University of Dundee

DOCTOR OF MEDICINE

Meniscectomy & osteoarthritis

Pengas, Ioannis

Award date: 2012

Awarding institution: University of Dundee

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 11. Oct. 2018
CHAPTER 1

INTRODUCTION
1.1 Introduction:

This thesis is a 40 year follow-up of patients who underwent open total meniscectomy as adolescents under the care of the late Professor Smillie in Tayside. The term “adolescent” in this study refers to patients under the age of 19.

Part of this patient cohort, of adolescent open total meniscectomy, was previously identified and studied at 17 and 30 years post-operatively (Abdon, Turner et al. 1990; McNicholas, Rowley et al. 2000). However, the desired group for this 40 year follow-up was identified as those who underwent radiographic evaluation in the latest, 30 year, follow-up. Those who had undergone TKA were noted as an endpoint and excluded from further investigations. The remaining, surviving and contactable, cohort was invited for review once appropriate ethical approval and sufficient funding were secured.

Three main areas were evaluated:

1. Complete Radiographic & clinical assessment, comparing where possible the index vs. opposite knee.

2. Patient reported (subjective) outcome measure scores.

3. Biochemical osteoarthritis markers from synovial and serum fluid analysis were assessed for any correlations with the other outcome measures.
1.1.1 Study’s relevance to current clinical practice

Meniscal tear is the commonest knee injury, with the incidence of meniscectomy reported as 61/100,000 of population per year (Baker, Peckham et al. 1985). These crescent-like fibrocartilage wedges have well-recognised functions in load sharing, shock absorption, secondary stabilisation (Seedhom, Dowson et al. 1974; Markolf, Mensch et al. 1976; Voloshin and Wosk 1983; Allen, Wong et al. 2000), along with proprioception, joint lubrication and nutrition of articular cartilage (MacConaill 1950; Zimny, Albright et al. 1988; Renstrom and Johnson 1990). Their importance is highlighted by the shift towards preservation by repair and indeed more recently, replacement rather than debridement or excision (Verdonk, Almqvist et al. 2007; Paxton, Stock et al. 2011).

Several authors have reported that partial or total meniscectomy has detrimental effects and leads to radiological knee osteoarthritis (OA) in up to 50% of the patients within 5-15 years post procedure (Appel 1970; Jorgensen, Sonne-Holm et al. 1987; Hede, Larsen et al. 1992). Unfortunately variable inclusion and exclusion criteria, inconsistent reporting on coexisting knee pathologies as well as a lack in standardised means of data collection and analysis, are identifiable factors that make drawing firm concussions challenging and fraught with bias (Roos, Lauren et al. 1998; Lohmander, Brandt et al. 2005).

The amount of arthroscopically resected tissue with respect to the remaining functioning peripheral rim can be difficult to judge intraoperatively. This coupled with cadaveric biomechanical findings indicating that posterior horn tears of the medial meniscus are functioning as total meniscectomies, advocating their repair; raises questions as to how many “partial meniscectomies” are functioning as total ones (Hoser, Fink et al. 2001; Allaire, Muriuki et al. 2008).
In this study the clinical, radiographic and patient reported outcomes are evaluated at a mean 40 year follow-up on a cohort of patients who underwent their primary procedure prior to their 19th birthday, under the care of a single surgeon, following the same popularised open total meniscectomy technique and rehabilitation protocol (Smillie 1970); who at the time of operation no other identifiable intra-articular pathology was documented (McNicholas 2000). Offering a unique opportunity to study the long term effects of total meniscectomy, objectively and subjectively as well as further investigate biological markers of osteoarthritis.
1.2 Aims & Objectives:

The aim of this study was to evaluate the objective and subjective outcomes of “adolescent” open total knee meniscectomies 40 years post operatively. Inclusion criteria were patients who underwent an open total meniscectomy before the age of 19 and at the time had otherwise normal knees, as documented in their operative records.

The desired cohort was identified as the patients who underwent radiological evaluation during the 30 year follow-up of the Smillie adolescent meniscectomy study (McNicholas, Rowley et al. 2000).

In particular the objectives of this study were:

1. To determine the number of patients from this cohort who reached the specific hard end point of TKA and speculate its prevalence against the general population of the same age/sex from current databases (such as the Scottish arthroplasty project).
2. To assess the cohort via the use of validated objective (radiographic outcomes, range of motion, sagittal laxity, malalignment) and subjective (KOOS, IKDC 2000) patient reported outcome measures.
3. To compare the operated knee against the contralateral non-operated knee where possible.
4. To seek any correlations, if any, between meniscectomy and outcome variables.
5. To analyse specific osteoarthritis markers and their correlation with the objective and subjective outcomes.
CHAPTER 2

Background, Anatomy & Literature Review
Before embarking on the intricacies of this thesis it is important to present the basic anatomy of the knee along with the biomechanical properties and structural make up of the subunits in question i.e. the articular cartilage and the meniscus. This will help to understand their relationship with the ensuing knee osteoarthritis.

2.1 Osteoarthritis:

Osteoarthritis ensues when the stresses on joint tissues exceed their physiologic limits and overwhelm the protective mechanisms. It’s a slowly progressive joint disorder, usually occurring later in life, and primarily affecting the hands and weight bearing joints (Mankin 1993), with trauma being one of the predisposing factors (Sherman, Warren et al. 1988; Cicuttini, Forbes et al. 2002). Changes in cartilage metabolism precede the macroscopic and radiographic changes (Caterson 1992) of articular cartilage loss, associated with varying degrees of osteophyte formation, subchondral bone change, and synovitis (Pritzker 2003; Watt and Doherty 2003). Joint pain, stiffness, reduced activities of daily living and crepitus are the symptomatic consequences of the disease (Dieppe and Lohmander 2005).

As the causes of osteoarthritis are yet to be defined, “risk-factors” are used in an attempt to identify causation of the joint pathology. Attempts to identify the epidemiology and by extent the “risk-factors” of knee osteoarthritis were undertaken in the “Framingham study” (McAlindon, Wilson et al. 1999). Heavy physical activity but not moderate activity was found to be of significance in the elderly and obese population. This pattern of joint injury, malalignment and obesity along with heavy physical activity was also identified in other studies (Anderson and Felson 1988; Kettelkamp, Hillberry et al. 1988; Felson, Zhang et al. 1997; Sharma, Lou et al. 2000).

Degeneration of articular cartilage in osteoarthritis is believed to be governed by two phases, the biosynthetic and the degradative phase. In the first, cells resident in cartilage
attempt to repair the damaged ECM (extracellular matrix) and in the latter matrix synthesis is inhibited with chondrocyte enzymes digesting the ECM leading to cartilage erosion (Goldring 1999; Goldring 2000).

Risk factors of osteoarthritis can be regarded as extrinsic or intrinsic. Extrinsic factors such as physical activity and injury, whilst intrinsic factors include malalignment, AP laxity, congenital abnormalities and meniscectomy (Sharma 2001).

Injuries resulting in ligamentous and/or cartilaginous damage have the potential to lead to knee osteoarthritis (Gelber, Hochberg et al. 2000) regardless if their mode of treatment is conservative or surgical (Noyes, Mooar et al. 1983; Casteleyn 1999). So powerful is the relationship between joint instability and osteoarthritis that current animal study models utilise this to induce osteoarthritis (Brandt 1991; Brandt 1991; Suter, Herzog et al. 1998; Setton, Elliott et al. 1999; Kamekura, Hoshi et al. 2005; Matsui, Iwasaki et al. 2009).

In animal studies where the meniscus was removed, more changes were noted than in the sham-operated knees (Messner, Fahlgren et al. 2001). Meniscectomy is associated with radiographic progression of osteoarthritis (McNicholas, Rowley et al. 2000; Fabricant and Jokl 2007) and with long-term functional limitations once radiographic osteoarthritis is established (Roos, Ostenberg et al. 2001).

Osteoarthritis overall affects 13.9% of adults ≥ 25 and 33.6% ≥65; an estimated 26.9 million US adults in 2005 up from 21 million in 1990 (Centers for Disease Control & Prevention USA, www.cdc.gov ). The Scottish Arthroplasty project (http://www.arthro.scot.nhs.uk/) and the Swedish Knee joint registry (http://www.knee.nko.se) reports indicate that the average age for a primary Total knee arthroplasty (TKA) is above 69y old.
Interestingly osteoarthritis along with Alzheimer’s has been characterised as a “high burden diseases with no curative treatments”, by WHO (World Health Organisation), as both are common and the available treatments are ineffective in reversing disease progression (Kaplan 2004). The major challenge characterising both diseases is the absence of biomarkers in diagnosing, monitoring progression and effect of treatment (Lohmander 2008).

Osteoarthritis has been regarded as a progressive condition, but several studies indicate that few individuals progress rapidly within the study group (Dieppe, Cushnaghan et al. 1997; Sahlstrom, Johnell et al. 1997; Paradowski, Englund et al. 2004). This may go some way in explaining why only a small proportion of the vast numbers affected by osteoarthritis in the community ultimately undergo arthroplasty surgery. The studies supporting this finding are of short to medium term follow-up.
2.2 The Knee:

2.2.1 Gross Anatomy & Function

The knee joint is the largest synovial joint in the body and was originally described as a hinge, but to view it as such would be a mistake. The joint movement is governed not only by the bony geometry but also by its ligaments and supporting soft tissue structures.

The knee joint comprises of the patellofemoral and tibiofemoral joints, collateral and cruciate ligaments, menisci and the joint capsule. Its primary stabilisers with regards to sagittal translation are the cruciate ligaments with the collaterals, capsule and menisci providing additional, secondary restraint (Noyes, Grood et al. 1980). The articular surfaces hold the bones apart and transmit compressive forces across their articular cartilage, whereas the ligaments hold the bones together resisting distraction by transmitting tensile stresses along their fibres (Butler, Grood et al. 1978).

2.2.2 Knee Biomechanics

The knee is capable of six degrees of freedom: three rotations and three translations. Knee motion is described according to three principle axis: the tibial shaft, the epicondylar and the anteroposterior axis (AP) which is perpendicular to the others (Grood and Suntay 1983). Any translation along these axes is referred as proximal-distal, medial-lateral and anterior-posterior; rotations about these axes are referred to as internal-external, flexion-extension and varus-valgus respectively (Figure 2.1).
As the normal tibia has a posterior slope of an average 10° (Matsuda, Miura et al. 1999; Chiu, Zhang et al. 2000) in conjunction with the geometry of its cruciate ligaments and distal femur, the femoral “rollback” phenomenon is observed during knee flexion. The femoral articular surface slides posteriorly during flexion allowing a greater range of movement before femoral and tibial impingement occurs (Figure 2.2).

Most knee motion takes place in the sagittal plane with knee flexion-extension; this varies from 5°-10° of hyperextension to 150° of flexion. The normal walking ROM has been recorded from up to 25° flexion in stance to 50° in swing phase and in stair
climbing up to 100° during swing phase (Nadeau, McFadyen et al. 2003). Maximum knee flexion during squatting activity reaches peak angle of up to 150° (Nagura, Dyrby et al. 2002).

As noted above the primary restraints of the AP translation are the cruciate ligaments, this has a typical range of 3-5mm (Fukubayashi, Torzilli et al. 1982) allowing enough laxity to facilitate optimum tibiofemoral contact and reduce shear effects.

A path of motion is found to be associated with the movement of an intact unloaded knee (Wilson, Feikes et al. 2000). The primary feature of this path is tibial internal rotation coupled with knee flexion; along with proximal, medial and posterior displacement of a reference point with flexion. Knees that showed substantial differences in their flexion/extension paths, in the above mentioned study, were found to have confirmed arthritis and/or MCL injury. These findings support the theory of altered biomechanics/kinematics in injured and arthritic knees.

2.2.3 The patellofemoral joint

In vivo patella tracking studies demonstrated that the patella is pulled laterally in terminal knee extension as the patella disengages from the femoral trochlear groove (Brossmann, Muhle et al. 1993). The force vector from vastus lateralis (the largest component of quadriceps muscle group) is roughly in line with this movement (Farahmand, Senavongse et al. 1998). In knee flexion the patella moves medially as it passes the trochlear groove and this engages the lateral patellar facet in the trochlea. Following trochlear engagement and as the knee flexes further, the patella moves laterally once again onto the distal femur (Heegaard, Leyvraz et al. 1994; Nagamine, Otani et al. 1995).
2.2.3.a Patellofemoral Joint Forces

The extensor mechanism is responsible for the reactive forces that arise in the patellofemoral joint. With the knee in extension the patellar (PT) and quadriceps tendon (QT) tension forces are almost in line with one another (in the sagittal plane) and there is little force to load the patella against the femur. In the coronal plane the Q angle results in a lateral force on the patella itself.

As knee flexion progresses, the sagittal angle between the PT and QT closes and their vectorally added tensions load the patella against the femoral groove (Figure 2.3).

![Figure 2.3](image)

**Figure 2.3** The extensor mechanism viewed in the sagittal plane: the forces acting onto the patella may be approximated by three major actions: Q (quadriceps) and (PT) patellar tendon tensions, and the JF (joint reaction force). The force passes through the distal part of the patella with the knee in extension and through the proximal part when in flexion. (Drawn by Ian Christie University of Dundee 2012)

The forces going through the patellofemoral joint whilst walking has been estimated to be around 1.5xBW at 30° of flexion with this rising to 6xBW at 90° of flexion (Huberti and Hayes 1984). The JF is estimated to be ~70% of the PT tension at 40° rising to three times that at 80°, beyond which the patellofemoral JF is limited by the tendontrochlear contact (Amis 1996; Insall 1996).
2.2.4 Kinetics of the Tibiofemoral Joint & Alignment

The accepted normal knee alignment in the coronal plane is in 6° of tibiofemoral valgus (Figure 2.4) created as a result of the tibiofemoral geometrical articulation. Independently the lateral distal femoral angle (LDFA) and the medial proximal tibial angle (MPTA) are a measurement between the perpendicular and their respective anatomic axis, with LDFA around 81° and the MPTA 87°, their combination creates the resultant tibiofemoral angle of ~6° of valgus known as the physiological valgus angle of the knee (Moreland, Bassett et al. 1987; Insall and Scott 2001).

Figure 2.4 Coronal alignment of the knee joint. (Drawn by Ian Christie University of Dundee 2012)
Knee joint loading up to three times body weight during walking has been noted
(Morrison 1970) with relatively greater loading of the medial as compared to the lateral
tibiofemoral compartment, approximately 70% of total load typically passes through the
medial compartment of the knee during walking (Schipplein and Andriacchi 1991). As
the slightly concave medial tibial plateau is more congruent with its femoral condyle
than the flat to convex lateral plateau, it offers a 1.6 times greater contact area than its
lateral counterpart. During normal gait, adduction places forces predominantly on the
medial compartment (Johnson, Leitl et al. 1980; Goh, Bose et al. 1993; Andriacchi
1994) as such for weight-bearing stresses to be shifted to the lateral tibial plateau a
valgus deformity of the knee is required.

The observation of higher forces being exerted over the medial compartment as
compared to the lateral one is supported by the fact that the medial side of the tibia has a
denser / stronger bone than the lateral side (Behrens, Walker et al. 1974; Harada,

The meniscus itself increases the tibiofemoral joint congruity by increasing the contact
areas, which was found to be 20.13-11.60cm² for intact menisci and 12- 6cm² with the
menisci removed (Maquet, Van de Berg et al. 1975). Three times the body weight of a
70Kg person would be loading the tibiofemoral joint (TFJ) with approximately 2100N,
with the stresses exerted on the tibiofemoral joint of 1MPa to 2MPa with menisci intact
and up to 5MPa with the menisci removed. These forces are cushioned and
accommodated largely by the meniscus and articular cartilage.

Rabbit joints studied after medial meniscectomy (Shapiro and Glimcher 1980)
demonstrated loss of articular cartilage “glistening”, medial osteophyte formation and
histological features consistent with osteoarthritic changes. After lateral meniscectomy a
widened medial compartment was observed, assumed to be due to the collapse of the
lateral compartment following the loss of meniscal wedging (Wojtys and Chan 2005). The role of the menisci in maintaining normal knee kinematics by preventing joint capsule and synovial invagination was proposed by Renstrom (1990).

Other than the lack of meniscal tissue, contact stresses can also be affected by joint malalignment. A varus malalignment of 5° can change the distribution of load between the medial and lateral compartments from 70-30% in a normally aligned knee, to 90-10% (Kettelkamp and Chao 1972; Johnson, Leitl et al. 1980; Harrington 1983). Medial tibiofemoral contact pressure increase of 106% and lateral compartment decrease of 89% was seen with 30° varus malalignment (McKellop, Sigholm et al. 1991). The maximal joint pressure centre shifts as the centre of gravity changes which may even be producing “condylar lift off” during walking (Noyes, Schipplein et al. 1992).

Increased dynamic loads in the medial compartment due to varus malalignment in osteoarthritis were found to aggravate the condition and posed the question of whether malalignment precedes or follows the onset of the disease (Baliunas, Hurwitz et al. 2002).

A small degree of varus malalignment was found to cause dramatic alteration in articular surface contact pressure, especially in the presence of chondral damage or medial meniscectomy (Guettler, Glisson et al. 2007), where medial meniscectomy equated to 1.5-2° of loss in anatomic valgus alignment and contributed to radiographic loss of medial joint space. Medial meniscectomy in knees with <4° of anatomic valgus seem to do worse following medial meniscectomy (Covall and Wasilewski 1992) and indeed that angle of <4° was observed as the only significant factor for the development of degenerative changes post meniscectomy (Fauno and Nielsen 1992).
Tibiofemoral contact pressures as a result of meniscal pathology, meniscectomy &
meniscal repair, studied by a knee simulator on human cadaveric knees, demonstrated
that partial meniscectomy led to increase in contact pressure and that meniscal repair, of
radial tears, did not restore contact pressures back to that of an intact knee (Bedi, Kelly
et al. 2010).

A controlled laboratory cadaveric study investigated how the extent of medial
meniscectomy alters tibiofemoral contact mechanics, by altering the degree of
meniscectomy from an intact meniscus to total meniscectomy (Figure 2.5).
Tibiofemoral pressures were recorded via a horseshoe-shaped K-Scan 4000 sensor is
composed of two 28x33mm (924 mm2) sensor pads, each with 2288 sensels (sensing
elements). Their findings demonstrated that all posterior medial meniscectomy
conditions resulted in significantly decreased contact areas, increased mean and peak
contact stresses as compared with an intact state. Of greater interest was their finding
that although the mean contact stresses increased in line with incremental meniscal
resection, the peak contact stress exhibited similar incremental changes throughout all
meniscectomy conditions. Their conclusion was that “loss of hoop tension is equivalent
to total meniscectomy in load-bearing terms” (Lee, Aadalen et al. 2006).
Malalignment following meniscectomy, with medial meniscectomy in an already varus knee demonstrated a higher risk of osteoarthritis than in a normally valgus-aligned one (Allen, Denham et al. 1984) but as the rate of osteoarthritis progression observed seemed to be similar in mild or moderate varus malalignment, it was postulated that articular cartilage in the absence of a “breech” may be able to tolerate the changes in load distribution following the removal of the meniscus.
2.3 Articular Cartilage:

Cartilage exists in different forms, with hyaline cartilage on the articulating surfaces of joints, and fibrocartilage in menisci (Mankin 1974).

Hyaline cartilage literally means “glass-like” as macroscopically it has a white glistening appearance. Microscopically it consists of cells, water and a matrix macromolecular framework from which it derives its mechanical properties (Buckwater, Rosenberg et al. 1990). The gel-like extracellular matrix (ECM) consists of proteoglycan ground substance, in which an architecturally structured collagen network is embedded along with a scattering of specialised chondrocyte cells (Figure. 2.6).

Articular cartilage is considered to be one of the simplest tissues in the human body, as it possesses only a single cell type, the chondrocyte. Nevertheless, this avascular (aneural, alymphatic, non-immunogenic), anisotropic, dynamically biphasic, highly ordered monocellular connective tissue can maintain a permanent state of turgor due to the expansile proteoglycan’s (PG) osmotic pressure being counterbalanced by tension in the ordered arcades of collagen fibres (Buckwalter and Mankin 1998).
2.3.1 Composition

2.3.1.a Chondrocytes

Chondrocytes are rounded cells contained within lacunae, surrounded by their extracellular matrix and form 1-5% by wet weight the ECM (Buckwalter and Mankin 1997a). After completion of skeletal growth, chondrocytes most likely never divide again but continue to synthesize and maintain the matrix framework by predominantly
secrneting type II collagen (Benjamin and Ralphs 2004). Enzymes produced by the chondrocytes are deemed responsible for the degradation of matrix macromolecules as well as their synthesis. Chondrocyte activity is influenced by the frequency and intensity of joint loading (Buckwalter 1995), aging (Martin and Buckwalter 2001) as well as the composition of the surrounding matrix, local growth factors, hormones, cytokines and injury (Ulrich-Vinther, Maloney et al. 2003).

Maintenance of the articular surface requires a turnover of matrix macromolecules. To do this the chondrocytes must be able to sense changes in the composition of their surrounding matrix (which may be due to either macromolecule degradation or demand changes), and respond accordingly by synthesising the appropriate amounts and types of macromolecules (Buckwalter and Mankin 1997a).

2.3.1.b Extracellular Matrix

The mechanical properties of articular cartilage are due to the interactions between tissue fluid and macromolecular framework of the extracellular matrix (Buckwalter and Mow 1992).

Tissue fluid

Approximately 75-80% of the wet weight in articular cartilage is water; its interaction with the matrix macromolecules substantially alters the mechanical properties of the tissue (Linn and Sokoloff 1965; Maroudas and Schneiderman 1987). Some of the water can move freely in and out of the tissue, but the concentration and volume is dependent on the macromolecules (large aggregating proteoglycans) which help to maintain the electrolytes and fluid within the matrix. Other than water, tissue fluid contains gases, small proteins, cations, enzymes and metabolites (Buckwalter and Mankin 1997a).
The Proteoglycans

Proteoglycans, produced by chondrocytes, are part of the ground substance and are large hydrophilic polysaccharide protein molecules largely responsible for the compressive strength of the articular cartilage. They consist of 50-100 GAG (glycosaminoglycan) subunits (Buckwalter 1997a) mainly of two subtypes, chondroitin and keratin sulphate disaccharide polymers, which are bound by sugar bonds onto a core protein to make the so called proteoglycan aggrecan molecule.

