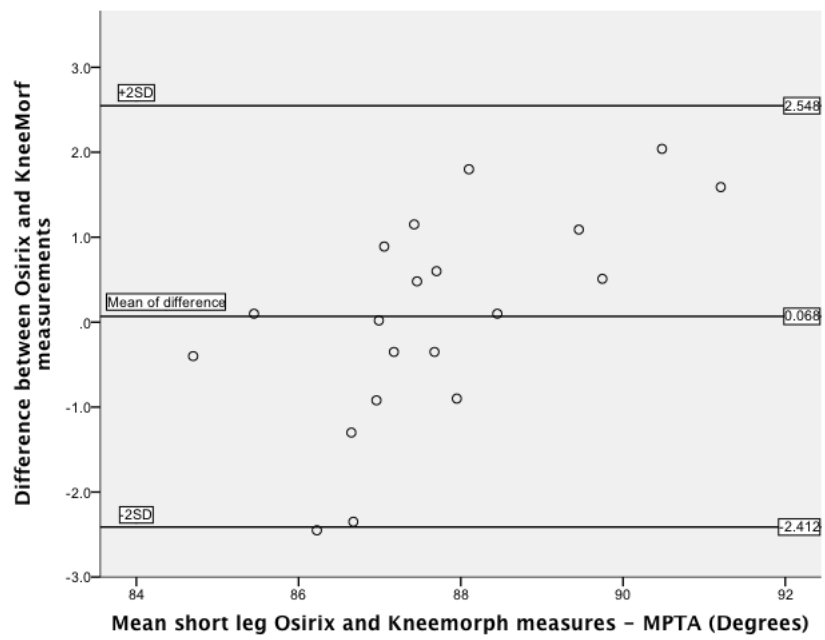
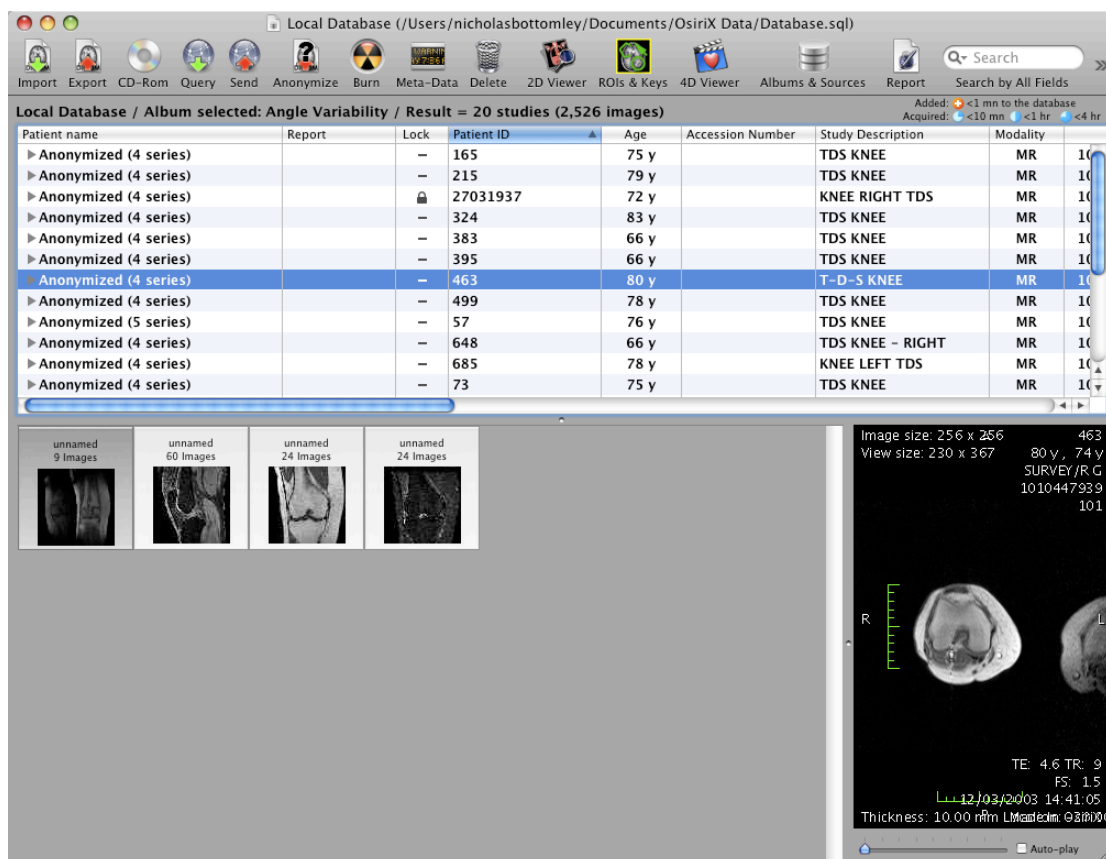


