OSTEOARTHRITIS AND ULTRA-DISTANCE MARATHON RUNNING

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The Degree of Master of Philosophy in Sports Medicine

by

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DEDICATION

This dissertation is dedicated to the following:

My late parents Ralph and Frances Leaver,

My late uncle, who was my mentor and close friend, Dr P.J.J. (Piet) Barnard M.B.,Ch.B.(UCT), F.R.C.P.(Edin), F.R.C.Path., M.D.(Pret.).

My old school Rondebosch Boys High School, and

All those who made this dissertation possible, the ultra-distance marathon runners

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Mr Terry Boxall for proof-reading this dissertation.

DECLARATION

This thesis is the original work of the author, both in its conception and execution. The results of the work and ideas of others mentioned in the text are fully referenced. Where data, collected with the help of others in collaborative studies, has been reproduced, this has been with their full permission and I have fully acknowledged the source of such data.

Portions of the work described in this thesis have already been published:

1. Leaver, R: The risk of osteoarthritis in the hips and knees of ultra-distance runners. CME, 1999; 17(2): 132-133.

An abstract entitled "Does distance running decrease the risk of osteoarthritis" and based on this dissertation has been accepted for submission to the 46th Annual Meeting of the American College of Sports Medicine to be held from 2 to 5 June 1999 in Seattle, Washington, U.S.A.

ABSTRACT

Osteoarthritis (OA) is the most common degenerative joint disease. The impact loading on the articular cartilage of the large weight bearing joints (hip, knee, and ankle joints) during distance running might be a potential precipitating factor in OA. The aim of this case-control study was to investigate the relationship between total accumulated running volume and OA in the weight-bearing joints. In this study, OA was defined as pain and/or stiffness and/or swelling in the weight-bearing and non-weight-bearing joints (wrists and fingers). The subjects for this study were selected from previous and current runners of the Two Oceans Ultra-marathon (56 km) in Cape Town (South Africa). The database (1356) consisted of all the runners who participated in this race between 1970 and 1983. From this data-base a random group of male runners (n =128) were divided into six 10-year age groups of runners (18 and 79 years). There was a random sample of 25 runners in five of these groups and three in the 70-79 year age group. Runners were age matched with a random sample of past pupils (n=204) of a school who were in their final year between 1923 and 1994. This was the control group. A questionnaire to diagnose OA was designed and validated with a sensitivity of 92% and a specificity of 71%. The questionnaire was posted to the runners and controls. Incentive prizes were offered to improve the response rate, which was 59%. Completed information was obtained from 76 ultra-distance marathon runners (response rate 59%) and 114 controls (response rate 56%). In the control group there was a group who participated in running. This group was combined with the runners who were then divided into three groups according to their total running volume which was calculated by the following formula; years involved in running x months/year running x 4x hours/week running. The subjects were thus divided into four groups: 1) controls (non-runners) (n=60), 2) low volume runners (n=43), 3) medium volume runners (n=43), and 4) high volume runners (n=44). Of these, 22 low volume runners, 7 medium runners, and 7 high volume runners stopped running. The prevalence (%) of OA in all groups was compared.

The mean age of the control group was significantly higher than the three running groups. The

mean height and weight of the medium volume group was significantly higher than the other groups. There was no significant difference in the BMI in each group. The frequency of professional and retired people was significantly higher in the control and each running group. A significantly greater percentage of controls had a history of admission to hospital. There were more controls on long-term medication, compared to runners.

A significant number of injuries to the weight-bearing joints (specifically the knee joint) occurred in all groups, due to other sports ($p = 0.007$). There were no significant differences in symptoms suggestive of OA in all groups when not adjusting for age and previous injuries. However, when assessing the odds ratio to determine the risk for OA in the weight-bearing joints, adjusting for age and previous injuries, the low volume group had the highest risk to develop OA (O.R. = 3.2, 95% C.I. = 1.0-10.3); the medium group had the second highest risk (O.R. = 1.7, 95% C.I. = 0.6-4.8) and the high volume group(O.R. = 1.1, 95% C.I. = 0.4-3.1) and control groups (O.R. = 1.0) had equally the lowest risk to develop OA. This study confirmed that distance running is unlikely to be a predisposing factor in the development of OA in the weight-bearing joints, even at high running volumes commonly seen in ultra-distance running.