Link proteins (glycoprotein) stabilise these aggrecan molecules onto a hyaluronic acid (hyaluronan) to form a proteoglycan aggregate (McDevitt and Webber 1990). These aggregates are amongst the largest proteins produced and form gels which occupy a large volume relative to their mass (Figure. 2.7). Aggregate formation helps to anchor the proteoglycans within the matrix by preventing their displacement as the tissue undergoes deformation during load. Their negatively charged side chains, carboxylate or sulphate group, attract positively charged ions (cations) and this causes a high osmolality.

These hydrophilic gels draw in considerable quantities of water, to decrease the osmolality, resulting in high tissue pressure but the integrity of the highly interconnected type II collagen matrix prevents it from swelling and thus conferring high compressive strength properties to the tissue (Bryant and Anseth 2001). The concentration of these molecules varies amongst sites within the articular cartilage as well as with disease, age and injury (Buckwalter and Mankin 1997a).
Figure 2.7 Schematic diagrams showing the proteoglycans subunit with a hyaluronate-binding region at the base of a linear protein to which longer chains of chondroitin sulphate (CS) and shorter keratin sulphate (KS), along with oligosaccharide moieties are attached. Many of these proteoglycan subunits arranged at right angles along a filament of hyaluronic acid are attached to it via their hyaluronate-binding region via a link protein. The resulting extremely long proteoglycan aggregate macromolecule reaches up to 150x10^6 daltons with a characteristic bottlebrush appearance. (Adapted from http://cal.vet.upenn.edu/projects/saortho/chapter_05/05mast.htm).

Fibrillar components

GAGs and proteoglycans are associated and contained within the fibrous collagen network of the articular cartilage which accounts for ~70% of the dry tissue weight, this level increases with age (LeBaron and Athanasiou 2000). The predominant type II collagen forms rope-like fibrils which aggregate into larger cable-like bundles or fibres resulting in a highly crosslinked and interconnected network of collagen fibrils (Heath and Magari 1996). This collagen network provides the articular cartilage with its tensile strength (Alberts 2002).

The normally slow collagen metabolism with fibril half-life measured in years can change in disease states and exceed the ability of chondrocytes to produce a well organised replacement matrix. Under such conditions the matrix undergoes rapid deterioration and mechanical failure resulting in degeneration and arthritis. Thus
enzymes, such as collagenases have been strongly implicated in the pathogenesis of arthritis (Ulrich-Vinther, Maloney et al. 2003).

2.3.2 Structure

These zones (Figure 2.8) are of functional importance (Buckwater, Rosenberg et al. 1990; Buckwalter and Mankin 1997a) as they differ in composition, morphology, mechanical properties, organisation and probably cell function of the articular cartilage according to depth from the surface and distance of the matrix from the cells (Kuettner 1992).

![Diagram of articular cartilage](image)

**Figure 2.8** A schematic diagram of the adult articular cartilage, with zones on the left and cell changing shapes on the right. Note the orientation of collagen fibres as they change from vertical in the deep zone to horizontal in the superficial zone where the chondrocytes are elongated. The chondrocyte shape changes in the deeper zones from ovoid in the transitional zone to round in the deep zone where they are arranged in short columns. The orientation, thickness and concentration of collagen fibres changes with depth as well. The sharply demarcated “Tide mark” separates the deep/radial zone from the calcified zone in which the cells are encrusted with apatitic salts (redrawn by Ian Christie University of Dundee 2012 from Ulrich-Vinther, M., M. D. Maloney, et al. (2003). "Articular cartilage biology." J Am Acad Orthop Surg 11(6): 421-430).
Articular cartilage is a soft tissue with a shear modulus of < 0.5MPa, a compressive modulus of < 1.5MPa and a Poisson’s ratio of 0-0.42 (Mow, Ateshian et al. 1993). It has the lowest friction coefficient known to man, around 0.01 (Mow, Ateshian et al. 1993). This low friction coefficient is important for the protection of the articular surfaces as it reduces shear forces.

The kinetic coefficient of friction is higher than the static coefficient, discussed above, as with cyclic loading the coefficient increases resulting in larger reaction forces, higher stresses and increased propensity to wear. This is due to the fact that cartilage fluid moves in and out of the matrix matter and the rate at which this is done determines the coefficient. The combined viscoelastic and deformation abilities of articular cartilage have been noted during joint motion and described as “ploughing” (Mow, Ateshian et al. 1993), essentially a combination of compression, tension and shear forces.

The matrix contains and at some instances stores nutrients, macromolecule substrates, degradation products, metabolic and regulatory products such as growth factors and cytokines. These products and others can pass through the matrix at varying rates depending upon the composition and maintenance of the matrix by chondrocytes. In return the matrix protects the chondrocytes from mechanical damage during normal joint activity and this interdependence renders the maintenance of a healthy functional articular cartilage possible throughout life.

Mechanical loading has been suggested as a mode of matrix nutrition via tissue fluid, metabolites and nutrient exchange with synovial fluid as well as a means for signal transmission to the chondrocytes. Joint loading history may be recorded by the matrix
which in turn can induce changes in the molecular organisation of the matrix, i.e. tissue remodelling (Buckwalter and Mankin 1997a).

A persistent abnormal decrease in joint-loading or immobilisation decreases the proteoglycan concentration and aggregation in the articular cartilage which in turn alters the mechanical properties of the cartilage (Buckwalter 1995). Return to activity restores the mechanical properties and composition of the cartilage towards normal, suggesting that to maintain a normal healthy articular cartilage a minimum level of joint loading and motion is required (Buckwalter and Mankin 1997a) (Figure 2.9).

![Figure 2.9](image)

**Figure 2.9** Articular cartilage subjected to different loads. High loads can cause pressure necrosis and ulceration and low loads or disuse can result in chondromalacia leading to fibrillation. (Re-drawn from Basic Orthopaedic Biomechanics, (Mow and Hayes 1997).)
2.3.4. Subchondral bone

Incongruent joint surfaces deform under load maximising the contact area of cartilage which in turn provides self-pressurised hydrostatic weeping lubrication needed for effortless motion (Radin and Paul 1970). As loads increase, cartilage deformation is insufficient and subchondral bone deformation takes place. Subchondral bone serves as a major shock absorber as it is stiffer than cartilage but softer than cortical bone. It can absorb up-to 50% of the load whilst cartilage absorbs around 1-3% instead (Radin, Paul et al. 1970; Hoshino and Wallace 1987).

This pliable bed upon which the articular cartilage is placed offers it protection as the undulations of the tidemark transform shear stresses into compressive and tensile stresses, which the cartilage is better adapted to withstand (Redler, Mow et al. 1975; Mente and Lewis 1994).

By constraining the radial deformation of cartilage under load the subchondral bone increases the threshold of cartilage damage (Finlay and Repo 1978) as joint lubrication is so effective that shear forces along the surface are unlikely to damage the cartilage (Radin and Paul 1972). Problems occur when rapidly applied impulsive loads take place precluding the subchondral bone’s viscoelastic properties from taking place, resulting in microdamage which reactivates the secondary centre of ossification leading to articular cartilage thinning by advancement of the tidemark (Burr and Schaffler 1997).

The osteoarthritic knee can only absorb half as much load as the normal knee (Hoshino and Wallace 1987) and cartilage thinning from subchondral bone advancement eventually causes cartilage fragmentation.
2.3.5 Microdamage protective mechanisms

Although articular cartilage properties make it an excellent shock absorber, at most sites it is too thin to serve as the only shock absorber adequately. During normal walking 3-4 times the body weight is transmitted through the knee and at deep knee flexion the patellofemoral joint experiences a load up-to 10 times the body weight. Periarticular muscles and subchondral bone are recruited to provide the additional mechanisms needed.

Joint motion can increase the tensile forces of an already stretched muscle resulting in large amounts of energy absorption by the muscles (Hill 1960; Radin 1986) but unexpected loads are damaging to the joints as muscles require around 75 milliseconds to prepare and small jolts from missed steps do not afford sufficient warning time compared to falls from greater heights (Jones and Watt 1971; Burr, Martin et al. 1985; Radin, Boyd et al. 1985). A relatively small increase in muscle strength was predicted to result in a 20-30% reduction in the chance of having knee osteoarthritis (Slemenda, Brandt et al. 1997). Thus muscle weakness can reduce the effectiveness of shock absorption.

2.2.6 Articular cartilage damage

Articular cartilage defects can be classified as intrinsic, confined to cartilage (Wakitani, Goto et al. 1994), or extrinsic, subchondral bone penetration (Mankin 1974). This differentiation seems to play a role in its ability to heal, as does age (Kreder, Moran et al. 1994).

Most tissues respond to injury by removal of necrotic matter and new tissue synthesis stimulated by vascular supply and growth factors reaching the site (Newman 1998). Even though low initial increase in chondrocyte mitotic activity has been observed (Rothwell and Bentley 1973; O'Driscoll 1998) compared with normal cartilage where
there is none, intrinsic defects rarely undergo classical tissue repair as cartilage is avascular and the ECM contains natural inhibitors to macrophage and vascular invasion. In addition containment of chondrocytes within the collagen meshwork seems to prevent their migration to the injured site (Newman 1998).

Extrinsic defects, however where subchondral bone has been penetrated, allow access to a more classical healing response with fibrin clot formation and hyaline like chondroid tissue formation. Unfortunately due to increasing amounts of type I collagen, in time, this tissue resembles fibrocartilage rather than hyaline cartilage (Shapiro, Koide et al. 1993). This fibrocartilage may not have the biochemical, histological or biomechanical properties of hyaline cartilage but permits asymptomatic joint function under physiological load and prevents further deterioration (Radin and Burr 1984).

2.3.7 Chondrocyte mechanobiology

Explants of articular cartilage subjected to non-injurious loading did not show damage to collagen network or loss of ECM molecules into the culture medium; mechanical stimulation of chondrocytes however was associated with alterations in aggrecan, collagen, metalloproteinases, growth factors and cytokine gene expression that led to altered metabolic responses (Fitzgerald, Jin et al. 2004). A single compression on cartilage explants demonstrated gene expression of 250-fold for stromelysin (MMP-3), 40-fold for aggrecanase and 12-fold for tissue inhibitor for matrix metalloproteinases (TIMP-1), proteins that would lead to breakdown of articular cartilage (Lee, Fitzgerald et al. 2005) possibly indicating an attempt for repair (Brandt, Dieppe et al. 2008).

Degradative enzyme activities are increased in osteoarthritis either by activation of proenzymes or by decreased inhibitor activity. MMP-3 (stromelysin) and others are elevated in all osteoarthritis cells by exposure of the cells to inflammatory cytokines
(Poole 1995) and their effects are agonised by reduced levels of TIMP-1 (Naito, Takahashi et al. 1999).

MMPs are extracellular enzymes that play a key role in normal and pathological tissue remodelling and have the ability to degrade all of the ECM components (Nagase and Woessner 1999). Their increased production in joint pathology has been demonstrated by high levels of mRNA in tissue and proMMPs in synovial fluid (Konttinen, Ainola et al. 1999). MMP-13 is responsible for the degradation of most of type II collagen, with MMP-3 cleaving the nonhelical telopeptide and causing the disruption of the collagen crosslink (Wu, Lark et al. 1991; Billinghamurst, Dahlberg et al. 1997) arguably resulting in disrupted fibril structure and function.

An imbalance between TIMPs and MMPs has been observed in various pathological conditions suggesting that once MMPs are activated they may not be sufficiently counteracted (Yoshihara, Nakamura et al. 2000).

Proteolysis of aggrecan is an early and critical feature of cartilage breakdown following injury or arthritis (Lohmander, Dahlberg et al. 1989); it is measurable in the synovial fluid as elevation of aggrecan. Aggrecanase (as well as MMPs) plays a major role in human joint disease.

Patients with known knee injuries demonstrate increased levels of aggrecan fragments (GAG), MMPs and COMP in their synovial fluid suggesting increased degradation of joint tissue (Lohmander, Saxne et al. 1994; Roos, Dahlberg et al. 1995; Lohmander, Ionescu et al. 1999).

The thinning of articular cartilage in osteoarthritis seems to be attributable to two processes; endochondral ossification moving towards the surface by duplicating and advancing the tidemark (Burr and Radin 2003), as well as the breaking off of
enzymatically weakened articular cartilage producing cartilage shards which when embedded into the synovial membrane can incite inflammation (Myers, Flusser et al. 1992).

2.3.8 Cytokines and growth factors

Osteoarthritis has traditionally been regarded as a non-inflammatory condition but cytokines and other signalling molecules released from cartilage the synovium and the bone affect chondrocyte function, suggesting an inflammatory element to the disease process (Brooks 2003; Abramson 2004).

Chondrocytes degrade and synthesise matrix macromolecules and the balance of this activity seems to rest with cytokines (Lotz, Blanco et al. 1995) and growth factors with both catabolic and anabolic roles. A delicate balance between synthesis and degradation exists in normal cartilage which seems to be lost in osteoarthritis when both of these processes are enhanced (Sandell and Aigner 2001).

Inflammatory cytokines act to increase synthesis of MMPs, decrease MMP enzyme inhibitors and decrease ECM synthesis, whereas anabolic cytokines and BMPs act to stimulate ECM synthesis. Although both anabolic and catabolic cytokines have an effect on chondrocytes no single cytokine is capable of stimulating all the metabolic reactions observed in osteoarthritis (Goldring 2000).

Mechanical load can cause direct deformation of the matrix which in turn acting as a signal transducer can cause electrical, mechanical and physiochemical signals that can lead to chondrocyte stimulation (Gray, Pizzanelli et al. 1988) and release of cytokines leading to matrix alteration.

Altered mechanical stimuli and increased structural needs in the matrix seem to be responsible for increased anabolic activities, whereas the degradative response seems to
stem from a complex cascade that includes the activation or inhibition of stromelysin, interleukin-1, aggrecanase, plasmin and collagenase by factors such as prostaglandins, TGF-β, Tumour necrosis factor (TNF), metalloproteases, tissue plasminogen activator, and others (Buckwalter and Mankin 1997a).

The articular cartilage and subchondral bone appear to have adapted in order to best withstand the variations in loading (Armstrong, Read et al. 1995; Appleyard, Burkhardt et al. 2003) but when ageing, pathological and or mechanical changes due to meniscectomy or otherwise occur, these can cause an alteration to the biomechanics of the tissue (Hudelmaier, Glaser et al. 2001).

Cartilage breakdown can be due to the action of matrix metalloproteinases stimulated by cytokines, produced by chondrocytes in response to abnormal mechanical loading and joint instability as a consequence of meniscectomy.
2.4 Meniscus:

2.4.1 Anatomy

The menisci are fibrocartilagenous structures situated between the convex femoral condyles and the tibial plateaus of the knee (Figure 2.10). They have a semilunar shape when viewed from above (C-shaped medial meniscus, unclosed O-shaped lateral meniscus) and appear wedge shaped, with the convex outer margin being much thicker than the inner margin when viewed in cross section (McDevitt and Webber 1990; Sweigart and Athanasiou 2001).

Their diameter is approximately 35mm (the medial meniscus is longer than the lateral) offering a capsular attachment along their ~110mm outer circumference (Kohn and Moreno 1995). The medial meniscus has a continuous attachment along its entire outer circumference whereas the lateral meniscus is interrupted by the popliteus tendon.

Insertion ligaments anchor the anterior and posterior horns of both menisci to the tibial plateau.

Figure 2.10 Bird’s-eye view of the tibial plateau depicting the arrangement of menisci and ligaments (drawn by Ian Christie, University of Dundee 2012).
Collagen fibres running circumferentially continue into the anterior and posterior insertional ligaments of the menisci. Interdigitations with subchondral bone through calcified and uncalcified fibrocartilage anchor the menisci to the bone (Benjamin, Evans et al. 1991).

Although the lateral meniscus shows more variation, with discoid meniscus more prevalent (Woods and Whelan 1990), the area of the tibial plateau coverage by each meniscus remains constant with the lateral meniscus covering around 80% and the medial meniscus 60% of their respective tibial plateaus (Wojtys and Chan 2005).

Their vasculature (Figure.2.11) is one of the most crucial features of the menisci with profound implications to their healing potential. The lateral, middle, and medial genicular arteries provide most of the meniscal blood supply forming the parameniscal capillary plexus (PCP), situated along their entire periphery and embedded within the synovial and capsular tissues, with radial branches terminating into small capillary loops (Arnoczky and Warren 1982).

Prenatally, these blood vessels traverse the entire body of the meniscus with the highest density in the peripheral 1/3. Postnatally this vascularity gradually subsides in the inner 2/3s along with a decrease in cellularity but an increase in the collagen content. Weight bearing seems to be the cause and this is supported by the observation of good blood supply retained at the non weight bearing meniscal horns throughout the adult life. In the adult meniscus the capillary loops penetrate no deeper than 25% in the lateral and 30% in the medial meniscus (Arnoczky and Warren 1982). Interestingly the posterolateral region of the lateral meniscus has an avascular region surrounding the popliteal tendon region (Wojtys and Chan 2005).

The innervations of the menisci mirrors their blood supply in the anterior and posterior horns with more encapsulated mechanoreceptors located in their body, free nerve endings are encountered throughout the body of the menisci except their inner 1/3 (Messner and Gao 1998).

2.4.2 Biochemistry & Ultrastructure

Adult meniscal tissue is principally composed of water ~70%, collagens ~70% in dry weight, 8-13% proteoglycans and ~1% hexosamine (Ingman, Ghosh et al. 1974; Herwig, Egner et al. 1984). Its cells are called fibrochondrocytes, a cross between chondrocytes and fibroblasts; they are responsible for the synthesis, assembly of the ECM macromolecules (mainly type I collagen), as well as the continual replacement of degraded matrix components (Buckwalter and Mankin 1997a). Collagens predominate at 60–70% of the dry tissue weight where Type I collagen has the highest concentration and Type II, III, V, and VI are also present (McDevitt and Webber 1990). The proteoglycan portion of the meniscus accounts for less than 1% of its dry weight and is found primarily in the inner region of the meniscus and less so in the predominant peripheral thick collagen fibre region (Ghosh and Taylor 1987).
The large sized anionic proteoglycans found in the meniscus attribute to its shock absorbing properties by essentially acting as a large sponge with water retention properties. These proteoglycans and collagen meniscal content increases with age until maturity and remains constant thereafter. This is in contrast with articular cartilage which demonstrates steady decrease in its proteoglycan content with age (McNicol and Roughley 1980).

Degenerative menisci exhibit less collagen content, more collagenous matrix protein, an increased ratio of chondroidin 6-sulphate to chondoidin 4-sulphate and greater H₂O content (due to accumulation of proteoglycans) as the disrupted collagen network is unable to resist the accumulation of H₂O caused by the increased proteoglycan content (Adams, Billingham et al. 1983).

The orientation of its collagen fibres initially were described to be mostly running circumferentially with some radial fibres present at either surface (Bullough, Munuera et al. 1970), subsequent studies revealed crimped fibres amongst the circumferential fibres in the surface region of the menisci. These are composed of radial fibres (~100µm in thickness) encircling the circumferential fibres (Fithian, Kelly et al. 1990) with some of the radial fibres passing from the surface into the central bulk region.
Figure 2.12 Schematic drawing of a meniscus demonstrating the circumferential, radial and random surface collagen fibres.

Scanning electron microscopy (SEM) revealed a complex arrangement of human meniscal collagen in three distinct layers (Petersen and Tillmann 1998): (1) a surface region covered by a network of fibrils without any preferred orientation, (2) a lamella-like layer featuring radial fibres towards its thicker periphery, but more random orientation in the rest of the layer, and (3) a central main portion composed of circumferentially oriented fibres along with occasional radial tie fibres (Figure 2.12).

The effects of exercise upon the meniscal composition was investigated, mainly by animal studies, demonstrating an increase in collagen, proteoglycan and calcium concentrations in meniscal areas (posterior horn of rat lateral meniscus) where most of the weight bearing took place (Vailas, Zernicke et al. 1986); whereas in another study the number of cross-linked collagen decreased but the amount of proteoglycan aggregates increased (Pedrini-Mille, Pedrini et al. 1988) demonstrating a correlation between the amount and size of proteoglycans with compressive stiffness in response to load stimulation.
2.4.3 Normal function

One of the first identified meniscal functions was that of load transmission (King 1936), later in vitro studies demonstrated that 70% of the load in the lateral and 50% of that in the medial compartments was transmitted through their corresponding menisci (Ahmed, Burke et al. 1983). It was demonstrated through these studies that the posterior horns transmitted 50% of the compressive load in extension and 85% in 90° of flexion.

This ability of the meniscus to dissipate loads effectively stems from its shape, which bridges the incongruence between the convex femoral condyles and the tibial plateaus. It increases the contact area and by doing so decreases the central portion pressures in each compartment.

Studies which calculated the tibiofemoral contact areas (Maquet, Van de Berg et al. 1975; Fukubayashi and Kurosawa 1980) demonstrated a decrease in the tibiofemoral contact areas from 1,150mm² to 520mm² and peak pressures recorded as 3MPa and 6MPa with and without menisci respectively.

Maintenance of joint congruity by the meniscus limits excessive motion of the tibia on the femur in all directions, the effects of (medial) meniscectomy on sagittal (anterior-posterior) and rotational laxity (valgus/varus) when studied demonstrated an increase against baseline of 1.8 times and 1.3 times respectively with the knee in flexion (Markolf, Mensch et al. 1976; Markolf, Bargar et al. 1981).

Another meniscal role, closely related to load transmission, is that of shock absorption. This ability to dissipate forces is attributed to its biphasic structure (the solid and liquid phase) and its unique architecture which enables the meniscus to convert vertical forces into tangential and radial forces, as it moves peripherally under load. The firm anterior and posterior attachments of the intact meniscus enable the recruitment of its
circumferential fibres to tense and elongate and hence convert vertical load into horizontal “hoop stresses” (Pedrini-Mille, Pedrini et al. 1988).

As stated above, the menisci and their insertions into bone (entheses) represent a functional unit. At the enthesis, the fibres of the insertional ligaments attach to bone via uncalcified and calcified fibrocartilage, and this gradual transition from soft to hard tissue, identical to other ligament entheses, is certainly essential for normal mechanical function and probably protects this vulnerable transition between 2 biomechanically different tissues from failure (Messner and Gao 1998).