Figure A-5 - Bland-Altman plot comparing measurement of the medial proximal tibial angle with KneeMorf to the OsiriX gold standard – From plain radiographs

Appendix B – Methodology for tibial upslope reproducibility study

Measuring The Tibial Upslope

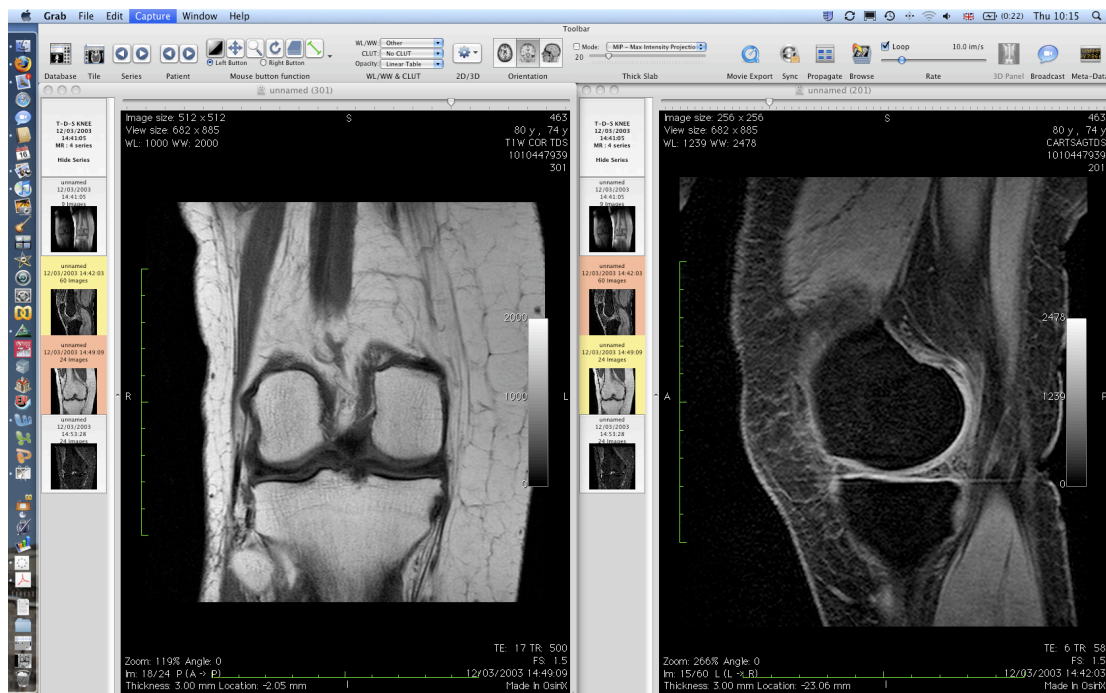
1. In the OsiriX database window select the patient ID as listed in the anonymised database. Double click on this to open a single viewer window.



2. Single click the T1 coronal image as highlighted in orange.



- To open a second viewer window to enable cross-referencing, press the 'cmd ⌘' button and single click on the T2 sagittal series (the sagittal with approx 60 images)