LIST OF ABBREVIATIONS

A.C.R	American College of Rheumatology
AMP	Adenosine 5' monophosphate
ATPase	Adenosine tri-phosphotase
BMD	Bone mineral density
BMI	Body Mass Index
CT	Computerised axial topography
DNA	Deoxyribonucleic acid
ESR	Erythrocyte sedimentation rate
IL-1	Interleukin 1
IO	Iodoacetate
L1	first lumbar vertebra
LPS	Lipo-polysaccharide
MRI	Magnetic Resonance Imaging
OA	Osteoarthritis
PAI	Plasminogen activator inhibitor 1
PG	Proteoglycans
PGE2	Prostoglandin E2
SD	Standard deviation
TIMP	Tissue inhibitor mettalloproteinase

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CHAPTER 1

INTRODUCTION AND SCOPE OF THE THESIS

Osteoarthritis (OA) is the most common joint disorder in humans (Resnick et al 1981). It results in many hours of absenteeism from work and negatively affects the quality of life of many people. It is therefore not surprising that a vast amount of research has been conducted to determine the predisposing factors related to this condition. Yet, no single definition or classification referring to osteoarthritis is universally accepted.

Osteoarthritis is loosely recognised as a joint disease characterised by osteophyte formation, bone sclerosis, and cartilage degeneration. However, this is a description and not a definition of the condition (Resnick et al 1981). Until recently, osteoarthritis was regarded as part of the normal aging process. However, it is now thought that osteoarthritis is a pathologic process that is influenced by age (Resnick et al 1981).

Recently a "funnel" hypothesis for the development of osteoarthritis has been suggested (Hutton 1994). This hypothesis states that multiple insults feed into a final common pathway which might trigger the processes leading to osteoarthritis. The development of osteoarthritis is also characterised by attempts to repair damage to joint surfaces that might have resulted by these processes. Further damage then leads to joint failure. Osteoarthritis is a result of this failure.

Traditionally osteoarthritis was classified as primary (idiopathic) or secondary. Primary osteoarthritis described a condition where there was no obvious pre-existing factor leading to the development of OA. Secondary OA implied that there was a predisposing factor. It now appears that primary joint disease does not truly exist because, more often than not, an identifiable mechanical factor is present in OA (Resnick et al 1981).

An alternative classification for OA proposes that it may result from either an abnormal concentration of force across an articulation with normal articular cartilage matrix, or a normal concentration of force across an abnormal joint. Thus, OA is not a single disease entity but is a pathological process with specific tissue changes that arise in response to a variety of different initiating agents (Jeffery 2 1994).

One of the factors that may predispose to the development of OA is excessive, repetitive impact loading on the cartilage of weight-bearing joints during distance running or other sports. The resultant damaged cartilage might then predispose to the early development of OA. Recently, a study indicated that recreational or even marathon (42km) running did not appear to predispose to early development of OA (Lane 1995). However, the increased intensity, frequency and volume of mechanical loading on the weight-bearing joints during ultra-distance running (> 55 km) may predispose to the development of early OA. It is important to note that it is not the actual distance that is involved in ultra-marathon events, but the amount of training required in preparing for these events that could be a risk factor for OA.

Ultra-distance marathon running is a popular sport world-wide. In South Africa there are between eight to ten thousand participants in the Comrades and Two Oceans ultra-marathons held in Natal and Cape Town respectively each year.

In this thesis the relationship between ultra-distance running and the development of OA in the weight-bearing joints will be investigated. The hip, knee and ankle joints are diarthrodial joints, consisting of two articulating surfaces. Therefore, the first chapter will be devoted to a brief discussion on the structure and function of a diarthrodial joint.

The second chapter of this thesis is devoted to the condition of OA with emphasis on the difficulty in defining osteoarthritis. Relevant aspects of the pathology, pathogenesis and epidemiology of

osteoarthritis will also be discussed. Specifically, this chapter will include a review of the role of impact loading on joint surfaces.

In the fourth chapter animal studies and human epidemiological studies relating distance running with OA will be reviewed.

The fifth chapter describes the findings of a study that was conducted to relate the risk of ultra-distance running and the prevalence of OA.

CHAPTER 2

THE STRUCTURE AND FUNCTION OF A TYPICAL DIARTHRODIAL JOINT: A BRIEF REVIEW

2.1 Introduction

Normal joint function depends on three factors, 1) the geometry of the articular surfaces, 2) mechanical properties of extra-articular tissues (bone, cartilage, and other connective tissues), and 3) the integrity of the muscles, ligaments, and tendons around the joints (Hamerman et al 1970). The structure and function of a typical diarthrodial joint will now be discussed.

2.2 Articular Cartilage

2.2.1 Structure of Articular Cartilage

A feature of an ideal joint structure is that the surfaces should be congruent. However, this situation does not exist. For example, the incongruency that exists in the tibio-femoral joint is partially corrected by the meniscus (Bullough 1992). This allows the forces between the joint surfaces to be more evenly distributed. Maldistribution of forces between joint surfaces can

predispose to the development of OA.