Interestingly the greater load-bearing function of the lateral meniscus was noted by observing greater calcification in its anterior and posterior horn entheses (Messner and Gao 1998). Therefore if either the anterior or posterior horn attachments of the meniscus is disrupted this will lead to failure of load-transmission, hoop stresses cannot be maintained and a functional meniscectomy ensues, a finding supported by recent studies (Allaire, Muriuki et al. 2008).

Partial meniscectomy is “always preferable to total excision as long as some circumferential fibres remain intact” (Wojtys and Chan 2005) as loss of the meniscus results in at least 20% loss in shock absorption (Voloshin and Wosk 1983). The crucial role of the circumferential fibres has been discussed but the radial fibres that bind them together play an equally important role during meniscal compression by preventing their separation (Bullough, Munuera et al. 1970). Their tensile strength has been estimated to be approaching that of the circumferential fibres (Wojtys and Chan 2005).

The biphasic composition, primarily of water and a smaller solid portion of proteoglycans and other proteins, of the menisci plays an important determinant role of
its function. The meniscus behaves as a fibre-reinforced composite that is both porous and permeable (Pedrini-Mille, Pedrini et al. 1988), accounting for its plastic deformation and its ability to dissipate loads acting as a large sponge. Compression causes the water to flow through the meniscus, this is resisted by the negatively charged proteoglycans but with increasing weight bearing load some water escapes into the synovial joint space. This is drawn back when the load is removed. This “sponge” phenomenon, not only dissipates forces but also allows for the circulation of nutrients that are vital for the maintenance of a healthy meniscus, as it is inner 2/3s are avascular (Renstrom and Johnson 1990).

The menisci remain in contact with the femoral and tibial articulating surfaces throughout knee motion and demonstrate excursion more in their anterior horns than the posterior ones. The medial meniscus showed less than half the excursion of the lateral one (5.1mm as compared with 11mm) with flexion extension (Thompson, Thaete et al. 1991). Minimal displacement and height variation was observed with axial loading, an observation consistent with meniscal function (Vedi, Williams et al. 1999). If radial expansion of the menisci was observed this would decrease the force dissipation function of the meniscus which in turn would increase contact stress on the tibiofemoral region. In knees with observed cartilage degeneration less AP motion of the menisci is noted which indicates decreased contact area between the menisci and the femoral condyles (Kawahara, Uetani et al. 2001) resulting in greater contact stresses being generated.

2.4.4 The Effects of Meniscectomy

Frequently sports-related but also associated with activities of daily living, meniscal tears can result in significant physical impairment and often require surgical intervention. Their management can be either operative or non-operative. Operative
options include total or subtotal meniscectomy, transplantation, or repair. Whilst procedural choice depends on many factors including size and location of lesion and patient activity level, meniscectomy is still an extremely common orthopaedic procedure with 12,869 procedures in 2008 according to the Swedish diagnosis/procedure database (a figure obtained from personal Communication with M.Forssblad in November 2010) or an estimated 61 per 100,000 population per year (Baker, Peckham et al. 1985).

Menisci were once dismissed as functionless vestigial structures and were routinely removed (Sutton 1897), it was argued that their excision “resulted in perfect restoration of joint movement” (Annandale 1885) and meniscectomy was considered a benign procedure (McMurray 1942).

The practice of open total meniscectomy continued even though King (1936) reported degenerative changes post meniscectomy and proposed meniscal repair; whilst others observed good results with partial meniscectomy and proposed this as an alternative to total meniscectomy (Lipscomb and Henderson 1947). It has been postulated (Macnicol and Thomas 2000) that the technical difficulty in achieving an open partial menisectomy coupled with the functional distrust in the residual rim, along with the then flawed belief of meniscal tissue regeneration, lead to the popularisation of open total menisectomies by the late Prof Smillie (1970).

His theory of tissue regeneration was supported by some (Wigren, Kolstad et al. 1978; Burr and Radin 1982) whilst not believed by others (McGinty 1991). It was subsequently answered by an MRI study on Smillie’s cohort at a mean 30 years post total meniscectomy where “no convincing in vivo MRI evidence of long term meniscal regeneration” was observed (Barker, McNicholas et al. 1998).
Whilst total meniscectomy had been advocated for even the most trivial meniscal pathology (Smillie 1970), Fairbank (1948) and Jackson (1968) were amongst the first to document radiographic changes consistent with osteoarthritis following such procedure. Fairbank studied the effects of total meniscectomy in 107 cases three months to four years after operation and found that 37% of patients showed flattening and “ridging” of the femoral condyle with narrowing of the joint space. He suggested that these changes might be a precursor of osteoarthritis, concluding "that meniscectomy is not wholly innocuous; it interferes at least temporarily with the mechanics of the joint. It seems likely that narrowing of the joint space will predispose to early degenerative changes, but a connexion between these appearances and later osteoarthritis is not yet established and is too indefinite to justify clinical deductions." (Fairbank 1948).

After recognising that the orthopaedic literature was “replete with confusing and contradictory statements regarding the ultimate effect of meniscectomy on the knee joint”, Tapper & Hoover (Tapper and Hoover 1969) completed a retrospective study and developed a questionnaire to assess the long term outcomes of open total knee meniscectomy by reviewing 213 patients between 10-30 years after meniscal surgery and noted the following:

- there was no difference in results between total and partial meniscectomy except in bucket-handle tears (which did better perhaps due to an intact peripheral rim)
- continuing in a physical occupation or participation in non-contact sports seems not to alter the course after meniscectomy
- it was usually, but not invariably, possible to correlate roentgenographic appearance with the clinical result
• patients under the age of twenty years old at the time of operation had fewer excellent and good results

• Concluding that 68% of patients had satisfactory results but only 45% of men and 10% of women had symptom-free knees

Total meniscectomy studies of various follow-ups all have demonstrated an association with radiographic osteoarthritis (Table 2.1). The observed frequency of osteoarthritis in these studies varied perhaps due to the different length of follow-up, radiographic methodology and osteoarthritis scoring systems.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>f/u (years)</th>
<th>Observed OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fairbank</td>
<td>1948</td>
<td>107</td>
<td>≤4</td>
<td>37%</td>
</tr>
<tr>
<td>Jackson</td>
<td>1968</td>
<td>380</td>
<td>≥5</td>
<td>21%</td>
</tr>
<tr>
<td>Tapper &amp; Hoover</td>
<td>1969</td>
<td>213</td>
<td>10-30</td>
<td>88%</td>
</tr>
<tr>
<td>Johnson</td>
<td>1974</td>
<td>99</td>
<td>5-37</td>
<td>74%</td>
</tr>
<tr>
<td>Meldar</td>
<td>1980</td>
<td>26</td>
<td>4-15</td>
<td>100%</td>
</tr>
<tr>
<td>Allen</td>
<td>1984</td>
<td>210</td>
<td>10-22</td>
<td>18%</td>
</tr>
<tr>
<td>Abdon</td>
<td>1985</td>
<td>89</td>
<td>16.8</td>
<td>48%</td>
</tr>
<tr>
<td>McNicholas</td>
<td>2000</td>
<td>53</td>
<td>30</td>
<td>77%</td>
</tr>
</tbody>
</table>

Table 2.1 Table depicting a selection of Total meniscectomy studies

Some total meniscectomy studies, including the ones who previously looked at the cohort studied here, noted radiographic progression of osteoarthritis but surprisingly improvement of symptoms between follow-ups (McNicholas, Rowley et al. 2000; Messner, Fahlgren et al. 2001), whilst others noted deterioration in long-term functional outcomes, once radiographic osteoarthritis was established (Roos, Ostenberg et al. 2001).

Specifically at the 30 year follow-up study, of the cohort, reported satisfaction rates went up by 3% to 71% between reviews (Abdon 1985; McNicholas, Rowley et al. 2000), despite their reported reduction in sporting activities, range of motion and progression of radiographic osteoarthritis. Out of the 63 patients reviewed only 14 were
disappointed with their knees in both reviews, whereas according to Tapper & Hoover system those who were enthusiastic or satisfied went up by 2 (Tapper and Hoover 1969). Similarly the disappointed number was the same (14) as per WOMAC (Bellamy, Buchanan et al. 1988). Their observed mean reduction in total range of motion between reviews was 11º for the index knee and 6º for the non-index knee. The improvement in patient satisfaction was attributed to their reduction in sporting activities, perhaps due to increasing age. Another way of explaining would be to criticise the subjective evaluation systems used, especially the Tapper & Hoover which used to report meniscectomy outcomes by grouping together the “excellent” with the “good” (Jorgensen, Sonne-Holm et al. 1987; Hede, Larsen et al. 1992; Jaureguito, Elliot et al. 1995; Burks, Metcalf et al. 1997; Schimmer, Brulhart et al. 1998). The demonstrated expression of satisfaction in studies using this system can be misleading.

Studies looking specifically at open partial vs. open total meniscectomies with intermediate length follow-up (McGinity, Geuss et al. 1977) demonstrated reduced hospital stay, time with walking aids and complications in the group undergoing open partial meniscectomies. “Subjective outcomes” were again better in the partial meniscectomy group, with objective assessment demonstrating increased instability and a two-fold increase of osteoarthritic changes in the total group.

A further randomised trial of 200 patients of open partial vs. total meniscectomies with a mean follow-up of 7.8 years (Hede, Larsen et al. 1992) showed no significant difference as per Tapper & Hoover criteria, p=0.18, nor any difference in their radiographic findings. Knees with open meniscectomies, however, were found to have greater mediolateral instability and lower functional scores.

Three different types of meniscectomy in 219 knees with no other knee pathology at 4.3 year follow-up were compared; arthroscopic partial (71) with open partial (45) & open
total meniscectomy (103) (Northmore-Ball, Dandy et al. 1983). A clear gradation was observed between the results, with partial arthroscopic meniscectomy fairing best, followed by open partial and open total meniscectomy with the worst outcome.

Despite the belief that partial meniscectomy should give better results than a total one, based upon evidence demonstrating increased peak stresses proportional to the amount of central tissue removed (Burke 1978) and the degree of microscopic and gross arthritic changes being directly proportional to the amount of tissue removed (Cox and Cordell 1977); medium to long-term studies of partial meniscectomy observed high incidence of arthritic changes (Benedetto and Rangger 1993; Jaureguito, Elliot et al. 1995; Burks, Metcalf et al. 1997). With a number of authors documenting that meniscectomy partial or total has detrimental effects and leads to radiological knee osteoarthritis in up to 50% of the patients within 5-15 years post injury (Appel 1970; Jorgensen, Sonne-Holm et al. 1987; Fauno and Nielsen 1992; Hede, Larsen et al. 1992).

Radiographic, symptomatic and asymptomatic, osteoarthritis was also observed in patients who underwent arthroscopic limited meniscal resection 15-22 years post operatively (Englund and Lohmander 2004) with those that underwent partial meniscectomy demonstrating a 42% of tibiofemoral osteoarthritis, whilst those with subtotal and total a rate of 39% and 56% instead.

However knee osteoarthritis following meniscectomy can also depend on several other parameters such as alignment, instability, body habitus and the state of the articular cartilage at the time of intervention.

The anatomical differences between the two tibiofemoral compartments (medial tibial plateau concavity and lateral tibial plateau convexity) and the menisci that occupy them dictate their load sharing ability and function, with the lateral meniscus carrying 70% of the load as opposed to the 50% of the medial meniscus. Studies comparing the site of
meniscectomy seem to consolidate this theory (Johnson, Kettelkamp et al. 1974; Yocum, Kerlan et al. 1979; Abdon, Turner et al. 1990) by noting worse outcomes following lateral than medial meniscectomy, whilst others don’t (Rangger, Klestil et al. 1995; Maletius and Messner 1996; Burks, Metcalf et al. 1997; Schimmer, Brulhart et al. 1998).

Alterations in the forces and contact area of the tibiofemoral compartment were observed with stresses increasing three fold after meniscectomy and contact areas reduced to a third whilst compressive deformation of the tibial plateau doubled (Krause, Pope et al. 1976; Fukubayashi and Kurosawa 1980; Wilson, van Rietbergen et al. 2003; Song, Greve et al. 2006). These findings linked total meniscectomy with articular cartilage degeneration.

Varus or valgus knee deformity displaces the weight bearing line through the knee joint increasing the load on the compartment that it falls in respectively. The normal mechanical axis of the leg runs from the centre of the femoral head to the centre of the talus passing through the medial tibial spine in the knee joint, the resulting tibiofemoral angle between the mid-medullary lines of the tibia and femur is approximately 6-7º of valgus in the normal leg (Moreland, Bassett et al. 1987; Insall and Scott 2001). Meniscectomy in knees with an already abnormal leg alignment observed significantly higher degenerative changes (Allen, Denham et al. 1984) especially when the knees were <4º of valgus (i.e. in varus) (Covall and Wasilewski 1992).

Significant increases in anterior tibial translation were observed following medial meniscectomy in knees without a functioning ACL at 30º, 60º and 90º of flexion (greatest at 60º) indicating the significance of the medial meniscus as a secondary stabiliser (Levy, Torzilli et al. 1989), with knees suffering from chronic ACL deficiency demonstrating a higher incidence of medial meniscus tears as compared to lateral ones,
86.9% vs. 29% (Kornblatt, Warren et al. 1988; Keene, Bickerstaff et al. 1993). This was attributed to medial meniscus being more rigidly fixed as compared to the lateral meniscus. Subsequent studies of lateral meniscectomy and ACL sectioning confirmed this theory (Levy, Torzilli et al. 1989).

Knees with a ruptured ACL demonstrate a high incidence of meniscal tears (Cerabona, Sherman et al. 1988) and meniscectomy in ACL deficient knees poor results (Covall and Wasilewski 1992; Sommerlath and Gillquist 1992; Burks, Metcalf et al. 1997), with hastening of osteoarthritic progression (Sherman, Warren et al. 1988). The consequences of meniscectomy in an unstable knee may be exacerbated by a combination of elevated contact stresses leading to abnormal loading and kinematics of the joint surfaces, inducing pathological changes as a result of elevated shear stresses.

Age was speculated as a factor affecting outcomes in some studies, where an odd ratio of 5 was observed between those over 35 years old and those under, in terms of radiological changes (Chatain, Robinson et al. 2001) whilst in others this did not seem to matter, attributing this observation down to reduced activity levels as one ages (Burks, Metcalf et al. 1997).

Body mass index was also deemed an influential factor in a long term follow-up study of patents with lateral meniscectomy where a correlation with lower percentage of excellent/good outcomes was observed (Scheller, Sobau et al. 2001), whilst in other studies similar findings were not evident (Bonamo, Kessler et al. 1992; Roos, Lauren et al. 1998).

The ability of the meniscus to heal is closely related to its blood supply which changes with age and knee motion confined to the outer third. As such meniscal tears are classified according to the location of the tear in relation to the available blood supply, with “red-red” having the best capacity of healing whilst the “white-white” the least
(Arnoczky and Warren 1982; Dehaven 1994). However this is not the only factor influencing healing capacity, the type of tear also plays a part. In a retrospective study 80 out of 3612 meniscal tears were deemed stable and were left alone, 70 of these were vertical longitudinal tears and 10 were radial tears, 52 were reviewed between 2-10 years observing poor healing potential for radial tears and good for vertical longitudinal ones (Weiss, Lundberg et al. 1989).

Long term follow-up studies indicate that patients with pre-existing degenerative changes of the articular cartilage, had worse long term outcomes (Appel 1970). Although this did not seem to have a detrimental influence until several years post operatively, it was noted that only 62% of patients with cartilage damage rated excellent or good as opposed to 95% of those without (Schimmer, Brulhart et al. 1998).

Prior to the inception of the arthroscopic meniscectomy in 1962 (Watanabe 1979), most knee meniscectomies were commonly performed through an arthrotomy, which was the treatment of choice for half a century. Open (or even closed) total meniscectomy is now a rare operation with few remaining indications under the current standard of care (Noble 1992; Bell and Glaser 2001). However, personal communication revealed: “In our Swedish diagnose/procedure database for 2008, we had 12869 NGD11 (meniscus resection arthroscopic) and just 4 NGD12 (open)” (Forssblad 2010), suggesting that even though extremely uncommon open meniscectomy procedures still do take place.

It is now common knowledge that these fibrocartilaginous tibial extensions should be preserved where possible as hoop stresses are lost if there is radial discontinuity of the meniscal body (Shrive, O'Connor et al. 1978).

Significant changes in contact pressure and knee joint kinematics due to a posterior root tear of the medial meniscus was demonstrated in a cadaveric biomechanical study utilising a Fuji Prescale film (Fujifilm USA, Valhalla, New York) where root repair
successfully restored joint biomechanics to within normal limits. It was noted that, in the medial compartment, a posterior root tear of the medial meniscus caused a 25% increase in peak contact pressure compared with that found in the intact condition \( (p < 0.001) \). Both a total medial meniscectomy and a posterior root tear of the medial meniscus significantly altered knee kinematics (Allaire, Muriuki et al. 2008). Of particular interest was the finding that no difference was detected between the peak contact pressure (or any measured variable) after total medial meniscectomy and that associated with posterior root tear. This finding strongly suggests that debridment for posterior root tears of the medial meniscus equates with functional meniscectomy. In addition the amount of arthroscopically resected tissue with respect to a remaining functioning peripheral rim along with cadaveric biomechanical studies indicating that a minimum 3mm residual peripheral rim is required for hoop stress function (Jones, Keene et al. 1996; Hoser, Fink et al. 2001; Allaire, Muriuki et al. 2008), questions as to how many “partial meniscectomies” are functioning as total ones. Making a long term follow-up of total meniscectomy a worthwhile exercise.

Long term studies, other than the Tayside cohort, on total knee meniscectomy mostly hail from Sweden where one of the longest follow-up studies (21 years post-operatively) identified 107 patients with isolated meniscus tear treated by open total meniscectomy and compared them to a pristine knee matched control group; a relative risk of 6 fold for radiographic tibiofemoral osteoarthritis after total meniscectomy was observed (Roos, Lauren et al. 1998).

Most previous long term follow-up studies performed to assess the outcome of meniscectomy utilised different inclusion and exclusion criteria, some with coexisting knee pathology, different patient populations as well as a lack of standardised means for
data collection and PROMs for assessing patient satisfaction, making drawing firm conclusions from them tricky.
2.5 Radiographic evaluation of knee Osteoarthritis

The earliest series defining radiographic osteoarthritis was based upon non-weight bearing knee views and gained acceptance by WHO (WHO 1963). It was subsequently demonstrated that weight bearing played an important role (Ahlback 1968; Leach, Gregg et al. 1970) in re-defining radiographic osteoarthritis with the cut-off of 3mm in JSN as suggested by Ahlback correlating with MRI studies on knee osteoarthritis (Boegard, Rudling et al. 1997).

Articular cartilage defects typically occur in areas of bony contact and these are best visualised with the knee in a weight bearing semi-flexed position (Rosenberg, Paulos et al. 1988; Boegard, Petersson et al. 1997; Davies, Calder et al. 1999).

The lateral knee radiographic view offers some extra information amongst them the assessment of patella height, patellofemoral joint osteoarthritis assessment (McAlindon, Snow et al. 1992), osteophyte formation, loose bodies, knee effusion as well as tibial translation in cruciate ligament injuries (Keyes, Carr et al. 1992).

By far the most under-estimated (Davies and Glasgow 2000) and under-imaged compartment in the knee joint is the patellofemoral joint (Vince, Singhania et al. 2000) despite being responsible for around 30% of knee pathology. Various ways in obtaining a dedicated radiographic imaging of the patellofemoral joint (PFJ) have been described (Settegast 1921; Hughston 1968; Merchant, Mercer et al. 1974; Laurin, Dussault et al. 1979; Merchant 2001).

Plain radiography remains the investigation of choice when assessing osteoarthritis disease in the knee joint (Davies and Glasgow 2000). In this study, knee positioning was consciously based upon the positioning of the previous 30 year review and upon the
“standard” method used in the department with the exception of weight bearing skyline views for which a device was constructed.
2.6 Joint Pain:

If osteoarthritis wasn’t a painful condition it possibly would have been ignored. Even though radiographic osteoarthritis prevalence is high, with a 1/3 of all those over 63 years old demonstrating radiographic evidence (Felson, Naimark et al. 1987), symptoms wax and wane independently of radiographic progression (Hadler 1992), which is usually slow and unpredictable (Massardo, Watt et al. 1989) with patients exhibiting radiographic changes of osteoarthritis not necessarily having proportional pain (Lawrence, Bremner et al. 1966; Hannan, Felson et al. 2000). This raises questions relating not only to the definition of the disease but also to the origin of joint pain.

Studies dating back to 1966 (Lawrence, Bremner et al. 1966) demonstrated people with radiographic evidence consistent with osteoarthritis are more likely to have joint pain than those without such changes, however severe radiographic changes could be present with few or no symptoms (Davis, Ettinger et al. 1992; Felson, Lawrence et al. 2000). In short the severity of radiographic joint damage is not solely related to the degree of experienced pain (Dieppe and Lohmander 2005).

Cartilage is aneural; as such it cannot be the responsible tissue for joint pain generation. The rest of the synovial joint is composed of joint capsule, synovium, subchondral bone and ligaments which could be the source of nociceptive stimuli in osteoarthritis (Kidd, Photiou et al. 2004).

Imaging studies have shown a correlation between the degree of pain with joint synovitis and subchondral bone changes suggesting that these two tissues could be the source of pain in osteoarthritis (McCrae, Shouls et al. 1992; Creamer, Hunt et al. 1996; Felson, McLaughlin et al. 2003). However MRI studies demonstrated only a modest correlation between synovial thickening and knee pain (Hill, Gale et al. 2001; Hill, Hunter et al. 2007), suggesting that synovitis is not the only or the major source of pain.
Bone marrow lesions (BML) and joint effusions were found to be associated independently with pain in osteoarthritic knees (Lo, McAlindon et al. 2007).

In a multicentre study on the natural history of knee osteoarthritis, a strong association between meniscal maceration and BML was found. Aberrant load distribution or instability resulting from meniscal damage was suggested to be the cause behind the BML noted. BML were noted to be more prevalent in the medial compartment of varus knees and the lateral compartment of valgus knees (Lo, Hunter et al. 2007).