4. Selecting the coronal slice.

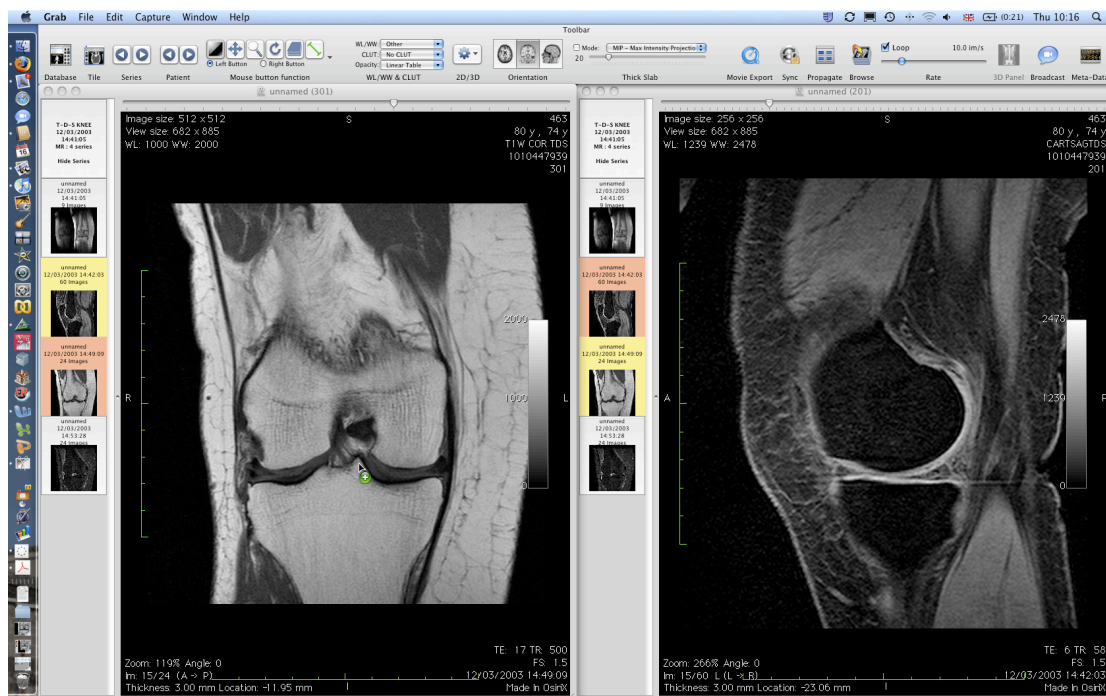
Highlight the coronal series by clicking in the window (the frame will now be red).

Scroll using the mouse or ← and → buttons

Define the medial and lateral compartments by identifying the fibula.

Identify the slice, which has the most pronounced (specifically highest) medial tibial spine. If there is the same height in more than one slice, choose the slice, which also has the highest lateral tibial spine.

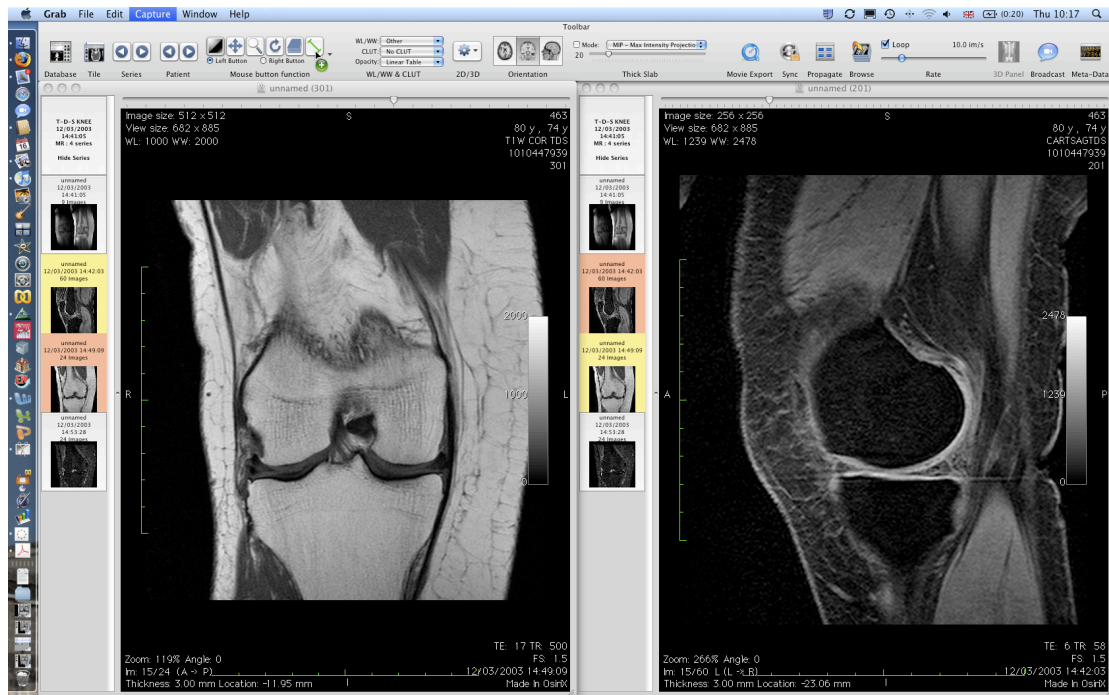
Note this image no. in the datasheet under 'coronal slice'



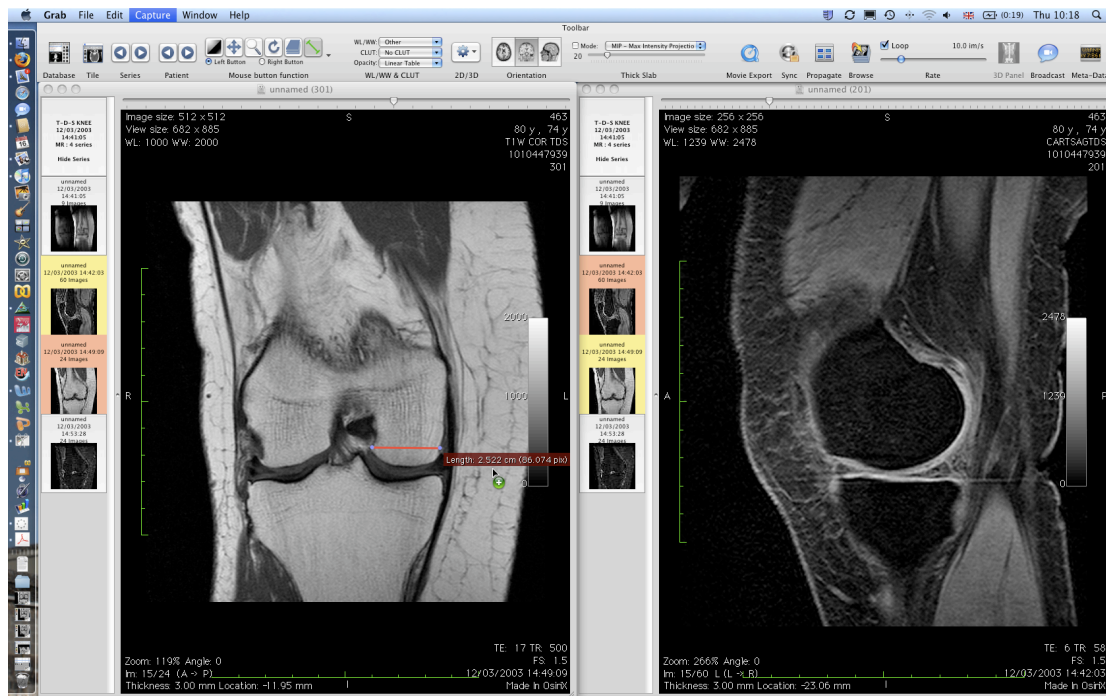
5. Selecting the sagittal slice

The angle on 2 consecutive sagittal slices is measured.