Risk factors of joint pain, other than the disease itself (osteoarthritis), may have something to do with the epidemiology of pain without assuming a disease course (Kaila-Kangas, Kivimaki et al. 2004). Various physical activities, psychological wellbeing, depression, anxiety, hypochondriasis and negative affect, the way the questions are asked, the educational level of the patient as well as their ethnic origin have all been shown to affect data on reporting of knee pain (Lichtenberg, Swensen et al. 1986; Hochberg, Lawrence et al. 1989; Davis, Ettinger et al. 1992; Dekker, Tola et al. 1993; Creamer, Lethbridge-Cejku et al. 1999; Hannan, Felson et al. 2000; Keefe, Affleck et al. 2004; Kim, Han et al. 2011).

As widespread chronic pain is common (Brandt, Fife et al. 1991), with regional joint pain being commoner, reaching 25% in cross sectional studies (Linaker, Walker-Bone et al. 1999) it is difficult to state which people with original joint pain have osteoarthritis. Peripheral joint sensitisation has been suggested as a feature of osteoarthritis, perhaps mediated by cytokines and nerve growth factors (Farrell, Gibson et al. 2000; Kidd, Inglis et al. 2003; Bradley, Kersh et al. 2004). Pain could be due to local and central sensitisation pathways resulting in normal stimuli becoming painful which suggests that there is no single pathway linking joint damage and pain.
2.7 PROMs (patient reported outcome measures)

Perceived patient satisfaction does not always correlate with clinical or radiological findings (Lawrence, Bremner et al. 1966; Davis, Ettinger et al. 1992; Felson, Lawrence et al. 2000) and radiographic joint damage not solely related to the degree of experienced pain (Dieppe and Lohmander 2005). However joint pain and disability may result in poor quality of life (Bentley and Minas 2000) and lead down the path of joint replacement (Brittberg, Lindahl et al. 1994; Shortkroff, Barone et al. 1996; Gugala and Gogolewski 2000).

Evidence in the current literature confirms that few scoring systems have satisfactory levels of reliability and validity. Those systems which employ a high degree of patient involvement, such as the KOOS and IKDC, perform better as a patient-based assessment tool due to their greater reproducibility and reliability (Tilley 2010).

The Knee injury and Osteoarthritis Outcome Score (KOOS) was developed for younger and/or more active patients as an extension of the WOMAC osteoarthritis index, with the purpose of evaluating short-term and long-term symptoms and function in subjects with knee injury and osteoarthritis. It has been validated for several orthopaedic interventions, such as anterior cruciate ligament reconstruction, meniscectomy and total knee replacement. The five subscales of KOOS are: Pain (9 items), other symptoms (7 items), ADL Function (17 items), Sport and Recreation Function (5 items), knee-related Quality of Life (4 items). The KOOS may be at least as responsive as the WOMAC (Roos and Toksvig-Larsen 2003) but with improved validity and an ability of identifying symptomatic from asymptomatic knees making it an invaluable tool (Englund, Roos et al. 2003).

The IKDC was initially developed as a ligament scoring system from concerned surgeons considering the then available scoring systems as problem (Hefti, Muller et al.
The IKDC is knee-specific rather than disease-specific and has been validated for patients with a wide variety of knee problems. In its current modified form (Irrgang, Anderson et al. 2001) is straightforward to use. It is divided into documentation, qualification and evaluation sections, and examines four areas (subjective assessment, symptoms, range of movement and ligament examination). The qualification section is unique in that it has no numerical scores, merely a qualitative range from normal to severely abnormal. Rather than being cumulative, if a low grade is obtained for any section then the overall score can never be higher than this, however well the patient scores on the other parameters.

Factor analysis revealed a single dominant component, making it reasonable to combine all questions into a single score. Internal consistency and test-retest reliability were 0.92 and 0.95, respectively. Analysis of differential item function indicated that the questions functioned similarly for men versus women, young versus old, and for those with different diagnoses.

In effect the IKDC 2000 is a reliable and valid knee-specific measure of symptoms, function, and sports activity that can be utilised as an instrument allowing comparisons of outcome across groups with different knee problems (Irrgang, Anderson et al. 2001). In particular this scoring system was assessed in patients with meniscal injuries and it demonstrated acceptable psychometric performance for outcome measures (Crawford, Briggs et al. 2007).
2.8 Biomarkers:

Although plain radiographic evaluation has been invaluable in diagnosing osteoarthritis, it has been noted that radiographic imaging alone does not correlate well with patients perception and symptoms (Lawrence, Bremner et al. 1966; Hadler 1992; Felson, Lawrence et al. 2000; Hannan, Felson et al. 2000; Lohmander 2004), as radiographic changes are relatively insensitive to change and prone to technical difficulties despite the recent advances in radiological evaluation means. For example MRI may be better in assessing damage to articular cartilage but this is also unable to provide us with an understanding of the process leading to the destruction of the articular surface.

Ideally the onset of Osteoarthritis should be detected early, its progression stopped in order to prevent further damage to the joint. The current “gold standard” when unable to control pain derived from progression of joint osteoarthritis is to replace the joint via arthroplasty. It is highly likely that at some point in the future we may be able to facilitate re-growth and regeneration of the damaged cartilage, provided we detect the changes early.

With these goals in mind it is apparent that the sole use of radiographic changes as a marker of osteoarthritis progression is currently inadequate. Other methods of monitoring osteoarthritic outcome measures have been suggested, one of which is PROMs and another biological markers.

These “markers” should be indicative of biological process and in theory respond to interventions (De Gruttola, Clax et al. 2001). Markers such as proteases or fragments of cartilage matrix macromolecules have been suggested to act as indicators of the pathologic or biologic osteoarthritis process and monitor response to interventions.
With relation to osteoarthritis, a number of enzyme proteases within the cartilage attack the molecular and architectural make up of cartilage therefore altering the function of the joint. These proteases are generated by the synovial membrane and chondocytes, causing degradation of cartilage matrix resulting in a generation of molecular fragments which are subsequently released from the cartilage in the synovial fluid (Figure 2.13). Once in the synovial fluid these metabolic products are transported via the lymphatic into the bloodstream circulation where they are cleared by the kidneys and excreted in the urine (Lohmander 1991).

This oversimplification of molecular markers is far from straightforward as these “markers” may be actively metabolised in the liver and or the kidneys and there may be some interchange between the plasma, interstitial and synovial fluid of joints other than the index joint. Also other non-articular sources may contribute to the serum and or urine levels of our chosen marker. The movement and metabolism of these markers make their measurements and levels, difficult to interpret.

Figure 2.13 Biomarkers in body fluids. After their release from the articular cartilage, cartilage matrix molecules, or fragments thereof, travel through synovial fluid, plasma, and urine, in which their concentration may be quantified. Often, metabolic products generated in the joint are further processed in the more distal compartments. With permission from Prof S.L. Lohmander, Acta Orthop Scand 1991;62:623-32.
When articular cartilage is injured, either due to inflammation, increased load or trauma, a number of molecular mechanisms may be responsible for its remodelling and destruction.

Degradation of the two major constituents of extracellular articular cartilage matrix, Collagen type-II and aggrecan, involves aggrecanases and various matrix metalloproteinases (Jones and Riley 2005). Among them MMP-1 (collagenase) and MMP-3 (stromelysin) have had the most extensive studying (Poole 2003).

2.8.1 MMP-3 & GAG

MMP-3 is produced by cells in the synovial membrane and chondrocytes. It hydrolyses macromolecules in the extracellular matrix, including aggrecan, fibronectin and type-II collagen by attacking their telopeptide regions or by activation of other MMPs (Poole 2003).

Although not all investigators agree that there is a significant increase in the levels of MMP-3 or indeed MMP-1 in patients with osteoarthritis (Keyszer, Lambiri et al. 1999; Garnero 2003); increased levels of MMP-3 have been found in patients suffering with hip and knee osteoarthritis, exhibiting greater increases as compared with MMP-1 levels (Lohmander, Hoerrner et al. 1993; Iwase, Hasegawa et al. 1998; Ishiguro, Ito et al. 1999; Green, Gough et al. 2003). Such data suggest that it may be reasonable to consider MMP-3 as a potential biomarker for osteoarthritis.

An early critical feature of cartilage degradation is proteolysis leading to a measurable elevation of aggrecan released from the cartilage into synovial fluid (Lohmander, Dahlberg et al. 1989; Saxne, Glenas et al. 1993). Although other proteins can be involved (Struglics, Larsson et al. 2009) aggrecanase seems to be mainly responsible
for aggrecan degradation in joint disease (Sandy, Flannery et al. 1992; Struglics, Larsson et al. 2009).

Proteoglycans (PGs) consist of core proteins to which glycosaminoglycans (GAGs), polyanionic polysaccharides composed of repeating disaccharide units, are attached. These can be divided into four classes based on the composition of their disaccharide units, including the presence of sulphate or carboxyl groups: heparan sulphate (HS), chondroitin sulphate (CS) and dermatan sulphate, hyaluronic acid (HA), and keratan sulphate (KS).

KS is the only class of GAGs that does not have uronic acid in its structure (Ernst, Langer et al. 1995). In most cases of KS, the hydroxyl group at the C-6 position of the GlcNAc residue is sulphated. (Yoon, Brooks et al. 2002). The degree of the sulphation of KS changes with disease and during normal physiological development. It has been shown to increase in degenerative disc disease (Theocharis, Kalpaxis et al. 1985) and in corneal cataracts (Hart 1976).

Several types of detection methods for GAGs are in use. The most widely used is a uronic acid assay (Blumenkrantz and Asboe-Hansen 1973). This was based on colorimetric detection of uronic (both glucuronic and iduronic) acid units and as such this assay does not identify GAGs, like KS, that lack uronic acid. Thus the detection of microquantities of glycosaminoglycans (GAGs) in biological samples been hampered by the lack of sensitive methods.

A modified Alcian blue dye precipitation assay (Bjornsson 1993), detecting total GAGs, in which the dye binds to the negatively charged GAGs, compares favourably with the widely used uronic acid assay in terms of its sensitivity and ability to detect all classes of GAGs, including KS (Yoon, Brooks et al. 2002).
In order to validate a potential osteoarthritis marker, account should be taken of a number of changing parameters which can increase as well as decrease. For this reason radiographic images alone, which demonstrate disease progression albeit with time lag, cannot be used. As such we should incorporate examination findings as well as PROMs which would include feelings of improvement or not and change in function.

It has been argued that such an approach, possibly in combination with biomarker technology application, may increase our ability to understand and manage the osteoarthritis disease process (Lohmander 2004).

For this reason clinical examination complemented by radiographic evaluation, PROMs as well as disease markers was employed in an attempt to assess this cohort of patients.

The hypothesis, that a relationship exists between these markers and radiographic osteoarthritis as well as PROMs will be examined in this thesis acknowledging the fact that thus far the scientific community has been unable to identify “cut-off” values for either of these markers; confirmed by personal communication with Prof S. Lohmander (2012).
CHAPTER 3
Materials and Methods
3.1. Introduction:

In the period between January 1953 and June 1973 around 8,500 patients in Tayside underwent total knee meniscectomy. It was believed that removal of the meniscus is “invariably followed by replacement by a structure consisting of fibrous tissue which is almost a replica of the original” (Smillie 1970; Wigren, Kolstad et al. 1978; Burr and Radin 1982).

As this cohort underwent their operations under the auspices of the late Professor I.S. Smillie, it is imperative to describe the technique used as well as the post-operative management as taken from the book *Injuries of the knee joint* that the Professor wrote and published (Smillie 1970).

3.1.1 The technique of total meniscectomy

The Operation

A slightly oblique skin incision terminating a finger’s breath below the joint line and aiming backwards was made and the capsule was incised in line with that. Toothed forceps were used to lift the meniscus off the tibia and a small incision between the meniscus and the tibia was made with a knife. The central attachment of the anterior third was subsequently divided under direct vision following this step the specialised “Smillie knives” were passed between the meniscus and the capsule aiming backwards. Once the meniscus was removed, evaluation of all the other soft tissues of the knee took place (as far as possible) and the wound was closed in layers with interrupted catgut.

Post operative treatment

A three layer thick compression bandage consisting of cotton wool was applied to the limb and following a four day recovery period an hourly exercise regime in the form of rhythmic quadriceps drills and progressively loaded straight-leg-raising was
commenced. Once the post operative effusion settled down and quadriceps control
returned weight bearing activity was permitted, although for the first week this was
restricted between chair and bathroom. Progression to weight bearing exercises was
allowed at the five week mark. Dressings and sutures were removed on the tenth day.
Return to work was as follows: a clerk could return in the fourth week whereas manual
workers usually after twelve weeks.

3.2 Cohort Selection:

Out of three hundred and thirteen patients (313) who had an open total meniscectomy as
adolescents, one-hundred (100) with operative records demonstrating otherwise intact
knees (no other pathology) were reviewed for the first time at 17 years post operatively
in 1982-83 (Abdon 1985). This cohort was “considered to be a representative group
since the only difference between them and those failing to attend for review was the
length of time since surgery” (McNicholas, Rowley et al. 2000). They formed the
cohort for the 30 year follow-up where out of the 95 traced patients, 32 were not seen
(TKA, illness, deceased, too far etc) and 10 refused radiography leaving 53 patients who
agreed to undergo bilateral knee radiographic evaluation (McNicholas, Rowley et al.
2000) (Figure 3.1).

Figure 3.1 Flow chart of total cohort of adolescents at 30 year follow-up.
Ethical approval and funding were secured for the 40 year follow-up of this patient cohort (n=53). At the 40 year follow-up 5 had passed away, 7 had had a total knee arthroplasty-TKA, 6 were lost to follow-up (had not responded to letters sent to their registered address and were untraceable by phone or through their General practitioner), 3 declined to be assessed, one was unable to attend due to severe MS (Multiple sclerosis) and one completed the subjective questionnaires over the phone but was unwilling to travel for assessment (Figure 3.2). Totalling those not assessed at all in this review and without an endpoint (TKA, housebound or deceased) to 9 (16.9%).

**Figure 3.2** Flow chart of current study cohort

All patients were seen by one assessor (I.P.P) at two different sites in Tayside at specifically ran clinics. Following meeting and greeting the patients, informed consent for all procedures was obtained (radiographic, biochemical, synovial fluid sampling and clinical assessment of both knees).

Patient’s BMI was calculated from their recorded height and weight. They were asked to complete self administered subjective questionnaires of KOOS (Knee Osteoarthritis Outcomes Score) and IKDC 2000 (International Knee Documentation Committee).
3.3 Methods of Subjective evaluation and Objective assessment:

3.3.1 Objective Data Collection

3.3.1.a BMI

All patients reviewed in this study had their height and weight measured three times and averaged to give their final BMI score. BMI has been identified to have a strong correlation with Osteoarthritis (Manek, Hart et al. 2003).

3.3.1.b Sagittal Laxity

To confirm that the cohort under study had the meniscectomy as their only variable with regards to knee laxity their sagittal laxity was evaluated, as meniscectomy alone does not produce a measurable degree of AP laxity (Bargar, Moreland et al. 1980).

Testing for sagittal laxity by a lachman’s test on a presumed ACL deficient knee, is done at specific knee flexion which allows 5 degrees of freedom (Fukubayashi, Torzilli et al. 1982); this is either compared to the contralateral intact side or to the accepted “normal range” of 3-5mm of anterior tibial translation.

Their Sagittal laxity was measured by the Rolimeter (now DJO previously of Aircast®), a proven instrument in measuring sagittal laxity, as effective as the KT-1000 with inter & intra tester reliability (Ganko, Engebretsen et al. 2000; Muellner, Bugge et al. 2001; Schuster, McNicholas et al. 2004). These measurements were recorded after three consecutive readings obtained at 90° and 30° of flexion by the same assessor were averaged.
Other examination findings, such as knee crepitation, palpable osteophytes etc were not recorded or utilised as these were deemed “subjective” examination findings and potentially have poor inter & intra-observer reliability.

3.3.1.c Range of Motion

All patients were seen and assessed by one assessor who recorded their range of motion in both knees using a long levered goniometer by recording the average of three consecutive readings. Active knee flexion/ extension range of motion (ROM) measurements were collected with the patient in a supine position with the axis of the goniometer placed over the lateral femoral condyle with its distal arms aligned with the greater trochanter of the femur proximally and the lateral malleolus tip distally.

During knee extension, the patients were asked to maximally extend their knee and during knee flexion, they were requested to maximally flex the hip and knee and draw the heel toward the buttocks.

3.3.1.d Radiographic Evaluation

When ordering plain radiographs of any joint one must ensure that maximum information is obtained. In the case of the knee proper visualisation of all three compartments is important with standardisation of such views being paramount in a research project.

In our case the knee joint is assessed for features of osteoarthritis which include joint space narrowing, osteophyte formation, subchondral sclerosis and cyst formation (Ahlback 1968; Ahlback and Rydberg 1980). Joint space reduction signifies progression (Altman, Fries et al. 1987) of the disease whereas osteophytes, the presence of the disease (Altman, Asch et al. 1986).
All patients who attended the clinics were assessed radiographically with 3 different knee views (in coronal, sagittal and axial plane) of both knees following consent. These were standardised as follows to eliminate position-related changes in joint space evaluation (Brandt, Mazzuca et al. 2002).

3.3.1.e AP Weight Bearing

Although the PA/ MTP view has been recently shown to be superior in assessing tibiofemoral joint space narrowing (Buckland-Wright 2006) it is more difficult to obtain successfully as it is not routinely performed; standardisation is fiddly and would require training time for both the radiographer and myself. Also AP radiographic evaluation was the method of choice at the 30 y follow-up and as such repeating this radiographic modality would give the opportunity, if desired, to be able to compare these findings to those of the previous study.

All patients underwent bilateral knee tibiofemoral evaluation in a weight bearing AP manner with the knee flexed at 15°. This was achieved by placing the weight bearing foot’s 1st metatarsophalangeal joint (MTPJ) straight and at 90° with the cassette plate and the patella centralised over the femur. The beam aimed at 2cm below the lower pole (apex) of the patella (utilising fluoroscopy). The cassette used for this image was 30x40cm and the image was coned to include the distal 1/3 of the femur and the proximal 1/3 of the tibia. This type of knee standardisation has been evaluated and was found to produce an accurate and reproducible measurement of JSW (Buckland-Wright, Macfarlane et al. 1995; Mazzuca, Brandt et al. 2002; Mazzuca, Brandt et al. 2003).
3.3.1.f Lateral Knee:

This image of both knees was taken non-weight bearing with the patient lying on the affected side, knee flexed to 15° over an 18x24cm cassette. The tube was angled 5° cephalad and centred on the medial femoral condyle. As this image was not taken weight bearing it was not utilised to assess the degree of osteoarthritis in the knee joint. In addition it has been demonstrated that a standardised skyline view reproducibly gives more information of the PFJ than a lateral one (Jones, Ledingham et al. 1993; Cicuttini, Baker et al. 1996; Boegard, Rudling et al. 1998).

3.3.1.g Weight bearing Skyline

In this view, patients were asked to stand, weight bear, on their knee undergoing the radiograph. A purpose built device (Figure. 3.3) was utilised to standardise and capture the dynamic configuration of the patellofemoral joint (PFJ).

Again the cassette was 18x24cm and the beam was centred on the upper pole of the patella at exactly 1m from the cassette. This design standardised knee flexion to be ~40° by allowing a mobile radio-translucent “knee rest” to be adjusted in accordance to patient height. The role of the “knee rest” was to aid in the standardisation of the radiographic image but not to withstand the patients’ weight.
Figure 3.3 Diagram Demonstrating the Weight Bearing Skyline view device built as seen in Englund, M. and L. S. Lohmander (2005). "Patellofemoral osteoarthritis coexistent with tibiofemoral osteoarthritis in a meniscectomy population." Ann Rheum Dis 64(12): 1721-1726. Personal communication with Prof Lohmander did not offer specific dimensions for constructing this device, such information is not elsewhere available and can be found in the appendix 2 of this thesis. (Drawing by Ian Christie University of Dundee 2012).

3.3.1.h Radiographic Scoring system(s) used

Evaluation of all weight bearing AP and skyline radiographs was performed by multiple assessors, blinded as to operated vs. non-operated knee and by two different scoring systems, in the hope of eliminating scoring system bias. All radiographs were scored in darkened rooms and from the same “set” distance of 60cm without magnifying
equipment. Where joint space measurement was required this was recorded by a transparent ruler in increments of 1mm.

Intra- observer agreement reproducibility was ensured by scoring all the radiographs three times with each scoring system. “First pass” was utilised to familiarise oneself with the scoring systems and subsequent scoring to tabulate and average particular scores.

All AP knee radiographs were evaluated with Ahlback (Ahlback and Rydberg 1980) and Kellgren & Lawrence (Kellgren and Lawrence 1957) grading systems (Table 3.1).

<table>
<thead>
<tr>
<th>Ahlback</th>
<th>Ahlback Definition</th>
<th>Kellgren &amp; Lawrence</th>
<th>Kellgren &amp; Lawrence Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>JSN (&lt;3mm)</td>
<td>Grade 1</td>
<td>Minute osteophyte</td>
</tr>
<tr>
<td>Grade II</td>
<td>Joint space Obliteration</td>
<td>Grade 2</td>
<td>Definite osteophyte</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unimpaired Joint Space</td>
</tr>
<tr>
<td>Grade III</td>
<td>Minor bone attrition (0-5mm)</td>
<td>Grade 3</td>
<td>Moderate diminution of Joint Space</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Moderate bone attrition (5-10mm)</td>
<td>Grade 4</td>
<td>Joint space greatly impaired with sclerosis of subchondral bone</td>
</tr>
<tr>
<td>Grade V</td>
<td>Severe bone attrition (&gt;10mm)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.1** The Ahlback and Kellgren & Lawrence grading systems for tibiofemoral osteoarthritis.

The Ahlback classification system had demonstrated a high (acceptable) intra-observer reliability but poor inter-observer reproducibility (Weidow, Cederlund *et al.* 2006), this was attributed to the ability to determine if a visible joint space represents remaining
cartilage along with the degree of bone attrition. Its reliability as a radiographic osteoarthritis scoring system was brought into question previously (Galli, De Santis et al. 2003). The insensitivity of plain radiographs in detecting early osteoarthritis has been reported by a number of authors (DeHaven and Collins 1975; Lysholm, Hamberg et al. 1987), such difficulty however has not been described for advanced osteoarthritis disease.

The KL (Kellgren and Lawrence 1957) grading system was used as studies have demonstrated it to be as good (Brandt, Fife et al. 1991; Scott, Lethbridge-Cejku et al. 1993) if not better than other known systems (Spector, Hart et al. 1993).