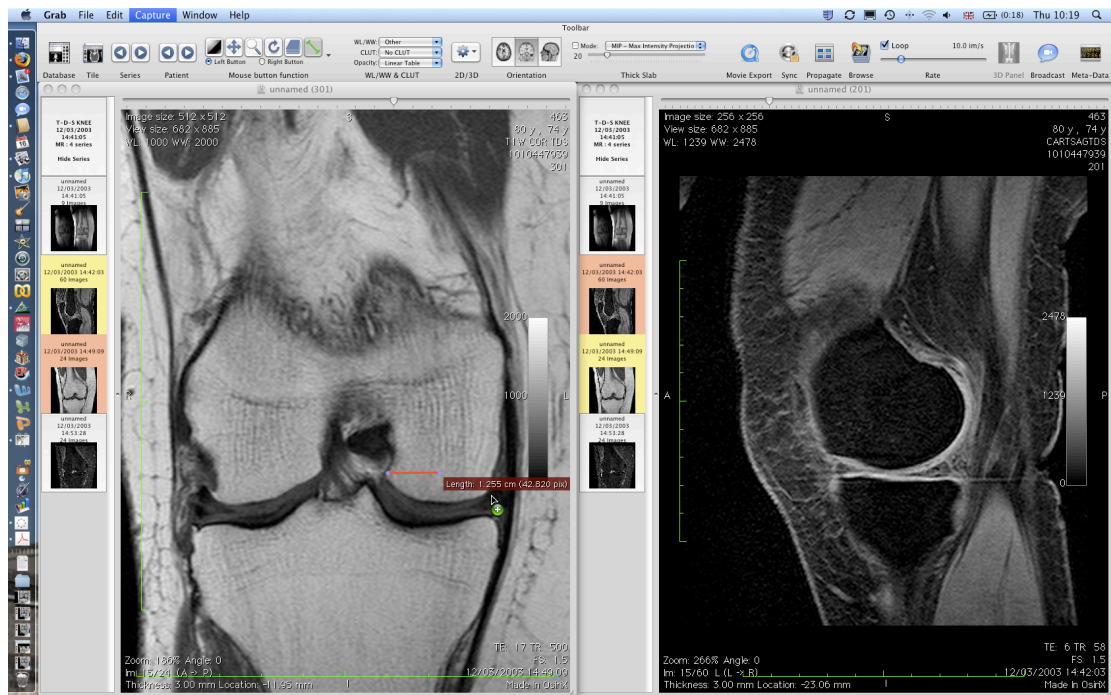
With the coronal window highlighted, select the 'measure' tool by clicking as shown below.



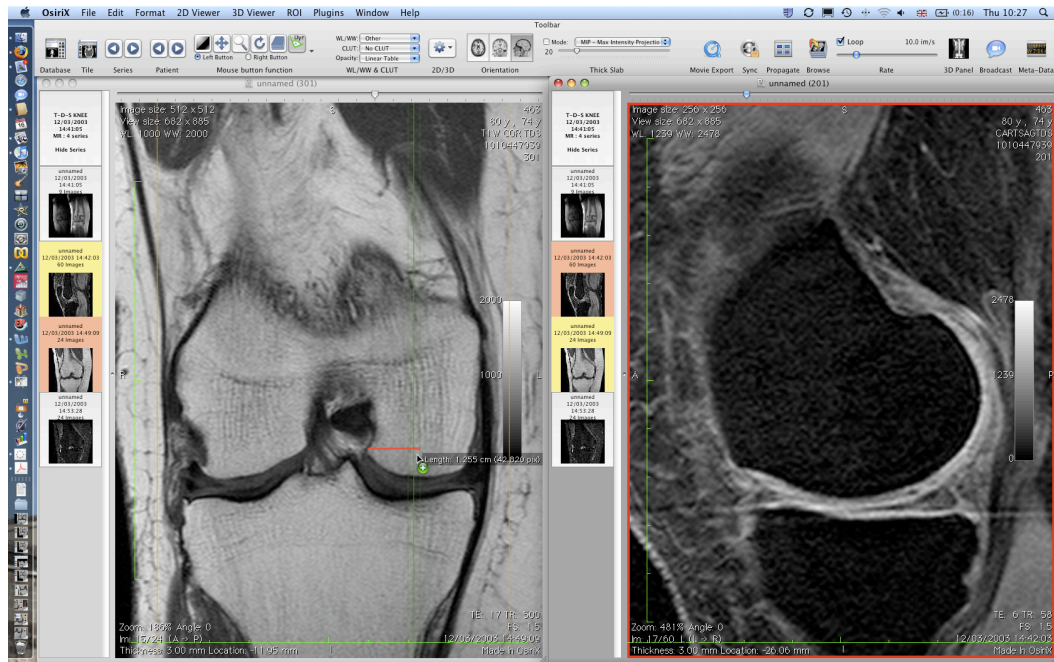
Measure the width of the medial femoral condyle at the point where the curved articular surface finishes. If there is osteophyte here, place the marker just above or below. Drag a horizontal line. Note the length of this line in the datasheet.