Evaluating the patellofemoral joint (PFJ) in terms of osteoarthritis is a more challenging affair requiring return to basic principles of presence and progression of osteoarthritis (Altman, Asch et al. 1986; Altman, Fries et al. 1987), as the scoring system proposed by Jones does not offer clear distinctions between the grades with regards to joint space narrowing (JSN) (Jones, Ledingham et al. 1993). Attempting to clarify this particular question was a study looking at JSN in mm and MRI findings of osteoarthritis. The cut-off point of 5mm i.e. if joint space in either the lateral or medial facet of the PFJ was less than 5mm was found to have a high specificity for MR-detected cartilage defects.

In addition, a separate paper during the same year the same team (Boegard, Rudling et al. 1998; Boegard, Rudling et al. 1998), demonstrated that a PFJ with JSN< 5 mm, osteophytes had sensitivity and a positive predictive value of 90% and 95% respectively for MR detected cartilage defects but not if the joint space was greater than the 5mm cut-off. Hence JSN of less than 5mm +/- presence of osteophytes are in-keeping with presence of osteoarthritis in the patellofemoral joint (PFJ).

The standardised weight bearing skyline views of both the index and non-index knees were assessed in the same fashion as the AP views, described above, and scored in
terms of presence of osteophytes and the joint space (in each facet) measured by a ruler in increments of 1mm.

### 3.3.1j Assessing Coronal alignment

The physiological valgus angle of the knee has been defined as 6º as measured by taking accurate long leg weight bearing radiographs (Moreland, Bassett et al. 1987). However in most hospitals coronal knee radiographs are obtained with the knee centred on short films depicting the proximal and distal thirds of the tibia and femur. Good inter observer agreement was seen when seven orthopaedic surgeons were asked to calculate the tibiofemoral angle on short films with varying degree of rotation (Lonner, Laird et al. 1996), however intra and inter-observer errors of as high as 7º were noted in other studies (Laskin 1984) stressing the need for standardised films and meticulous evaluation.

As the reliable inter and intra observer agreement method of determining the coronal alignment of the knee, using computerised radiographs developed in the University of Dundee (Prakash, Wigderowitz et al. 2001) was not available, the tibiofemoral angles were obtained by identifying, at multiple levels, the outer cortices of both the femur and tibia and a best fit line drawn through their mid-points to provide lines which give the tibiofemoral angle at their intersection (Figure 3.4). This is a modification of the Petersen technique of using 2 points from each bone (Petersen and Engh 1988).

All hard copies of the films were scored in darkened room from the set distance of 60cm utilising a goniometer and pencil for marking. Unfortunately drawing these lines on hard films resulted in the inability to reliably perform the same measurements again without bias. As such this particular reading could only reliably be performed once.

Valgus angles were designated as positive while varus angles were designated negative. Using the tibiofemoral angle, the magnitude of malalignment was calculated as the
deviation from the perceived normal of 6° of valgus. Magnitude of malalignment by its very nature was always given as a positive value regardless of direction from the physiological valgus angle.

Figure 3.4 Measuring the Tibiofemoral Angle
3.3.1.k Sampling, Treatment and Storage of Synovial and Serum Fluid

Serum

Blood was collected into 3 plain 6 mL EDTA vacutainer tubes, inverted 8 times and allowed to clot at room temp for 30 minutes.

Joint Fluid

This was collected undiluted by aspiration of both knee joints under aseptic techniques and transferred in plain tubes. The maximum volume possible was aspirated and this was recorded at the time. Ethical approval for this project did not consider the possibility of knee lavage aspiration at a clinic setting and thus if no synovial fluid was produced this was recorded as Ø aspirate.

Treatment

Subsequently all the samples were transferred to the biochemistry laboratory where they were centrifuged at 1800 g for 10 minutes, the supernatant was transferred into cryotubes by pipetting (in the case of Serum, at least six 1 mL aliquots were obtained), placed in dry ice whilst awaiting transfer and storage at -70°C in the tissue lab.

Storage

All samples in 1mL marked aliquots were stored in cryotubes at -70°C (tissue lab) until their transfer to Prof S. Lohmander, Lund University, Sweden, for analysis. The samples were safeguarded against repetative freeze-thawing.
3.3.1.1 Analysis

MMP-3

Once the samples were thawed at room temperature, MMP-3 values were determined by a stromelysin-trapping enzyme-lined immunosorbent assay (Walakovits, Moore et al. 1992). The assay measures the proenzyme, active MMP-3, and the MMP-3 complex with tissue inhibitor of metalloproteinases-1, but does not detect the active enzyme complexed to 2-macroglobulin (Lohmander, Hoerrner et al. 1993). MaxiSorp surface (96-well) plates (Nunc, Roskilde, Denmark) were coated overnight at 4°C with 100 l/well of a 1.0 g/ml solution of the murine stromelysin anti-dog monoclonal antibody MAC085 (Celltech, Slough, UK) in phosphate buffered saline (PBS) coating solution (KPL, Gaithersburg, MD). The plates were then washed 4 times in a solution of 2 mM imidazole buffered saline and 0.02% Tween 20 (KPL) and incubated for 20 minutes at room temperature with 1% bovine serum albumin (BSA) in PBS (BSA blocking solution; KPL) to block nonspecific protein binding to the wells.

Subsequently the BSA was washed from the plates, standard recombinant human prostromelysin (Merck, Rahway, NJ) or samples of plasma were added (100 l/well) for 1 hour at room temperature and the samples were then diluted with 0.67% BSA in PBS (BSA diluent solution; KPL), which also was used as a blank. The plates were washed and were then incubated with a 10g/ml solution of rabbit polyclonal anti-human stromelysin IgG (Merck) in BSA diluent solution. The plates were then washed again, after which they were incubated for 1 hour at room temperature with peroxidase-labelled goat anti-rabbit IgG (KPL) diluted to 125 ng/ml in BSA solution (100 l/well). After which they were washed again and the plates were incubated for 5 minutes with a tetramethylbenzidine (TMB)– hydrogen peroxide ($H_2O_2$) solution (0.2 gm/litre TMB, 0.01% $H_2O_2$), after which the reaction was stopped by the addition of 1M phosphoric
acid. Absorbance at 450 nm was measured spectrophotometrically using a Multiscan
Multisoft plate reader (Labsystems, Helsinki, Finland) and the software Ascent 2.4.2
(Thermo Electron, Waltham, WA).

**GAG**

Concentration of sGAG was measured by a modified, Björnsson, Alcian blue
precipitation (Björnsson 1993). This measures Alcian blue dye binding in proportion to
the number of negative charges on GAG chains.

Samples and chondroitin sulphate standards (25 μl) were precipitated for two hours at
4°C with 0.04% w/v Alcian blue, 0.72 M guanidinium hydrochloride, 0.25% w/v Triton
X-100, and 0.1% v/v H₂SO₄ (0.45ml). The precipitates were collected after
centrifugation (16,000 g, 15 minutes, 4°C), then dissolved in 4 M guanidinium
hydrochloride, 33% v/v 1-propanol (0.25 ml), and transferred to 96-well micro-titer
plates prior to absorbance measurement at 600 nm (Larsson, Lohmander *et al.* 2009).

**3.3.2 PROMs (Subjective Evaluation)**

During the 30 year follow-up, Tapper & Hoover along with the WOMAC (Tapper and
Hoover 1969; Bellamy, Buchanan *et al.* 1988) were utilised as a self administered
questionnaires for subjective evaluation. In this 40 year follow-up the KOOS (Roos,
Roos *et al.* 1998) and the subjective part of IKDC 2000 (Irrgang, Anderson *et al.* 2001)
questionnaires were utilised instead (see appendix ).

All subjective data were collected by patient completed self administered questionnaires
of KOOS and IKDC 2000 apart from one patient whose subjective outcomes were
completed by a telephone interview who’s scores were excluded from statistical
analysis purposes. This reasoning was based on published literature supporting that a
standardized self-administered questionnaire be used as the method of choice for obtaining subjective data in clinical settings (Hoher, Bach et al. 1997).
3.4 Statistical Analysis:

All statistical analysis was performed with the SPSS version 17.0 (SPSS Inc., Chicago). The level of statistical significance was set at 0.05. Numerical data were assessed for normality of distribution using the Shapiro-Wilk statistic. The Shapiro-Wilk test (Shapiro SS 1965) statistic (W) gives a value between 0 and 1. The closer the test statistic is to 1, the greater the likelihood that the distribution of the data is normal. The null hypothesis for the test is that the data is plausibly normally distributed. If a p value > 0.05 was found then the data can be assumed to be normal. All data analysis was performed by using a two-tailed hypothesis. Data found to behave in a Non-parametric manner were analysed with non-parametric tests.

Comparison of means between two groups was performed by paired t-test if data were found to be parametric or by Wilcoxon test for non-parametric (for large group data). However, for smaller group parametric data were tested with unpaired t-test if parametric or Mann-Whitney if non-parametric (small subset of data e.g. meniscectomy type or osteoarthritic / non-osteoarthritic patellofemoral joint group).

Comparison of means between three groups was performed by one-way ANOVA if parametric and Kruskal-Wallis if non-parametric data.

Data were assessed for correlations by Pearson’s correlation for parametric data; Spearman’s Rank for non-parametric data, with Kendall’s tau for non-parametric data with very small numbers. The strength of correlation was based upon the table taken from relationship between variables- http://www.experiment-resources.com/statistical-correlation (Table 3.2).
<table>
<thead>
<tr>
<th>Value of r</th>
<th>Strength of relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.0 to –0.5 or 1.0 to 0.5</td>
<td>Strong</td>
</tr>
<tr>
<td>-0.5 to –0.3 or 0.3 to 0.5</td>
<td>Moderate</td>
</tr>
<tr>
<td>-0.3 to –0.1 or 0.1 to 0.3</td>
<td>Weak</td>
</tr>
<tr>
<td>–0.1 to 0.1</td>
<td>None or very weak</td>
</tr>
</tbody>
</table>

Table 3.2 Strength of correlation table.
CHAPTER 4
RESULTS
4.1 Descriptive statistics:
Out of 53 patients who underwent radiographic evaluation at the 30 year follow-up, 7 had by the time of 40 year follow-up undergone a TKA. This was an important finding as it brings the number of TKAs potentially to 8 (only 1 from previous follow-ups and 7 from this one).

Thirty patients were physically reviewed with an added one having their PROMs and status accessed via a telephone interview (Table 4.1). At review it was noted that 8 patients had subsequently (after the age of 19) undergone further contralateral knee interventions which in effect reduced the number of patients who had one knee intervention at the time of review to 22 (22+1 who filled questionnaires over the phone).

The main aim of this study was to document the outcome of adolescent meniscectomies 40 years down the line and compare when possible the index to non-index knee.

4.1.1 The whole group

<table>
<thead>
<tr>
<th>Sample population</th>
<th>31</th>
<th>25♂</th>
<th>6♀</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age at meniscectomy</td>
<td></td>
<td>15.6</td>
<td></td>
</tr>
<tr>
<td>Average age at assessment</td>
<td></td>
<td>56.5</td>
<td></td>
</tr>
<tr>
<td>Average BMI at assessment</td>
<td></td>
<td>28.3</td>
<td></td>
</tr>
<tr>
<td>Unilateral Medial Meniscectomy</td>
<td></td>
<td>9</td>
<td>7♂</td>
</tr>
<tr>
<td>Unilateral Lateral Meniscectomy</td>
<td></td>
<td>8</td>
<td>7♂</td>
</tr>
<tr>
<td>Unil Med. &amp; Lat. Meniscectomy</td>
<td></td>
<td>6</td>
<td>5♂</td>
</tr>
<tr>
<td>Bilateral Medial Meniscectomy</td>
<td></td>
<td>3</td>
<td>3♂</td>
</tr>
<tr>
<td>Bilateral Lateral Meniscectomy</td>
<td></td>
<td>4</td>
<td>4♂</td>
</tr>
<tr>
<td>Bilateral Knee Medial &amp; lateral meniscectomies</td>
<td></td>
<td>1</td>
<td>0♂</td>
</tr>
</tbody>
</table>

Table 4.1 Demographic data for the whole cohort
Patient reported outcome measures: as per KOOS & IKDC score for the whole group (excluding the over the phone interview) were recorded (Table 4.2).

<table>
<thead>
<tr>
<th>Subjective Outcomes</th>
<th>Number</th>
<th>Mean</th>
<th>Std</th>
</tr>
</thead>
<tbody>
<tr>
<td>KOOS- Symptoms</td>
<td>30</td>
<td>65.5</td>
<td>23.2</td>
</tr>
<tr>
<td>KOOS- Pain</td>
<td>30</td>
<td>74.4</td>
<td>20.4</td>
</tr>
<tr>
<td>KOOS- ADL</td>
<td>30</td>
<td>79.1</td>
<td>19.3</td>
</tr>
<tr>
<td>KOOS- Sports</td>
<td>30</td>
<td>62.6</td>
<td>28.5</td>
</tr>
<tr>
<td>KOOS- QoL</td>
<td>30</td>
<td>65.3</td>
<td>27.0</td>
</tr>
<tr>
<td>IKDC</td>
<td>30</td>
<td>59.37</td>
<td>11.98</td>
</tr>
</tbody>
</table>

Table 4.2 Whole group PROMs

Range of motion, sagittal laxity, knee biomarkers, radiographic outcomes were not statistically analysed for the whole group as it would not distinguish between the operated and not operated knee. The results will therefore concentrate on the group with total meniscectomy on one knee only.
4.1.2 The Unilateral group

Twenty-two (+ 1 over the phone) patients had meniscectomy in one knee only, 9 had medial meniscectomy, 8 lateral and 6 both medial and lateral meniscectomies. Their average age at the time of surgery was 15.4 and at review 55.7. Their BMI (Figure 4.1) at review was 28.65 (Std 3.38).

Figure 4.1 Histogram of unilateral group BMI stratified as per WHO (WHO 2012).
4.2 Preliminary Statistical Analysis:

4.2.1 Site of Meniscectomy

Firstly, it was important to identify if there was a difference in outcomes with regards to the site of meniscectomy (i.e. if medial meniscectomy differed from lateral meniscectomy and both medial & lateral meniscectomy) Table 4.3.

<table>
<thead>
<tr>
<th>Type of meniscectomy</th>
<th>MM (n=9)</th>
<th>LM (n=7)</th>
<th>MLM (n=6)</th>
<th>All 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>KL (Median)</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Ahlback (Median)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Flexion (Mean / SD)</td>
<td>120.7(14.8)</td>
<td>132.9 +/- 8.1</td>
<td>121.0 +/- 7.4</td>
<td>126.0 +/- 11.6</td>
</tr>
<tr>
<td>Hyperextension (Mean / SD)</td>
<td>- 5.7 +/- 5.3</td>
<td>- 2.1 +/- 7.0</td>
<td>- 8.0 +/- 8.4</td>
<td>- 5.2 +/- 6.6</td>
</tr>
<tr>
<td>IKDC score (Mean /SD)</td>
<td>59.6 (10.9)</td>
<td>69.3 (9.4)</td>
<td>57.7 (11.3)</td>
<td>62.3 (11.25)</td>
</tr>
</tbody>
</table>

Table 4.3 Unilateral group values as per site of meniscectomy.

This was tested against both radiographic scoring systems (KL & Ahlbback), the ROM and IKDC score and proved not to have any significance as per Kruskal-Wallis test.

1. MM vs. LM vs. MLM as per KL score – p=0.099
2. MM vs. LM vs. MLM as per Ahlbback score – p= 0.22
3. MM vs. LM vs. MLM as per ROM – p= 0.057
4. MM vs. LM vs. MLM as per IKDC – p= 0.163

Based upon these findings the unilateral group of patients was taken as a whole. This enabled comparisons with the contralateral un-operated (non-index) knee where this was feasible.
4.2.2 BMI

Although BMI is recognised as a potentially fluctuating variable with time & age, it was assessed against KL/ Ahlback / IKDC & ROM score via Kendall’s Tau demonstrating to have a positive moderate correlation with both osteoarthritis scoring systems (KL r=0.34, p=0.048 & Ahlback r=0.34, p=0.047), but there was no correlation between BMI and IKDC r= 0.03, p=0.87 or ROM r= -0.19, p=0.24.
4.3 Statistical Analysis & Correlations for Clinical Outcomes:

The values observed between index and non-index knee were as follows:

4.3.1 Sagittal Laxity (Anterior Tibial Translation- ATT)

It was important to assess if there was a subsequent ACL tear or dysfunction post meniscectomy in the cohort. This was tested by assessing the sagittal laxity of both index and non-index knees. Anterior tibial translation was measured for both index and non-index knee by the same operator (Table 4.4) with the Rolimeter device (Aircast®).

The average reading of 3 measurements was recorded.

<table>
<thead>
<tr>
<th>Rolimeter</th>
<th>Average (mm)</th>
<th>std</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index knee at 30º</td>
<td>5.5</td>
<td>1.98</td>
</tr>
<tr>
<td>Non-Index at 30º</td>
<td>4.37</td>
<td>2.15</td>
</tr>
<tr>
<td>Index knee at 90º</td>
<td>5.18</td>
<td>2.4</td>
</tr>
<tr>
<td>Non-Index knee 90º</td>
<td>4.18</td>
<td>1.89</td>
</tr>
<tr>
<td>Difference at 30º</td>
<td>0.30</td>
<td>2.0</td>
</tr>
<tr>
<td>Difference at 90º</td>
<td>0.18</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Table 4.4 Demonstrating the observed sagittal laxity

No significance was observed in either 30º or 90º between the index & non-index knees indicating that anterior tibial translation/ sagittal laxity did not vary between the knees of the same patient. ATT at 30º and 90º – paired t-tests (normal data distribution) did not demonstrate a significant difference either at 30º (p=0.475) or 90º (p= 0.585) flexion (p>0.05).
4.3.2 ROM

Out of the 22 knees that underwent unilateral meniscectomy only 7 (32%) had a fixed flexion deformity of ≥10º and only one (~5%) less than 100º of maximum flexion in comparison to one (~5%) with ≥10º and none with <100º for the contralateral non-index knee. The mean total ROM for the index knees was 120º (std 16.5) with the non-index knees at 135º (std 13.1). Where a –ve value indicates fixed flexion and a +ve value hyperextension (Table 4.5).

<table>
<thead>
<tr>
<th>ROM</th>
<th>Number</th>
<th>Mean</th>
<th>Range</th>
<th>95% CI for Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index Hyperextension</td>
<td>22</td>
<td>-5.45</td>
<td>-15 to +10</td>
<td>1.39</td>
</tr>
<tr>
<td>Non-index Hyperextension</td>
<td>22</td>
<td>+2.72</td>
<td>-10 to +10</td>
<td>1.26</td>
</tr>
<tr>
<td>Index Max Flexion</td>
<td>22</td>
<td>125.4</td>
<td>90 to 140</td>
<td>2.45</td>
</tr>
<tr>
<td>Non-index Max flexion</td>
<td>22</td>
<td>132.9</td>
<td>100 to 140</td>
<td>1.93</td>
</tr>
<tr>
<td>Index Total</td>
<td>22</td>
<td>120.0</td>
<td>75 to 150</td>
<td>3.52</td>
</tr>
<tr>
<td>Non-Index Total</td>
<td>22</td>
<td>135.6</td>
<td>90 to 150</td>
<td>2.79</td>
</tr>
</tbody>
</table>

Table 4.5 ROM observed in the unilateral group, all values are in degrees (º).

The index knees showed fixed flexion of -5.45º (std 6.5) with the non-index demonstrating a hyperextension of +2.7º (std 5.9) and Max flexion of 125.4º (std 11.5) for the index knee and 132.9 (std 9.0) for the non-index knee. (Figure 4.2)
Total RoM and Fixed-Flexion deformity between the index & non-index knee tested with Wilcoxon Signed Rank test demonstrated a significant difference (p<0.001) with Fixed flexion p=0.0006, max flexion p=0.0088 and total ROM p=0.0001.

Correlations were sought between the ROM and other measured variables and outcomes. The significant correlations were identified between ROM & IKDC (r=0.497, p=0.0031) as per Kendall tau, & an inverse correlation with KL (r= -0.612, p=0.0009) as per Kendall tau.
4.4 Statistical Analysis & Correlations for Radiographic outcomes:

Radiographic analysis was performed on standardised AP and skyline weight bearing views.

4.4.1 Tibiofemoral

Two different scoring systems were used to grade the degree of osteoarthritis (Table 4.6) in both the operated & non-operated knees for coronal radiographs (AP). These were namely: Ahlback and Kellgren & Lawrence (KL).

Ahlback score for index knees vs. non-index knees demonstrated a significant difference (Wilcoxon Signed Rank test shows significant difference p<0.001). Also KL index vs. KL non-index – Wilcoxon Signed Rank test shows significant difference (p<0.001). A strong and significant correlation between KL & Ahlback grading systems was observed (Kendall’s tau r = 0.850, p<.001).

The index knees with a demonstrated KL score of ≥2 was 81% (18/22), whereas in the non-index knees this was 18%. Ahlback score of ≥1 in index knees was 77.2% (17/22).

The relative risk (RR) of developing osteoarthritis in the operated vs. non-operated knee was calculated for both the KL & Ahlback grading systems with presumed osteoarthritis as ≥2 for KL & ≥1 for Ahlback. This was found to be 4.5 as per KL (95% C.I. 1.8-11.2) & 4.25 as per Ahlback (95% C.I. 1.7-10.6).

<table>
<thead>
<tr>
<th>Median</th>
<th>Ahlback</th>
<th>Kellgren &amp; Lawrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>INDEX Knee</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Non-Index Knee</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4.6 Grading tibiofemoral osteoarthritis
4.4.2 Patellofemoral Joint

Established osteoarthritis is identified by presence of osteophytes and its progression by joint space narrowing (Altman, Asch et al. 1986; Altman, Fries et al. 1987). The patellofemoral joint (PFJ) was evaluated by standardised weight bearing images at approx 40° of flexion.

There was a significant difference between the index and non-index knees as per presence of disease, osteophytes (Jones, Ledingham et al. 1993), wilcoxon test p< 0.05 (0.0015). This demonstrates established disease in the index knees as opposed to non-index knees within the patellofemoral joint compartment (PFJ) and by extrapolation an association with meniscectomy.

The relative risk (RR) of developing osteoarthritis in the operated vs. non-operated knee in the PFJ was calculated to be 1.8 (95% C.I. 1.13-2.96) as per presence of osteophytes.