The datasheet will calculate the half distance of this line. Now drag the most medial marker point so that the measure of this line is as close to the calculated half distance. This marker is the position of the sagittal slice to be used.

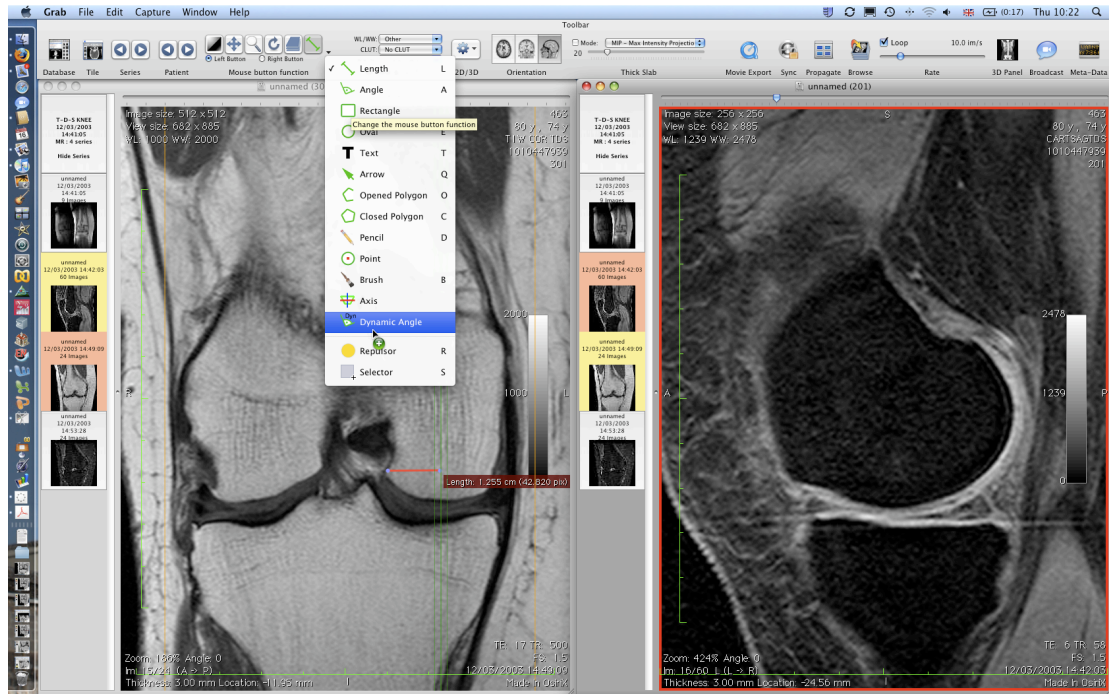


Click in the sagittal window to highlight it (the border will go red). Scroll with the mouse or ← and → buttons until the cross-reference line lies over the medial point on the coronal image. If it does not lie directly over this point, take the slice with the cross-reference line just medial to the point. This is the first slice to be measured. Note the sagittal image number in the datasheet. The second slice to be measured is the consecutive slice lateral to this. Again, note the image no and ensure that it is consecutive.



6. Measuring the tibial upslope

With the 1st sagittal image highlighted, select the 'dynamic angle' tool as shown.