When the unilateral knee cohort was broken down as per site of procedure the observed patellofemoral joint osteoarthritis was as follows: for the lateral meniscectomy 4/7 (57%) patellofemoral joints with observed disease (as per presence of osteophytes) were identified, for medial meniscectomies this was 6/9 (66%) and for those knees with both medial and lateral meniscectomies the rate was 6/6 (100%). There was no significant difference between the presence of patellofemoral joint osteoarthritis and the site of meniscectomy as per Kruskal Wallis test p= 0.288.

No significant difference in joint space narrowing (JSN) between the two facets of the same knee was identified by Paired T-test (p>0.05). Correlations (Table 4.7) were carried out with Kendall’s Tau test for ROM, IKDC as well as both radiographic tibiofemoral (TFJ) scoring systems.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Medial PFJ</th>
<th></th>
<th>Lateral PFJ</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r value</td>
<td>p value</td>
<td>r value</td>
<td>p value</td>
</tr>
<tr>
<td>ROM</td>
<td>0.25</td>
<td>0.1</td>
<td>0.47</td>
<td>0.006*</td>
</tr>
<tr>
<td>IKDC</td>
<td>0.25</td>
<td>0.1</td>
<td>0.425</td>
<td>0.007*</td>
</tr>
<tr>
<td>Ahlback</td>
<td>-0.398</td>
<td>0.027*</td>
<td>-0.33</td>
<td>0.058**</td>
</tr>
<tr>
<td>KL</td>
<td>-0.57</td>
<td>0.0047*</td>
<td>-0.45</td>
<td>0.011*</td>
</tr>
</tbody>
</table>

Significance = *, nearing significance **

**Table 4.7** Depicting correlations PF JSN of medial & lateral facets with other parameters.

The lateral joint space was chosen to be further investigated with regards to JSN of less than 5mm as it correlated better with most investigated parameters above.

When the PFJ (patellofemoral joint) space narrowing in the lateral compartment with a cut-off of 5mm or less was analysed (Boegard, Rudling et al. 1998), mean differences between the osteoarthritic PFJ with <5mm joint space and non-osteoarthritic PFJ with joint space >5mm the following were noted:

There was a significant difference between the scores for tibiofemoral osteoarthritis in the index knees with lateral PFJ <5mm and those knees with lateral PFJ >5mm, as noted by Independent t-test (p<0.05) for both KL & Ahlback grading systems (p=0.013 & p=0.011 respectively).
Furthermore, unpaired t-test demonstrated a significant difference between ROM on index knee for PFJ joint space less than 5mm vs. ROM on index knee for joint space greater than 5mm (p<0.05, p=0.00000). A significant difference between IKDC of index knees with PFJ joint space less than 5mm vs. IKDC of those with greater than 5mm joint space (p<0.05) was observed as per Mann-Whitney U test.

These results confirm the significance of this 5mm cut-off measure in the patellofemoral joint (PFJ) with regards to osteoarthritis disease progression as demonstrated by both osteoarthritis grading systems, range of motion (ROM) & patient reported outcome measures (PROMs-IKDC).

### 4.4.3 Malalignment

Does meniscectomy affect the coronal tibiofemoral angle resulting in malalignment?

Tibiofemoral angles as measured on the AP weight bearing films were used to assess the degree of malalignment, whilst “magnitude of malalignment” was calculated to indicate the deviation from the physiological 6º valgus angle regardless of the direction from that value.

All 38 knees (30 patients) that underwent meniscectomy were assessed: 15 underwent medial meniscectomy, 15 underwent lateral meniscectomy and 8 underwent both medial and lateral meniscectomy.

The average tibiofemoral angle was 3.2º of valgus (std 4.8º), this was significantly lower (i.e. more varus) for the MM group -0.5º (±4.5º) when compared to the LM 5.5º (±2.9º) or MLM 5.9º (±3.9º) groups (MM vs. LM p=0.0004, MM vs. MLM p=0.003, Wilcoxon two sample test).
This difference was also observed when the magnitude of malalignment was compared. Magnitude of malalignment in MM 6.5° (±4.5°) was significantly higher than for LM 2.3° (±1.8°) or MLM 3.0° (±2.0°) (MM vs. LM p=0.002, MM vs. MLM p=0.045 Wilcoxon two sample test).

**Malalignment in the unilateral group (22 patients)**

This group demonstrates a mean of 3.2° (std 4.4) in terms of pure tibiofemoral angle and 4.1° (std 3.1) in terms of magnitude of malalignment.

Subgroups demonstrated a mean of -0.6° (std 3.7) for MM, 4.4° (std 3.6) for LM and 6.2° (std 4.2) in terms of tibiofemoral angle and 6.6° (std 3.7), 3.0° (std 2.3) and 4.1° (std 3.1) as magnitude of malalignment respectively. Whereas the non index knee had a mean of 2.6° (std 2.6) in terms of pure valgus angle and 3.5° (std 2.4) in terms of magnitude of malalignment (Table 4.8).

<table>
<thead>
<tr>
<th></th>
<th>Medial (n=9)</th>
<th>Lateral (n=7)</th>
<th>Med &amp; Lat (n=6)</th>
<th>ALL (n=22)</th>
<th>Non-index knee</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean+/Std</td>
<td>Mean+/Std</td>
<td>Mean+/Std</td>
<td>Mean+/Std</td>
<td>Mean+/Std</td>
</tr>
<tr>
<td>Tibiofemoral angle (valgus)</td>
<td>-0.6+/3.7</td>
<td>4.4+/3.6</td>
<td>6.2+/4.2</td>
<td>3.2+/4.4</td>
<td>2.6+/2.6</td>
</tr>
<tr>
<td>Magnitude of malalignment</td>
<td>6.6+/3.7</td>
<td>3.0+/2.3</td>
<td>3.2+/2.3</td>
<td>4.1+/3.1</td>
<td>3.5+/2.4</td>
</tr>
</tbody>
</table>

**Table 4.8** Knee malalignment demonstrating the tibiofemoral angles in degrees (°) of index & non-index knees as measured and deviation from physiological valgus angle (magnitude of malalignment) for the 22 patients with unilateral knee meniscectomy.

When comparing tibiofemoral angle of the index knee vs. non index knee there is no significant difference between the two populations despite index knees being slightly more valgus overall (p=0.161). When this is broken down into MM, LM and MLM
groups, the MLM index knees are significantly more valgus than their non-index counterparts (p=0.011). Table 4.9

<table>
<thead>
<tr>
<th></th>
<th>Medial (n=9)</th>
<th>Lateral (n=7)</th>
<th>Med &amp; Lat (n=6)</th>
<th>ALL (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean +/- Std</td>
<td>Mean +/- Std</td>
<td>Mean +/- Std</td>
<td>Mean +/- Std</td>
<td>Mean +/- Std</td>
</tr>
<tr>
<td>Index Tibiofemoral angle</td>
<td>-0.6 +/- 3.7</td>
<td>4.4 +/- 3.6</td>
<td>6.2 +/- 4.2</td>
<td>3.2 +/- 4.4</td>
</tr>
<tr>
<td>Paired Non-Index Tibiofemoral angle</td>
<td>1.1 +/- 2.1</td>
<td>3.9 +/- 1.9</td>
<td>2.7 +/- 3.6</td>
<td>2.6 +/- 2.6</td>
</tr>
<tr>
<td>p value</td>
<td>0.104</td>
<td>0.232</td>
<td>0.014</td>
<td>0.161</td>
</tr>
</tbody>
</table>

Table 4.9 Paired Index vs. Non-index tibiofemoral angles as per site of meniscectomy.

Medial meniscectomies (MM) vs. Lateral meniscectomies (LM) vs. Medial & lateral meniscectomies (MLM) demonstrated significance of p= 0.027 (Kruskal Wallis test) indicating that patients who underwent medial meniscus removal resulted in lower tibiofemoral angles than those with either lateral or both medial & lateral site meniscectomies.

**Does malalignment affect the other measured variables (ROM, Ahlback & KL & PROMs)?**

Correlations were sought between both tibiofemoral angle and magnitude of malalignment with BMI and flexion along with Ahlback/ KL scores.

The tibiofemoral angle correlated inversely with Ahlback and KL scores (r= -0.379 p=0.034 and r= -0.377 p=0.035 respectively - Kendall tau correlation) indicating that
the more varus (and hence more –ve the value) the greater the degree of observed osteoarthritis. The magnitude of malalignment demonstrated these correlations even more strongly, with Ahlback and KL scores (r=0.430 p=0.018 and r=0.494 p=0.006 respectively - Kendall tau correlation) along with a significant correlation with BMI and an inverse correlation with range of flexion (r=0.335 p=0.039 and r= -0.437 p=0.013 respectively - Kendall tau correlation). However no significant correlation was observed between malalignment and IKDC (r= -0.20 p=0.22).
4.5 Statistical Analysis & Correlations for PROMs:

Subjective outcomes for this group as measured by KOOS & IKDC 2000 were as follows (Table 4.10):

<table>
<thead>
<tr>
<th>PROMs</th>
<th>All =30</th>
<th>Unilateral knee patients=22</th>
<th>Bilateral knee patients=8</th>
<th>Unilateral vs. Bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Std</td>
<td>Mean</td>
<td>Std</td>
</tr>
<tr>
<td>KOOS-Symptoms</td>
<td>65.5</td>
<td>23.2</td>
<td>70.45</td>
<td>24.45</td>
</tr>
<tr>
<td>KOOS-Pain</td>
<td>74.4</td>
<td>20.4</td>
<td>78.28</td>
<td>19.50</td>
</tr>
<tr>
<td>KOOS-ADL</td>
<td>79.1</td>
<td>19.3</td>
<td>82.02</td>
<td>18.24</td>
</tr>
<tr>
<td>KOOS-Sports</td>
<td>62.6</td>
<td>28.5</td>
<td>67.27</td>
<td>26.85</td>
</tr>
<tr>
<td>KOOS-QoL</td>
<td>65.3</td>
<td>27.0</td>
<td>70.45</td>
<td>24.94</td>
</tr>
<tr>
<td>IKDC</td>
<td>59.37</td>
<td>11.98</td>
<td>62.28</td>
<td>11.26</td>
</tr>
</tbody>
</table>

Table 4.10 Cohort's PROMs

A significant difference was observed between the subgroups of bilateral and unilateral meniscectomies (one and two knee procedures) as scored by IKDC (p=0.012). With KOOS subsections of Symptoms and QoL nearing significance with a p= 0.054.

However a definition of a symptomatic knee as defined by Englund & Roos (Englund, Roos et al. 2003) required that the score for the KOOS subscale QOL and 2 of the 4 additional subscales should be equal to or less than, the score obtained as follows: at least 50% of the questions within the subscale were answered with at least a 1-step decrease from the best response (indicating no pain/best possible function, etc.) on a 5-point Likert scale. After conversion to a 0–100 scale (0 worst, 100 best), the cut-offs were as follows: pain 86.1, symptoms 85.7, ADL 86.8, sport 85.0, and QOL 87.5.
If one considers the subjective KOOS outcomes observed in this follow-up it is easy to see that the mean values of this cohort is deemed symptomatic in all of the KOOS subscales as defined above (Table 4.11), with the patients who underwent bilateral knee meniscectomies fairing the worst.

<table>
<thead>
<tr>
<th>KOOS subscale</th>
<th>Symptomatic Score</th>
<th>Whole group (n=30)</th>
<th>Unilateral group (n=22)</th>
<th>Bilateral group (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>86.1</td>
<td>65.5</td>
<td>70.45</td>
<td>54.9</td>
</tr>
<tr>
<td>Symptoms</td>
<td>85.7</td>
<td>74.4</td>
<td>78.28</td>
<td>66.3</td>
</tr>
<tr>
<td>ADL</td>
<td>86.8</td>
<td>79.1</td>
<td>82.02</td>
<td>72.6</td>
</tr>
<tr>
<td>Sport</td>
<td>85.0</td>
<td>62.6</td>
<td>67.27</td>
<td>51.9</td>
</tr>
<tr>
<td>QOL</td>
<td>87.5</td>
<td>65.3</td>
<td>70.45</td>
<td>47.7</td>
</tr>
</tbody>
</table>

Table 4.11 Symptomatic KOOS scores as defined by (Englund, Roos et al. 2003) highlighted.

Correlations between the PROMs scoring systems and radiographic Ahlback/KL scores demonstrate the following: a moderate but significant inverse correlation between KOOS ADL and Ahlback (Kendall’s tau r = -0.437, p=0.013); between KOOS Sport and Ahlback (Kendall’s tau r = -0.355, p=0.045); between IKDC and Ahlback (Kendall’s tau r = -0.429, p=0.013) (figure 4.3).
Figure 4.3 Correlation between IKDC and Ahlback.

This means that as the degree of radiographic osteoarthritis increases (as scored by Ahlback, which has a linear strong correlation with KL) the score for sport, ADL & IKDC decreases i.e. the patients score worse with regards to sporting activities, ADL as their radiographic osteoarthritis increases.

Although the rest of the KOOS subscales did not reach significance levels (p<0.05) of correlation there was an observed similar tendency i.e. the subjective scores reduced as the osteoarthritis score increased. Hence one could postulate that significance could have been observed had there been a larger sample size. However, this is not a new finding as previous studies have demonstrated that there is no strict correlation between the radiographic appearance of osteoarthritis & the subjective reported outcome of patients.
4.6 Statistical Analysis & Correlations for Biomarkers:

All 22 patients had serum markers available for analysis and the marker used was MMP-3(ng/ml). It is important to state that not all knees had a positive aspiration, from a possible 22 index knees only 17 had a positive aspirate and from the non-index this number was reduced to 9 (Figure 4.4).

![Flow chart of positive knee aspirations.](image)

Out of the 17 patients with positive aspirates nine (9) scored symptomatically in all 5 parameters of KOOS. They all had a KL score of ≥3 (four out of these had a KL score of 4). There mean GAG was 92.4 µg/ml (18.8-245.4) and MMP-3 298.6 ng/ml (87.9-493.5). Out of the remaining eight (8) only 4 were asymptomatic in 4 or 5 of the 5 KOOS parameters, two had a KL of ≥3. There mean GAG was 147.3 µg/ml (35.6-223.9) and MMP-3 441.2 ng/ml (215.8-591.8).

As only 9 patients had a positive aspiration in both the index and non-index knees the numbers were small. Nevertheless, two markers were used with regards to synovial fluid analysis, GAG (µg/ml) & MMP-3 (ng/ml).
GAG showed an average of 108.6 (std 83.2) for index knees (n=17) and 149.9 (std70.0) for non-index knees (n=9), similarly MMP-3 showed an average of 370.0 (std 171.1) for index knees (n=17) and 305.1 (std 200.9) for non-index knees (n=9). Serum MMP-3 (n=22) showed an average of 23.34 (std 9.78).

**MMP-3**

**Serum** MMP-3 did not demonstrate any significant correlation with Ahlback, IKDC or all FIVE of the KOOS parameters, using Spearman’s rho non-parametric test.

1. Serum MMP3 v Ahlback - no significant correlation (p>0.05)
2. Serum MMP3 v KOOS (x5) - no significant correlation (p>0.05) in all five cases
3. Serum MMP3 v IKDC - no significant correlation (p>0.05)

**Synovial** MMP3 – paired t-test showed no significant difference was demonstrated between index vs. non-index knees (p>0.05) and no significant correlation (p>0.05) between MMP3 index vs. Ahlback index

**GAG**

This is only a synovial fluid marker.

The marker was tested for difference between index & non-index knees and this demonstrated significance (paired t-test p=0.049).

Subsequently GAG-index was tested against the osteoarthritis grading system of Ahlback (Figure 4.5) with a moderate and significant inverse correlation observed by Kendall’s tau (r = -0.506, p=0.012).
Figure 4.5 Correlation between GAG and Ahlback ($r = -0.506$, $p=0.012$)

Index GAG was tested for correlations against all other parameters with the only positive finding being with the IKDC score (Figure. 4.6). Whereas GAG vs. ROM & all 5 parameters of KOOS did not demonstrate any significant correlation as per Spearman’s test. GAG vs. IKDC – Kendall’s Tau demonstrated a strong and positive correlation ($r=0.468$, $p=0.009$).
The correlations observed between GAG and the radiographic Ahlback score and PROMs (IKDC) suggest that synovial GAG as a biomarker for osteoarthritis may indicate progression of disease and symptoms. However the wide range of its values and the small numbers in the study cast some doubt over the actual significance of this finding.

Correlations Matrix can be found in Appendix 1
CHAPTER 5

Discussion
5.1 Primary outcome:

Our cohort’s age at assessment averaged 55.6 years. The recorded incidence of TKA at this age, both in Scotland and in particular Tayside (Figure 5.1) is just over 100/100,000 (0.001%), with the majority of the population undergoing a primary knee arthroplasty over the age of 60, with a median age of 70 (as per Scottish Arthroplasty Project Report 2008). Similar values (Table 5.1) seem to be reproduced in other databases (Robertsson, Bizjajeva et al. 2010).

Figure 5.1 Rate of TKA/100,000 with Age.
<table>
<thead>
<tr>
<th>AGE</th>
<th>Denmark</th>
<th></th>
<th>Norway</th>
<th></th>
<th>Sweden</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>&lt;45</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>45-54</td>
<td>47</td>
<td>29</td>
<td>32</td>
<td>22</td>
<td>44</td>
<td>27</td>
</tr>
<tr>
<td>55-64</td>
<td>169</td>
<td>119</td>
<td>145</td>
<td>85</td>
<td>193</td>
<td>137</td>
</tr>
<tr>
<td>65-74</td>
<td>328</td>
<td>227</td>
<td>332</td>
<td>170</td>
<td>450</td>
<td>326</td>
</tr>
<tr>
<td>75-84</td>
<td>374</td>
<td>232</td>
<td>349</td>
<td>186</td>
<td>460</td>
<td>323</td>
</tr>
<tr>
<td>&gt;85</td>
<td>113</td>
<td>100</td>
<td>79</td>
<td>54</td>
<td>96</td>
<td>91</td>
</tr>
</tbody>
</table>

**Table 5.1** From "Knee arthroplasty in Denmark, Norway and Sweden." (Robertsson, Bizjajeva *et al.* 2010). Highlighted rows indicate the age group of this cohort.

In this cohort, it is evident that the incidence of TKA was much higher than the rest of the Tayside and Scottish population as per age with the extrapolated figure from this study suggesting 13,20/100,000 (7/53) indicating an 132 fold increase in comparison to an age matched general population following open total meniscectomy during adolescence!

Attempts to retrace the whole initial cohort of 313 patients from the original investigator (P. Abdon) via successful email communication proved unsuccessful as he no longer has the data available. This unfortunately means that depicting survivorship of the entire, initially identified, cohort in terms of TKA as an end point is not possible.

These outcomes go some way into answering the question posed at the 30 year follow-up as to whether the meniscectomised cohort will ultimately have a higher incidence of TKAs than its similarly age matched general public (McNicholas, Rowley *et al.* 2000).
5.2 BMI:

Obesity is an established risk factor for knee osteoarthritis (Felson, Zhang et al. 1997; Gelber, Hochberg et al. 1999) as is knee injury (Felson 1990; Gelber, Hochberg et al. 2000; Wilder, Hall et al. 2002). Little is known of the mechanisms that lead to osteoarthritis and indeed how an injured joint interacts with other risk factors.

Although BMI is a potentially fluctuating parameter through time, it has been shown via retrospective estimates that development of osteoarthritis does not equate to increased BMI and that obesity itself is an independent risk factor leading to osteoarthritis in meniscectomised patients (Englund and Lohmander 2004). These findings confirm the findings of the aforementioned study as to its correlation with radiographic osteoarthritis (in a meniscectomised cohort).

Studies on the effect of BMI on knee osteoarthritis seem to agree with its association with radiographic knee osteoarthritis but not all do with regards to its association with symptoms (Lethbridge-Cejku, Scott et al. 1995; Felson, Chaisson et al. 2001; Marks 2007). This study also failed to demonstrate a correlation between BMI and PROMs.

An explanation may be the observation that pain seems to be related with physical activity (Marks 2007). Even so, comparison of overweight and obese patients with established radiographic osteoarthritis against a normal cohort demonstrated a higher likelihood for knee pain in those subjects with BMIs >30 i.e. morbid obesity (Rogers and Wilder 2008).

Knee pain in patients with radiographic osteoarthritis, in general, has been also linked with bone marrow lesions, bone ulceration, quadriceps weakness, and psychological factors (Sharma L 2007). Depression has been linked with pain in general (Bair, Robinson et al. 2004) and specifically to knee pain (Jinks, Jordan et al. 2008). The link
between obesity, negative affect and depression has been confirmed, therefore weight loss may also have a positive effect on general well being feelings (Lichtenberg, Swensen et al. 1986; Hochberg, Lawrence et al. 1989; Davis, Ettinger et al. 1992; Dekker, Tola et al. 1993; Creamer, Lethbridge-Cejku et al. 1999; Hannan, Felson et al. 2000; Keefe, Affleck et al. 2004; Petry, Barry et al. 2008; Kim, Han et al. 2011) and not only in reduction of knee loading forces (Morrison 1970).

It is not surprising then that reduction in pain along with improvement in physical activity was noted following weight loss in obese patients (Felson, Zhang et al. 1992; Abu-Abeid, Wishnitzer et al. 2005; Miller, Nicklas et al. 2006), suggesting that obesity may indeed play a role in perceived pain.
5.3 Site of meniscectomy:

Radiological and clinical results documented in previous long-term total meniscectomy studies seem to indicate that lateral meniscectomies fair worse than medial ones (Johnson, Kettelkamp et al. 1974; Yocum, Kerlan et al. 1979; Abdon, Turner et al. 1990), however in other studies no significant difference in either radiological or clinical outcomes were noted (Ranger, Klestil et al. 1995; Maletius and Messner 1996; Burks, Metcalf et al. 1997; Schimmer, Brulhart et al. 1998).

In our study the site of meniscectomy did not seem to alter the grade of TF osteoarthritis as measured by KL and Ahlbach grading systems (no difference in the grade of osteoarthritis in the most affected compartment), the ROM or the PROMs (as per IKDC).

Whilst these findings seem to agree with previous studies of this cohort in terms of site of meniscectomy and ROM (i.e. the site did not affect ROM), there is disagreement in terms of PROMs and osteoarthritis grading.

PROMs: Previously it was observed at the 30 year follow-up that double meniscectomies fared worse than lateral ones, and lateral ones demonstrated a worse outcome than the medial meniscectomies as measured by Tapper & Hoover and WOMAC (McNicholas, Rowley et al. 2000). These findings at the time seemed to be in-keeping with some earlier studies (Johnson, Kettelkamp et al. 1974; Allen, Denham et al. 1984; Abdon, Turner et al. 1990; Englund and Lohmander 2005) but not all (Manzione, Pizzutillo et al. 1983). The difference between this current study and previous ones is the length of follow-up and the use of more appropriate patient reported outcome systems (Tilley 2010).
This study has as far as can be confirmed the longest follow-up to date as opposed to the above mentioned studies where the max was the 30 year follow-up with the rest being from 10-22 years.

Outcome systems used in previous studies have their weaknesses at evaluating the patient cohort. For example the Tapper & Hoover system has been utilised wrongly in published studies by grouping together the excellent with the good (Macnicol and Thomas 2000). The WOMAC used in other studies, has been shown to be reliable in measuring knee disability and more responsive than the SF-36 (Brazier, Harper et al. 1999; Garratt, Brealey et al. 2004). However it has been superseded by the KOOS, with improved validity, a system incorporating WOMAC (Roos, Roos et al. 1998).

The PROMs used in this study have been supported by recent evidence confirming their reliability, validity as well as their high degree of patient involvement, a factor which enables them to perform better as patient-based assessment tools (Tilley 2010).

Osteoarthritis grading: Poorer radiological outcomes following lateral as opposed to medial meniscectomy have been reported by most previous authors (Appel 1970; Allen, Denham et al. 1984; Jorgensen, Sonne-Holm et al. 1987; McNicholas, Rowley et al. 2000) but not all (Manzione, Pizzutillo et al. 1983; Wroble, Henderson et al. 1992).

Their findings seem to be in keeping with biomechanical theories of greater load sharing capabilities of the lateral meniscus coupled with the relatively incongruent lateral tibiofemoral joint. In vitro studies demonstrated that 70% of the load in the lateral and 50% of that in the medial compartments was transmitted through their corresponding menisci (Ahmed, Burke et al. 1983).

However, it was calculated that forces going through the tibiofemoral joint exert more loading in the medial as opposed to the lateral compartment (Schipplein and Andriacchi...
1991). The shape of the tibial plateau being more concave on the medial site and more convex on the lateral provides more congruency medially and more freedom laterally with the contact area being 1.6 times greater medially than laterally (Kettelkamp and Jacobs 1972).

This may go some way in explaining our findings, as one can deduce that even though forces through the medial compartment may be greater than those in the lateral, the contact stresses may not be different due to the increase congruency and contact area of the medial compartment. Therefore in a long term study, such as this one, the effects of total meniscectomy on either site or indeed with both menisci removed, did not demonstrate a significant difference in the degree of ultimate radiographic tibiofemoral osteoarthritis grade, a finding that has been supported in other open total meniscectomy studies (Roos, Lauren et al. 1998).
5.4 Sagittal Laxity:

Knee motion is controlled by the interactions between its supporting structures, damage to any one of them and the overall motion of the knee is likely to be altered. Complete disruption of a ligament or meniscus can lead to symptoms of instability and to the involvement of other structures and tissues (i.e. articular cartilage) which are asked to carry increasing loads rendering them more susceptible to injury. Varus–valgus laxity is greater in the non-arthritic knees of patients with idiopathic disease than in the knees of controls, suggesting that a portion of the increased laxity of knee osteoarthritis precedes disease development and may predispose to disease (Sharma, Lou et al. 1999). This type of instability has been induced in our cohort when they underwent total meniscectomy.

It has also been noted that sagittal plane or anterior–posterior laxity may be increased in knees with mild osteoarthritis but appears to decline with increasing severity of knee osteoarthritis (Brage, Draganich et al. 1994; Wada, Imura et al. 1996).

As meniscectomy in itself does not produce a measurable degree of AP laxity (Bargar, Moreland et al. 1980) it was important to assess if there was a measurable difference of sagittal laxity between the index and non-index knees (Ganko, Engebretsen et al. 2000) to confirm, as at the 30 year follow-up (McNicholas, Rowley et al. 2000), that there were no ACL ruptures between the 2 follow-ups and that meniscal pathology was the only “instability” variable between the two knees.

This was confirmed as no difference was observed in either 30° or 90° between the index & non-index knees indicating that anterior tibial translation/ sagittal laxity did not vary between the knees of the same patient; enabling comparison of various parameters between the two knees.
5.5 Range of Motion:

In our study we observed a significant difference between the total ROM and Fixed-Flexion deformity of the index vs. non-index knee, a finding that is in-keeping with other studies (Abdon, Turner et al. 1990; McNicholas, Rowley et al. 2000).

Reduction in the range of joint motion is considered a good indicator of disease progression, loss of function, both self-reported and observed. Loss of flexion/extension of the knee is closely associated with disability (Massardo, Watt et al. 1989; Steultjens, Dekker et al. 2000).

A close association between joint range of motion and radiographic scoring by Kellgren & Lawrence (Kellgren and Lawrence 1957) was observed, specifically a significant negative correlation was found between flexion and medial compartment osteoarthritis and extension (fixed flexion) with patellofemoral joint osteoarthritis (Ersoz and Ergun 2003). Here this was observed by a strong negative correlation between fixed flexion deformity and Ahlback grading (Ahlback grading demonstrated a strong and significant correlation with KL).

The incorporation of fixed flexion ROM, along with age and KOOS-ADL together, significantly predicted whether or not a person would undergo TKA (p <or= 0.001); demonstrating the importance of measuring ROM in patients with knee osteoarthritis (Zeni, Axe et al. 2010).
5.6 Radiographic Outcomes:

Meniscectomy is a strong recognised risk factor for tibiofemoral osteoarthritis (Fairbank 1948; Jorgensen, Sonne-Holm et al. 1987; Roos, Roos et al. 1998). A large proportion of patients treated with total or indeed partial meniscectomy demonstrate radiographic changes as early as 5 years post operatively (Lohmander and Roos 1994) with an estimated radiographic evidence of osteoarthritis 10-20 years earlier than patients with primary knee osteoarthritis (Roos, Adalberth et al. 1995).

5.6.1 Tibiofemoral joint

In this study two different accepted and validated radiological grading systems have been used in assessing the osteoarthritis grade of the most affected tibiofemoral compartment, the Ahlback & KL systems (Kellgren and Lawrence 1957; Ahlback and Rydberg 1980). Both grading systems demonstrated a significant difference between the operated index knee and the non-index knee. These were compared against each other revealing a very strong and significant correlation between them (Kendall’s tau $r = 0.850, p<.001$). The calculated relative risk of significant osteoarthritis as seen on radiographs was calculated at 4.5 as per KL $\geq 2$ (95% C.I. 1.8-11.2) & 4.25 as per Ahlback $\geq 1$ (95% C.I. 1.7-10.6).

A higher percentage of patients with radiographic tibiofemoral osteoarthritis, 81% with KL $\geq 2$ was noted, when compared with studies of patients undergoing a shorter review timescale which demonstrated this to be at 48% (Roos, Lauren et al. 1998).

It is a recognised weakness to use the contralateral knee of the same patient as a comparison (Roos, Lauren et al. 1998). Several studies have noted osteoarthritic changes in the contralateral, essentially control, knee (Allen, Denham et al. 1984; Fauno and Nielsen 1992; Dahlberg, Roos et al. 1994) and in an ideal situation a gender, age and BMI control group should be identified and utilised.
Osteoarthritic changes noted in the control non-index knee, contralateral knee, were higher than in studies utilising a matched control group. Specifically the non-index (contralateral) knee demonstrated a KL≥2 & Ahlback ≥1 grade of 18% whereas in studies with specific control groups these were 7% (Roos, Lauren et al. 1998) and 10% (Englund and Lohmander 2004). However in the latter study the contralateral knee of the meniscectomised cohort demonstrated a KL ≥2 of 27% at a 15-22 year follow-up.

The lack of control group and the recognition of contralateral knee osteoarthritis involvement goes some way in explaining the somewhat lesser relative risk of 4.5 (RR) observed in this study with that in studied utilising a matched control group of 6 fold (Roos, Lauren et al. 1998; Englund, Roos et al. 2003).

Length of follow-up and the cohort demographics, (such as age, BMI, and gender) however vary between studies; for example the aforementioned studies had a maximum follow-up of 22 years whereas this study has a mean follow-up of 40 years.

**5.6.2 Patellofemoral Joint**

Meniscectomy as a risk factor for tibiofemoral osteoarthritis is well documented (Fairbank 1948; Jorgensen, Sonne-Holm et al. 1987; Roos, Roos et al. 1998), in comparison there are fewer studies demonstrating its effect on the patellofemoral joint (Englund and Lohmander 2005). The same method of standardising a weight bearing skyline view as per the aforementioned study was utilised. It has been demonstrated that a standardised skyline view gives more information of the patellofemoral joint than a lateral, with greater reproducibility (Jones, Ledingham et al. 1993; Cicuttini, Baker et al. 1996; Boegard, Rudling et al. 1998).

Most of the knee osteoarthritis studies concentrate on changes of the tibiofemoral joint (TFJ) whilst ignoring the patellofemoral (PF) compartment (Englund and Lohmander 2005). As a result PF osteoarthritis risk factors and consequences have been less
investigated and documented, although similar risk factors of osteoarthritis elsewhere have been recognised. Previous reports point out the importance of PF osteoarthritis as a cause of knee pain (McAlindon, Snow et al. 1992) and as a consequence of knee meniscectomy (Englund and Lohmander 2005).

The importance of patellofemoral (PFJ) osteoarthritis in relation to disability is recognised (McAlindon, Snow et al. 1992), yet it has been demonstrated that not all orthopaedic surgeons in the UK utilise a dedicated view to assess the joint (skyline view) with around 75% not requesting one at all (Vince, Singhania et al. 2000). A complete evaluation of the knee joint should include the PFJ via a skyline view as it is superior to a knee lateral for patellofemoral osteoarthritis (Lanyon, Jones et al. 1996; Davies, Vince et al. 2002). The skyline view should be the method of choice to detect progression of patellofemoral osteoarthritis.

Patellofemoral joint osteoarthritis grading has been suggested by Jones, unfortunately in his paper there is no clear distinction between the grades given especially for joint space narrowing (Jones, Ledingham et al. 1993). This significant question was clarified when standardised radiographic evaluation of the patellofemoral joint was compared with magnetic resonance imaging findings (Boegard, Rudling et al. 1998), by identifying the cut-off point of 5mm i.e. if joint space in either the lateral or medial facet of the Patellofemoral joint was less than 5mm this had high specificity for MRI-detected cartilage defects. In addition, a separate paper during the same year the same team (Boegard, Rudling et al. 1998), demonstrated that in a patellofemoral joint with joint space narrowing (JSN)< 5 mm, osteophytes had sensitivity and a positive predictive value of 90% and 95% respectively for MRI detected cartilage defects but not if the joint space was greater than the 5mm cut-off. Hence joint space narrowing of less than
5mm +/- presence of osteophytes are in-keeping with presence of osteoarthritis in the patellofemoral joint.

In this study a significant difference was noted between the index and non-index knees as per presence of osteophytes indicating the presence of patellofemoral joint (PFJ) osteoarthritis in meniscetomised knees and by extrapolation its association with meniscectomy with an observed relative risk (RR) of 1.8 (95% C.I. 1.13-2.96) as per presence of osteophytes.

As no difference was noted between the joint space of the medial and lateral facet of index knees and the lateral facet joint space correlated better with most other measured variables: no correlation was observed between the medial joint space and either ROM or IKDC. The lateral Joint space on the other hand showed weak but significant correlation with the ROM (negative correlation) & IKDC (positive correlation). This indicates that the bigger the space (i.e. the lesser the narrowing & hence the disease) the better the ROM & the patients perception as per IKDC score.

The lateral joint space was chosen as the one to seek significance between the index knees with >5mm of joint space and those with <5mm as it correlated better with ROM, IKDC & Ahlback scores.

When patellofemoral space narrowing in the lateral compartment with a cut-off of 5mm or less (mean differences between osteoarthritic patellofemoral joint with <5mm and non-osteoarthritic patellofemoral joint (PFJ) with >5mm) was analysed the following was noted:

- There was a significant difference between the scores for tibiofemoral (TF) osteoarthritis in the knees with lateral PFJ <5mm and those knees with lateral PFJ >5mm, for both KL & Ahlback grading systems in the tibiofemoral joint.
- There was significant difference in ROM between the index knees with PFJ joint space < 5mm vs. ROM on index knee with joint space > 5mm.

- A significant difference between IKDC of index knees with PFJ joint space < 5mm vs. IKDC of index knees with PFJ space > 5mm.

These results confirm the significance of this 5mm cut-off measure in the PFJ with regards to osteoarthritic disease progression as demonstrated by both osteoarthritis grading systems (KL & Ahlback), ROM & PROMs (IKDC) and consolidate the link between tibiofemoral osteoarthritis and patellofemoral osteoarthritis as a consequence of meniscectomy.

Several possible explanations as to why patellofemoral osteoarthritis is seen as well as tibiofemoral osteoarthritis in patients with knee meniscectomy. Knee osteoarthritis in general has been shown to have an association with hand osteoarthritis suggesting that osteoarthritis could be a genetic, systemic as well as localised disease (Englund, Paradowski et al. 2004).

Activation of cytokine and protease cascades which act globally within the affected joint as well as systemically (Sandy 2003) could be one cause, whilst altered biomechanic loading patterns post meniscectomy could be another (Elahi, Cahue et al. 2000); with the resulting knee osteoarthritis leading to quadriceps weakness thereby increasing the risk of patellofemoral joint osteoarthritis.

These results confirm other studies in identifying the association of patellofemoral joint osteoarthritis with meniscectomy (Englund and Lohmander 2005).
5.6.3 Malalignment

An association between chondral damage and ensuing osteoarthritis has been established with worse long-term outcomes being reported for those patients who had an identified chondral lesion at the time of meniscectomy. These patients did even worse if their age was over 30 years old (Maletius and Messner 1996; Messner and Maletius 1996).

It has been documented that chondral lesions and meniscal pathology can occur concomitantly (Lewandrowski, Muller et al. 1997).

However, the cohort of patients in this study were under the age of 19 at the time of open total meniscectomy and in their records no other ligamentous or articular cartilage lesion was recorded at the time (Abdon, Turner et al. 1990; McNicholas, Rowley et al. 2000).

In this study so far the association between meniscectomy and osteoarthritis as well as reduction in ROM and PROMS has already been demonstrated.

A study of patients with early symptomatic knee osteoarthritis demonstrated a clear relationship between local knee alignment (as determined from short fluoroscopically guided standing anteroposterior knee radiographs) and the compartmental pattern and severity of knee osteoarthritis. Each degree of change from the physiological valgus angle into varus, was associated with a significantly increased risk of having predominantly medial compartment osteoarthritis. A similar association was found between further valgus angulation and lateral compartment osteoarthritis (Khan, Koff et al. 2008).
In the whole cohort (i.e. 38 meniscectomised knees) there was a significant difference between the type of meniscectomy and the tibiofemoral angle, as well as magnitude of malalignment (deviation from the assumed “physiological” 6° valgus angle) with medial meniscectomy fairing worse. This observation was also true when medial meniscectomies were compared with the rest (LM + MLM) in the unilateral group alone (22 patients). Indicating that the magnitude of malalignment was greater in the worst affected knees as identified by the reduced ROM and increased osteoarthritis score.

These findings are supported by other studies which implicate the association between meniscectomy, malalignment and osteoarthritis, with worse outcomes and malalignment following medial meniscectomies and varus deformities (Allen, Denham et al. 1984; Guettler, Glisson et al. 2007).

In this study no significant association between malalignment and patient reported outcome measures (PROMs) was observed when using the physiological 6° angle. Previous studies proposed that meniscectomy in already malaligned knees with a less than 4° angle to be associated with worse symptomatology (Covall and Wasilewski 1992; Fauno and Nielsen 1992). However, when this value was applied to the whole cohort (38 knees) and the unilateral cohort (22 knees) no such significant association was demonstrated.

Having said this it is still unclear if the resultant malalignment was simply due to the removal of the meniscus with an assumed 1-2° (Guettler, Glisson et al. 2007) of resultant malalignment, the change in force distribution across the tibiofemoral, the progression of ensuing osteoarthritis or a combination of all the above.
5.7 PROMs (Subjective Outcomes):

Severe joint pain and loss of function due to degeneration of articular cartilage may result in poor quality of life (Bentley and Minas 2000) and may lead to joint replacement (Britberg, Lindahl et al. 1994; Shortkroff, Barone et al. 1996; Gugala and Gogolewski 2000).

Although the cohorts’ perceived functional subjective reported outcome seemed to have improved between the 17 & 30 year follow-up. This was observed by utilising the Tapper & Hoover scoring system, in which grouping together the “excellent” with the “good” (Jorgensen, Sonne-Holm et al. 1987; Hede, Larsen et al. 1992; Jaureguito, Elliot et al. 1995; Burks, Metcalf et al. 1997; Schimmer, Brulhart et al. 1998) to demonstrate an expression of satisfaction seems to be misleading.

The WOMAC scoring system was utilised at the 30 y follow-up as well, it demonstrated that the type of meniscectomy had an effect on the scoring outcome with bilateral meniscectomies performing worse than lateral meniscectomies, and lateral meniscectomies in turn doing worse that medial ones. This seemed to be in agreement with previous studies (Johnson, Kettelkamp et al. 1974; Manzione, Pizzutillo et al. 1983; Abdon, Turner et al. 1990) but not all of the literature (Manzione, Pizzutillo et al. 1983). In this 40y follow-up no such relationship was observed between the type of meniscectomy and IKDC score.

Evidence in the current literature confirms that few scoring systems have satisfactory levels of reliability and validity. Those systems which employ a high degree of patient involvement, such as the KOOS and IKDC, perform better as a patient-based assessment tool due to their greater reproducibility and reliability (Tilley 2010).
Correlations between subjective scoring systems and the degree of osteoarthritis in the tibiofemoral joint as observed by Ahlback demonstrated moderate but significant inverse correlation for KOOS-ADL and KOOS-Sport as well as with IKDC with Kendall’s tau.

This means that as the degree of radiographic osteoarthritis increases (scored by Ahlback, which has a linear correlation with KL) the score for sport, ADL & IKDC decreases i.e. the patients score worse with regards to IKDC, sporting activities, ADL as their radiographic osteoarthritis increases.

However, these patients did not show significant correlation with Symptoms, QOL or Pain (\(p>0.05\)) with regards to their radiographic score. This is not a new finding as previous studies have demonstrated that there is no strict correlation between the radiographic appearance of osteoarthritis with the subjective patient reported outcomes (Tapper FM 1969; Jorgensen, Sonne-Holm et al. 1987). The suggested explanations for the observed discrepancies were put down to reduced demands and expectations of operated knees with increasing age. It was also suggested that younger patients have higher expectations and demands of performance levels, as such they are more reluctant to accept a decrease in activity and score poorer (Hede, Larsen et al. 1992).

Having said this it is evident that IKDC, possibly due to its ability to be translated into a single score, seems to correlate better with radiographic as well as other outcomes in this study.

If the scores identified for KOOS as symptomatic by (Englund, Roos et al. 2003) is accepted then we note that all of our patient cohort can be classed as symptomatic.

Finally, the bilateral knee meniscectomy subgroup of patients performed worse in all parameters of KOOS & IKDC score as compared with the unilateral knee group.
5.8 Biomarkers:

Clinical diagnosis of osteoarthritis relies on symptoms in combination with radiographic changes; these however may signal the establishment of the disease rather than its onset. Osteoarthritis ensues due to the gradual destruction of the articular cartilage, as a consequence of balance disruption between matrix synthesis and degradation (Sandy 2003).

Cartilage consists of a relatively small number of chondrocytes and abundant extracellular matrix (ECM) components, whose major constituents are mainly type-II collagen fibrils and aggrecan, a large aggregating proteoglycan. Their proteolysis is regarded as a critical event in joint disease (Fosang, Last et al. 1996; Lohmander, Atley et al. 2003; Cibere, Zhang et al. 2009; Little, Barai et al. 2009). It has been postulated that aggrecanolysis may be a prerequisite to collagenolysis (Pratta, Yao et al. 2003) with the resultant molecular fragments used as biomarkers for the diagnosis, severity, progression or even regression of the disease (Kraus 2005; Bauer, Hunter et al. 2006; Rousseau and Delmas 2007).

Synovial Fluid, due to its proximity with the environment, may be in a position to better reflect the local pathologic processes in the studied joint. Observed variations in markers are likely to reflect changes in local knee joint pathology. Whereas plasma levels may represent global progression of the disease and not be joint specific. The GAG fragments observed in SF originate in a major part from the joint cartilage, while minor proportions may be released from menisci and ligaments (McAlindien, Dudhia et al. 2001; Verdonk, Forsyth et al. 2005).

Early matrix damage and acute injury can be associated with increase aggrecan proteolysis and increased proteoglycan fragments in the SF (Lohmander, Dahlberg et al.
1989; Dahlberg, Ryd et al. 1992; Lohmander, Lark et al. 1992; Lohmander, Hoerrner et al. 1993; Pratta, Yao et al. 2003). However, these levels (proteoglycan) were seen to decline with time (Lohmander, Dahlberg et al. 1989; Lohmander, Ionescu et al. 1999).

This finding was confirmed in a study with mean 18 years follow-up post meniscectomy, measuring aggrecanase-generated ARGS neopeptite. Where, although no statistical difference was observed between the meniscectomy group and the normal cohort’s levels, low levels of SF ARGS were found to be associated with an increased risk of joint space narrowing. Therefore an inverse correlation with disease progression as measured by joint space narrowing was noted (Larsson, Englund et al. 2010).

A significant difference between index and non-index knees was noted in this study (p=0.049) for GAG, with index knees having lower values. However when comparing between symptomatic and asymptomatic patients a wide spread of GAG values was noted. This may indicate that the value of this marker a predictive tool is rather poor; however the numbers in this study group are small. Similar observations, with regards to spread of values were made for MMP-3.

A negative correlation ($r=-0.56$) between Ahlback grading system and GAG for index knees was observed, a finding which would suggest that, although at its onset the disease may produce an increased level of aggrecan fragments in the SF, possibly coinciding with increased levels of chondrocyte mitotic activity (Rothwell and Bentley 1973; O'Driscoll 1998), with time this is unsustained and their production tails off.