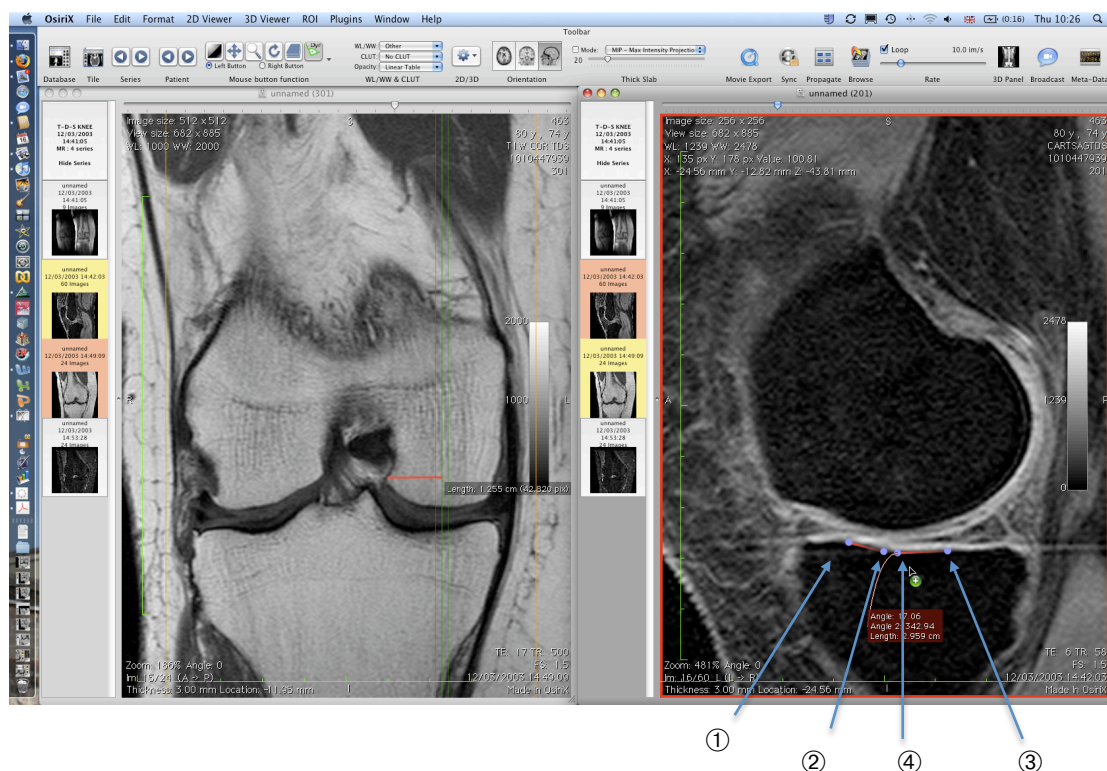
Place the pointer over the highest point at the anterior aspect of the upslope. ① Click.

Place the pointer over the bottom of the slope. ② . Click.

Move to the posterior aspect of the horizontal slope ③, not the posterior rim of the plateau. Click.

Move to the anterior aspect of the horizontal slope ④. Click.

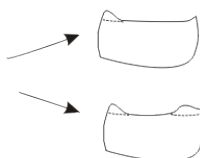
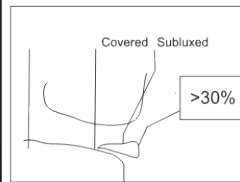
Click again on the last point to end the placement of markers. The lines can now be fine tuned to correct position if needed by click, holding and dragging the markers.



Note the angle in the datasheet.

Repeat for the next consecutive lateral slice.

Appendix C – MRI scoring summary sheet

Bone Marrow Lesion	Abnormal fluid signal abutting the subchondral plate assessed for each of the four joint surfaces
Full Thickness Cartilage Loss	Anywhere within the marked compartment
Posterior Cartilage Preservation	On the sagittal view, a preservation of the posterior tibial cartilage even with full thickness loss anterior to it. 0 = absent posterior cartilage 1 = present posterior cartilage 
Meniscal Extrusion	 0 = Tibial Overhang by <30% 1 = Tibial Overhang by >30% N = Not applicable, absent,† meniscus
Meniscal Tear	0 = Normal 1 = Tear (displaced or undisplaced) 2 = Absent or macerated to an extent that identification of a tear would be impossible
ACL - 0 	Normal
ACL - 1 	Broadly intact. Minor splaying of fibres, perhaps by ganglionic material, but otherwise intact
ACL - 2 	Significant disruption of structure or laxity but with preservation of integrity between origin and insertion
ACL - 3 	Ruptured
Osteophyte - 0	A smooth curve from the subchondral plate to the tibial or femoral rim with only one change in angle. No overlap over a line drawn vertically from the tibial or femoral ring.
Osteophyte - 1	A minor irregularity from above. Probably normal.
Osteophyte - 2	An obvious irregularity from above, probably abnormal.
Osteophyte - 3	A large irregularity, obviously abnormal.
Notch Osteophyte	Osteophyte in the intercondylar notch on the coronal view.
'Mickey Mouse' Osteophyte	'Mickey mouse' ear on the medial femoral condyle, visible on the axial view

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