This may suggest that the greater the interval between insult, in this case meniscectomy, and SF sampling for GAG the lower the concentration ($µg/ml$) observed. To confirm this theory long term studies such as this one should be conducted where the same markers are assessed through time from the same patients.
Previously it has been argued, for a number of years, that the collagen network does not crumble/degrade until much later following the original insult. It has now been suggested that the type II collagen network begins to degrade very soon after injury (Lohmander 2004).

In patients with osteoarthritis, high levels of MMPs have been linked with cartilage degradation. MMP levels in synovial fluid may be useful as an index of cartilage degradation in a single joint, whereas plasma levels may be useful in patients with generalised osteoarthritis (Naito, Takahashi et al. 1999). In this study, no significant difference was observed between the index and non index knee as per MMP-3 measured in SF.

More recent studies suggested that an association between serum MMP-3 and concurrent JSN exists, suggesting that the marker may be considered as a surrogate for radiography in clinical trials of osteoarthritis disease-modifying drugs (Lohmander, Brandt et al. 2005). Notably though no correlation between the levels of MMP-3 and symptoms such as knee pain was observed, a finding that was observed in this 40 y follow-up study.

Plasma levels of MMP-3 were found to be higher in patients with generalised osteoarthritis than in patients with single joint disease such as knee osteoarthritis (Naito, Takahashi et al. 1999; Takahashi, Naito et al. 2004). Whether the increased MMP-3 concentration was due to a greater total body burden of osteoarthritis, or to a more rapid turnover per cartilage mass unit, remains unclear. Such findings may suggest that the serum level of a systemic osteoarthritis marker, such as MMP-3, demonstrate greater variation according to the sum of joints affected and not just to the degree of single joint osteoarthritis destruction. Perhaps, offering a possible explanation towards the findings of this study, as no statistical difference or correlation between the plasma levels of
MMP-3 and the degree of osteoarthritis or indeed symptomatology as per PROMs was observed.
5.9 Strengths & Limitations:

The cohort utilised in this study was unique. An intervention of open total meniscectomy, which is considered a prelude to osteoarthritis, has taken place a mean 40 years previously in patients under the age of 19 years old, by the same surgeon following a specified surgical technique and rehabilitation pathway. Making this the longest review, post open total meniscectomy, worldwide.

A limitation, not unique to this type of study, was the lack of a “healthy” age, gender and race matched control group to compare outcomes with (Roos, Lauren et al. 1998), forcing the utilisation of the non-operated contralateral knee as control, something that has been utilised in most other studies on this subject (Allen, Denham et al. 1984; Abdon, Turner et al. 1990; Fauno and Nielsen 1992; Dahlberg, Roos et al. 1994; McNicholas, Rowley et al. 2000).

Other potential pitfalls mentioned in previous studies (Lohmander, Brandt et al. 2005) concerning the standardisation of radiographs for evaluation were taken into consideration when planning for the study and where avoided (see M&M).

In this cohort the observed reoperation of the index and contralateral non-index knee “muddied the waters” resulting in the exclusion of those with both knee meniscectomies from comparative statistical analysis. This observation is not a new phenomenon in long term follow-up studies. Reoperation rates of 22.8% in the same knee and 22% in the contralateral knee were observed at an average follow-up of 8.5 years (Fauno and Nielsen 1992), with 10% index and 17% non-index, in another study, with a follow-up of 15-22 years (Englund and Lohmander 2004) and 15% of index and non-index knee in yet another study with 16 year follow-up (Englund, Roos et al. 2003).
Long term follow-up studies invariably have a proportion of the cohort lost to follow-up. It would be wrong to criticise the 11.2% loss to follow-up of this study (16.9% if those traced but refused to be assessed is included) when other long term follow-up studies with shorter time intervals have demonstrated losses of 14% (Roos, Lauren *et al.* 1998) at 21 years and 30% at 15-22 years (Englund and Lohmander 2004).

Perhaps the small number of cohort subjects could have been improved if instead of the patients who underwent radiographic evaluation at the 30 year review all of the initially identified adolescent meniscectomy patients were sought for review. Although Abdon initially identified the cohort as 313, 104 were untraceable and 71 refused to take part. Out of the remaining cohort only 100 were finally reviewed at 17 years by Abdon and at the 30 years by McNicholas following a further 37 patient attrition only 53 went on to have bilateral knee radiographs. Unfortunately retrieving the original cohort proved impossible despite successful contact with the original and previous investigators.

However orthopaedic long term follow-ups of this magnitude are very rare indeed, as only two articles could be identified by pubmed search (Karlsson, Hasserius *et al.* 1993; Moller, Maly *et al.* 2007), making this an invaluable tool with regards to long term surgical outcomes.
CHAPTER 6
Conclusions
Previous studies do not seem to be in agreement with regards to which meniscectomy (medial or lateral) leads to worse outcomes. Several studies, including the previous 30 year follow-up concluded that lateral meniscectomy fairs worse (Johnson, Kettelkamp et al. 1974; Yocum, Kerlan et al. 1979; Abdon, Turner et al. 1990; McNicholas, Rowley et al. 2000), whilst others did not come to the same conclusion (Rangger, Klestil et al. 1995; Maletius and Messner 1996; Burks, Metcalf et al. 1997; Schimmer, Brulhart et al. 1998). In our study the site of meniscectomy did not seem to alter the grade of tibiofemoral osteoarthritis as measured by KL and Ahlback grading systems (no difference in the grade of osteoarthritis in the most affected compartment), the ROM or the PROMs (as per IKDC), a finding confirmed by a partial meniscectomy long-term study (Fabricant and Jokl 2007).

Total open (lateral) meniscectomy in children, age 3-14, demonstrated both radiographic as well as symptomatic osteoarthritis in over 50% at a mean follow-up of 20 years (Raber, Friederich et al. 1998). In this thesis osteoarthritis, $KL \geq 2$ or $Ahlback > 1$, was observed in 80% of meniscectomised knees demonstrating a RR $> 4$ between meniscectomised vs. non-meniscectomised knees in the tibiofemoral joint and RR $= 1.8$ as per patellofemoral joint.

One would rightly expect deterioration in function post arthroscopic partial and especially open total meniscectomy with time; but long term outcome studies for both these procedures seem to suggest that patient satisfaction and function do not necessarily deteriorate even in the presence of radiological progression of osteoarthritis (Fauno and Nielsen 1992; McNicholas, Rowley et al. 2000).

The explanation postulated for the discrepancy, between “functional” outcomes in younger, as opposed to older patients, was their diminishing functional demands. This
argument was used to partly explain the non-agreement between the extent of radiographic changes, clinical outcomes and PROMs as noted in the previous follow-up (McNicholas, Rowley et al. 2000).

In this thesis, the degree of observed osteoarthritis correlated with the cohort’s symptomatology as per IKDC score. With all of the patients in this follow-up cohort demonstrating symptomatology by both subjective scoring systems used when published work (Englund, Roos et al. 2003) on KOOS was taken into account. It also demonstrated correlations not only with tibiofemoral osteoarthritis but also with patellofemoral osteoarthritis, decreased ROM and malalignment (especially after medial meniscectomy).

There are other studies that have demonstrated the above findings either in isolation or in combination but never all together (Englund and Lohmander 2005).

Following previous studies, the relationship between meniscectomy and osteoarthritis has been unquestionable (Fairbank 1948; Jorgensen, Sonne-Holm et al. 1987), but both symptomatology and hard end points such as TKAs were surprisingly low and arguably unimpressive (Scheller, Sobau et al. 2001). At the time of writing no study could be identified in the literature stating an associated risk of any type of meniscectomy and arthroplasty. Here possibly for the first time such findings are demonstrated, with notable numbers of meniscectomised patients not only exhibiting substantial symptomatology but also loss of function to such an extend as to require a definitive intervention in the form of arthroplasty, years earlier than noted in their racial and geographical matched age groups.

Meniscectomy is a recognised risk factor for knee osteoarthritis. Previous studies demonstrated an association between the amount of removed tissue and the degree of ensued osteoarthritis (Rockborn and Gillquist 1996; Lee, Aadalen et al. 2006). It
follows that an attempt to evaluate biomarkers for osteoarthritis in this cohort was logical. Both synovial fluid and serum markers were utilised. An inverse association between the synovial fluid GAG and radiographic osteoarthritis was noted but not with serum MMP-3 marker. This, in my opinion, reiterates the view that “multisource feedback”, a combination of radiographic evaluation along with PROMs and possibly markers, is still required to evaluate the degree of disease progression or regression.

This thesis answered some of the burning questions posed by previous meniscectomy studies as well as reiterating the findings of others. However the quest for a simple, readily accessible osteoarthritis biomarker will continue. In theory once such a marker or a combination of markers is identified then articular tissue preservation, early identification of degenerative disease and monitoring will be possible. The fact that this has not materialised yet serves to underline the complexity of this “simple” monocellular tissue.
REFERENCES:


Kettelkamp, D. B. and E. Y. Chao (1972). "A method for quantitative analysis of medi-
al and lateral compression forces at the knee during standing." Clin Orthop Relat


Kettelkamp, D. B. and A. W. Jacobs (1972). "Tibiofemoral contact area--determination

gonarthrosis. Correlation with operation methods in 200 knees." Acta Orthop

MMP-3 and MMP-1, tissue inhibitor of metalloproteinases 1 (TIMP-1), and
MMP-1/TIMP-1 complex in rheumatic disease. Correlation with clinical activity
of rheumatoid arthritis versus other surrogate markers." J Rheumatol 26(2): 251-
258.


Kidd, B. L., J. J. Inglis, et al. (2003). "Inhibition of inflammation and hyperalgesia in
NK-1 receptor knock-out mice." Neuroreport 14(17): 2189-2192.

Kidd, B. L., A. Photiou, et al. (2004). "The role of inflammatory mediators on
nociception and pain in arthritis." Novartis Found Symp 260: 122-133; discus-
sion 133-128, 277-129.

Kim, K. W., J. W. Han, et al. (2011). "Association between comorbid depression and
osteoarthritic symptom severity in patients with knee osteoarthritis." J Bone

1069-1076.


metalloproteinases (MMP-1 to MMP-20) in the synovial membrane: different

ligament reconstruction using the quadriceps tendon substitution for chronic

641-646.


osteoarthritis: a comparison between two radiographic methods." Ann Rheum
Dis 55(12): 875-879.

Larsson, S., M. Englund, et al. (2010). "Association between synovial fluid levels of

fragments is a more sensitive marker of joint disease than glycosaminoglycan or


Appendix 1

Correlation matrix

<table>
<thead>
<tr>
<th>Correlation matrix</th>
<th>BMI</th>
<th>Ahlback</th>
<th>KL</th>
<th>Malalignment</th>
<th>RoM flexion</th>
<th>RoM Hyperextension</th>
<th>Index medial PFJ</th>
<th>Index lateral PFJ</th>
<th>IKDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>I</td>
<td>0.34</td>
<td>0.34</td>
<td>0.34</td>
<td>-0.20</td>
<td>0.04</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ahlback</td>
<td>0.34</td>
<td>I</td>
<td>0.85</td>
<td>0.43</td>
<td>-0.51</td>
<td>-0.45</td>
<td>-0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KL</td>
<td>0.34</td>
<td>0.85</td>
<td>I</td>
<td>0.49</td>
<td>-0.61</td>
<td>-0.40</td>
<td>-0.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malalignment</td>
<td>0.34</td>
<td>0.43</td>
<td>0.49</td>
<td>I</td>
<td>-0.44</td>
<td>-0.14</td>
<td>-0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RoM flexion</td>
<td>-0.20</td>
<td>-0.61</td>
<td>-0.44</td>
<td>I</td>
<td></td>
<td>0.47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RoM Hyperextension</td>
<td>0.04</td>
<td>-0.14</td>
<td>I</td>
<td>0.247</td>
<td>0.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index medial PFJ</td>
<td>-0.51</td>
<td>-0.40</td>
<td>I</td>
<td>0.26</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index lateral PFJ</td>
<td>-0.45</td>
<td>-0.34</td>
<td>0.47</td>
<td>0.247</td>
<td>I</td>
<td>0.43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IKDC</td>
<td>0.03</td>
<td>-0.43</td>
<td>-0.20</td>
<td>0.50</td>
<td>0.26</td>
<td>0.43</td>
<td>I</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Correlations Matrix for the unilateral knees highlighted
Appendix 2

How to construct the Skyline Weight Bearing View Device

The vertical beam is 100cm in length, this is in aid of standardisation with regards to magnification of the image i.e. keeping a set distance of beam source and cassette.

The horse shoe cut out should allow sufficient room for the tibia, space for the cassette and “force” approximately a 40° angle to the knee.

This simple device has demonstrated to be very consistent.
Appendix 3

PROMs (KOOS & IKDC 2000)

<table>
<thead>
<tr>
<th>KOOS KNEE SURVEY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Today’s date: <strong><strong>/</strong></strong>/_____ Date of birth: <strong><strong>/</strong></strong>/_____</td>
</tr>
<tr>
<td>INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to do your usual activities. Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.</td>
</tr>
<tr>
<td><strong>Symptoms</strong> These questions should be answered thinking of your knee symptoms during the last week.</td>
</tr>
<tr>
<td>S1. Do you have swelling in your knee?</td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?</td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>S3. Does your knee catch or hang up when moving?</td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>S4. Can you straighten your knee fully?</td>
</tr>
<tr>
<td>Always</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>S5. Can you bend your knee fully?</td>
</tr>
<tr>
<td>Always</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Stiffness</strong> The following questions concern the amount of joint stiffness you have experienced during the last week in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.</td>
</tr>
<tr>
<td>S6. How severe is your knee joint stiffness after first wakening in the morning?</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>S7. How severe is your knee stiffness after sitting, lying or resting later in the day?</td>
</tr>
</tbody>
</table>
P1. How often do you experience knee pain?

Never  Monthly  Weekly  Daily  Always

What amount of knee pain have you experienced the last week during the following activities?

P2. Twisting/pivoting on your knee

None  Mild  Moderate  Severe  Extreme

P3. Straightening knee fully

None  Mild  Moderate  Severe  Extreme

P4. Bending knee fully

None  Mild  Moderate  Severe  Extreme

P5. Walking on flat surface

None  Mild  Moderate  Severe  Extreme

P6. Going up or down stairs

None  Mild  Moderate  Severe  Extreme

P7. At night while in bed

None  Mild  Moderate  Severe  Extreme

P8. Sitting or lying

None  Mild  Moderate  Severe  Extreme

P9. Standing upright

None  Mild  Moderate  Severe  Extreme
**Function, daily living**

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A1. Descending stairs

None  Mild  Moderate  Severe  Extreme

A2. Ascending stairs

None  Mild  Moderate  Severe  Extreme

For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A3. Rising from sitting

None  Mild  Moderate  Severe  Extreme

A4. Standing

None  Mild  Moderate  Severe  Extreme

A5. Bending to floor/pick up an object

None  Mild  Moderate  Severe  Extreme

A6. Walking on flat surface

None  Mild  Moderate  Severe  Extreme

A7. Getting in/out of car

None  Mild  Moderate  Severe  Extreme

A8. Going shopping

None  Mild  Moderate  Severe  Extreme

A9. Putting on socks/stockings

None  Mild  Moderate  Severe  Extreme
A10. Rising from bed

<table>
<thead>
<tr>
<th>Degree of Difficulty</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A11. Taking off socks/stockings

<table>
<thead>
<tr>
<th>Degree of Difficulty</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A12. Lying in bed (turning over, maintaining knee position)

<table>
<thead>
<tr>
<th>Degree of Difficulty</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A13. Getting in/out of bath

<table>
<thead>
<tr>
<th>Degree of Difficulty</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A14. Sitting

<table>
<thead>
<tr>
<th>Degree of Difficulty</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A15. Getting on/off toilet

<table>
<thead>
<tr>
<th>Degree of Difficulty</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

<table>
<thead>
<tr>
<th>Degree of Difficulty</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A17. Light domestic duties (cooking, dusting, etc).

<table>
<thead>
<tr>
<th>Degree of Difficulty</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Function, sports and recreational activities**

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the last week due to your knee.

SP1. Squatting

<table>
<thead>
<tr>
<th>Degree of Difficulty</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SP2. Running
[Options: None, Mild, Moderate, Severe, Extreme]

SP3. Jumping
[Options: None, Mild, Moderate, Severe, Extreme]

SP4. Twisting/pivoting on your injured knee
[Options: None, Mild, Moderate, Severe, Extreme]

SP5. Kneeling
[Options: None, Mild, Moderate, Severe, Extreme]

Quality of Life

Q1. How often are you aware of your knee problem?
[Options: Never, Constantly, Monthly, Weekly, Daily]

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?
[Options: Not at all, Mildly, Moderately, Severely, Totally]

Q3. How much are you troubled with lack of confidence in your knee?
[Options: Not at all, Mildly, Moderately, Severely, Extremely]

Q4. In general, how much difficulty do you have with your knee?
[Options: None, Mild, Moderate, Severe, Extreme]

Thank you very much for completing all the questions in this questionnaire.
IKDC CURRENT HEALTH ASSESSMENT FORM *

Your Full Name
______________________________________________________

Your Date of Birth   _________/___________/___________
Day          Mon          Year

Today's Date   _____________/___________/___________
Day          Month         Year

1. In general, would you say your health is:
   □ Excellent  □ Very Good  □ Good  □ Fair  □ Poor

2. Compared to one year ago, how would you rate your health in general now?
   □ Much better now than 1 year ago  □ Somewhat better now than 1 year ago  □ About the same as 1 year ago
   □ Somewhat worse now than 1 year ago  □ Much worse now than 1 year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes, Limited A Lot</th>
<th>Yes, Limited A Little</th>
<th>No, Not Limited At All</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Vigorous activities, such as running, lifting heavy objects,</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>participating in strenuous sports</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Moderate activities, such as moving a table, pushing a</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>vacuum cleaner, bowling, or playing golf</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Lifting or carrying groceries</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>d. Climbing several flights of stairs</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>e. Climbing one flight of stairs</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>f. Bending, kneeling or stooping</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>g. Walking more than a mile</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>h. Walking several blocks</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>i. Walking one block</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>j. Bathing or dressing yourself</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

<table>
<thead>
<tr>
<th>Problem</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Cut down on the amount of time you spent on work or other activities</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>b. Accomplished less than you would like</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>c. Were limited in the kind of work or other activities</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>d. Had difficulty performing the work or other activities (for example,</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>it took extra effort)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

   a. Cut down on the amount of time you spent on work or other activities
   b. Accomplished less than you would like
   c. Didn’t do work or other activities as carefully as usual

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

   Not At All  Slightly  Moderately  Quite a Bit  Extremely

7. How much bodily pain have you had during the past 4 weeks?

   None  Very Mild  Mild  Moderate  Severe  Very Severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

   Not at All  A Little Bit  Moderately  Quite a Bit  Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks.
   For each question, please give the one answer that comes closest to the way you have been feeling.
   How much of the time during the past 4 weeks...

   Not difficult at all  Minimally difficult  Moderately Difficult  Extremely difficult  Unable to do

   a. Go up stairs
   b. Go down stairs
   c. Kneel on the front of your knee
   d. Squat
   e. Sit with your knee bent
   f. Rise from a chair
   g. Run straight ahead
   h. Jump and land on your involved leg
   i. Stop and start quickly
FUNCTION:
10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

FUNCTION PRIOR TO YOUR KNEE INJURY:

<table>
<thead>
<tr>
<th>Couldn’t perform Daily activities</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No limitation in Daily activities</th>
</tr>
</thead>
</table>

CURRENT FUNCTION OF YOUR KNEE:

<table>
<thead>
<tr>
<th>Cannot perform Daily activities</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>No limitation in Daily activities</th>
</tr>
</thead>
</table>
Scoring Instructions for the 2000 IKDC Subjective Knee Evaluation Form

Several methods of scoring the IKDC Subjective Knee Evaluation Form were investigated. The results indicated that summing the scores for each item performed as well as more sophisticated scoring methods.

The responses to each item are scored using an ordinal method such that a score of 0 is given to responses that represent the lowest level of function or highest level of symptoms. For example, item 1, which is related to the highest level of activity without significant pain is scored by assigning a score of 0 to the response "Unable to perform any of the above activities due to knee pain" and a score of 4 to the response "Very strenuous activities like jumping or pivoting as in basketball or soccer". For item 2, which is related to the frequency of pain over the past 4 weeks, the response "Constant" is assigned a score of 0 and "Never" is assigned a score of 10.

Note: Previous versions of the form had a minimum item score of 1 (for example, ranging from 1 to 11). In the most recent version, all items now have a minimum score of 0 (for example, 0 to 10). To score these prior versions, you would need to transform each item to the scaling for the current version.

The IKDC Subjective Knee Evaluation Form is scored by summing the scores for the individual items and then transforming the score to a scale that ranges from 0 to 100.

Note: The response to item 10a “Function Prior to Knee Injury” is not included in the overall score. To score the current form of the IKDC, simply add the score for each item (the small number by each item checked) and divide by the maximum possible score which is 87.

\[
\text{IKDC Score} = \left( \frac{\text{Sum of Items}}{\text{Maximum Possible Score}} \right) \times 100
\]

Thus, for the current version, if the sum of scores for the 18 items is 45 and the patient responded to all the items, the IKDC Score would be calculated as follows:

\[
\text{IKDC Score} = \frac{45}{87} \times 100 = 51.7
\]

The transformed score is interpreted as a measure of function such that higher scores represent higher levels of function and lower levels of symptoms. A score of 100 is interpreted to mean no limitation with activities of daily living or sports activities and the absence of symptoms.

The IKDC Subjective Knee Form score can be calculated when there are responses to at least 90% of the items (i.e. when responses have been provided for at least 16 items). In the original scoring instructions for the IKDC Subjective Knee Form, missing values are replaced by the average score of the items that have been answered.

However, this method could slightly over- or under-estimate the score depending on the maximum value of the missing item(s) (2, 5 or 11 points). Therefore, in the revised scoring procedure for the current version of a form with up to two missing values, the IKDC Subjective Knee Form Score is calculated as (sum of the completed items) / (maximum possible sum of the completed items) * 100. This method of scoring the IKDC Subjective Knee Form is more accurate than the original scoring method.

A scoring spreadsheet is also available at: www.sportsmed.org/research/index.asp This spreadsheet uses the current form scores and the revised scoring method for calculating scores with missing values.