Articular cartilage is a highly organised specialised connective tissue that is well adapted to withstand mechanical loads. To the naked eye articular cartilage appears smooth. Its colour varies with age, being bluish-white in children, white and glossy in young people, and ultimately changes to yellow-brown in the elderly. Articular cartilage varies in thickness depending on the mechanical load that is placed on it (Resnick et al 1981). Microscopic examination of the surface of articular cartilage in adults shows surface irregularities which are thought to be the result of wear and tear. Histological examination shows that articular cartilage consists of a cellular component (chondrocytes) which is embedded in a matrix of collagenous fibrils in a ground substance. Conventional staining shows that the matrix appears formless or "glassy", hence the term hyaline cartilage. The description of layers or zones within cartilage is based on the morphology and distribution of the chondrocytes within the matrix (Jeffery 1 1994) (Figure 2.1).

2.2.2 Biochemistry of Articular Cartilage

Water is the most abundant component in cartilage, comprising 80% of the volume of the superficial articular surface. The water content decreases with increasing depth and constitutes only 65% in the deeper layers of the cartilage. In its dry state, articular cartilage consists of 60% collagen (Type 2), 30% proteoglycans, and 10% glycoproteins, lipids, and chondrocytes (Mankin et al 1975). Relevant biochemical aspects of collagen and proteoglycans will now be discussed.

2.2.2.1 Biochemistry of Collagen

Collagen is the supporting tissue in the body. Collagen fibres consist of a triple helix of three polypeptide chains with repeated sequences of proline, hydroxyproline, and glycine. Type 2

collagen, which is seen in articular cartilage, has three identical chains in the triple helix. In Type 1 collagen, which is found in other tissues, the two chains differ in structure (Hamerman et al 1970; Jeffery 1 1994).

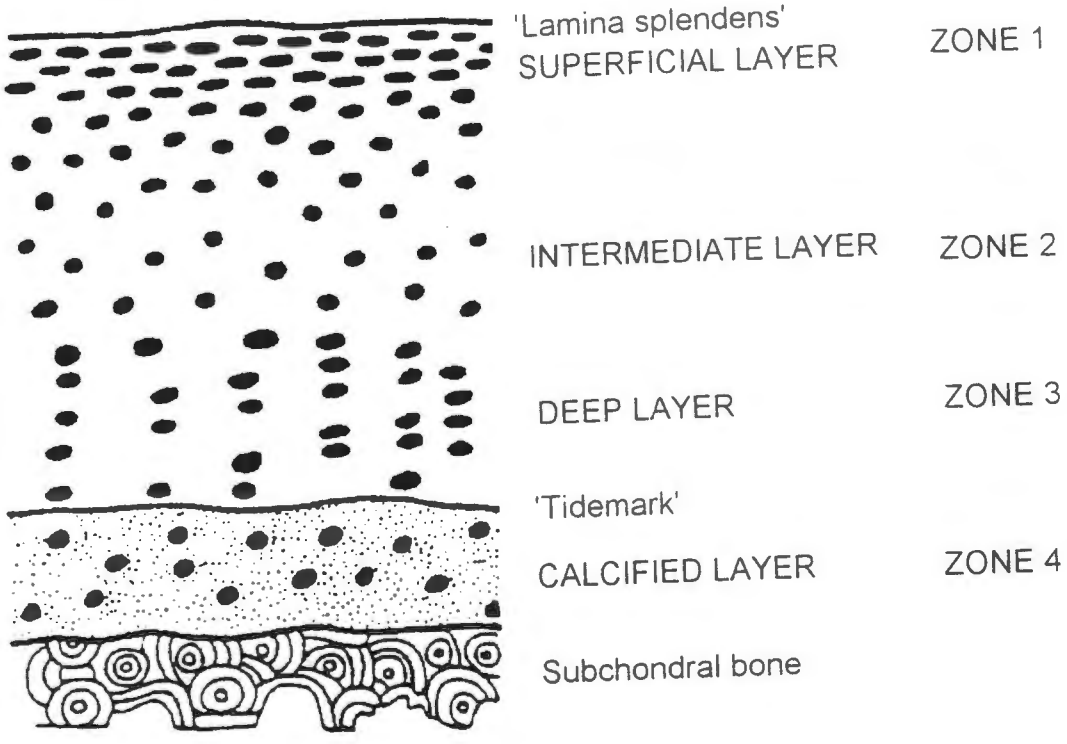


Fig. 2.1 A diagrammatic representation of the zonal structure of articular cartilage. (Jeffrey 1, 1994)

Alpha chains undergo coiling within the chondrocyte to form the triple helix. This precursor is known as procollagen. Procollagen is then transported extracellularly where cleavage of the terminal peptides occurs with the formation of rod-like structures called tropocollagen. Tropocollagen aggregates form the larger collagen fibres (Figure 2.2). Cross-linking of amino acids is vital to the maintenance of the strength of the collagen fibres, which are arranged parallel to the joint surface. This allows the joint surface to withstand the mechanical loads that are placed upon it. Although the majority of articular cartilage is of the Type 2 variety, there are

other collagens such as the Type 9 which contribute to the stabilisation of the fibre network by interacting electro-chemically between the collagen fibres at their intersections (Jeffery 1 1994; Hamerman 1989).

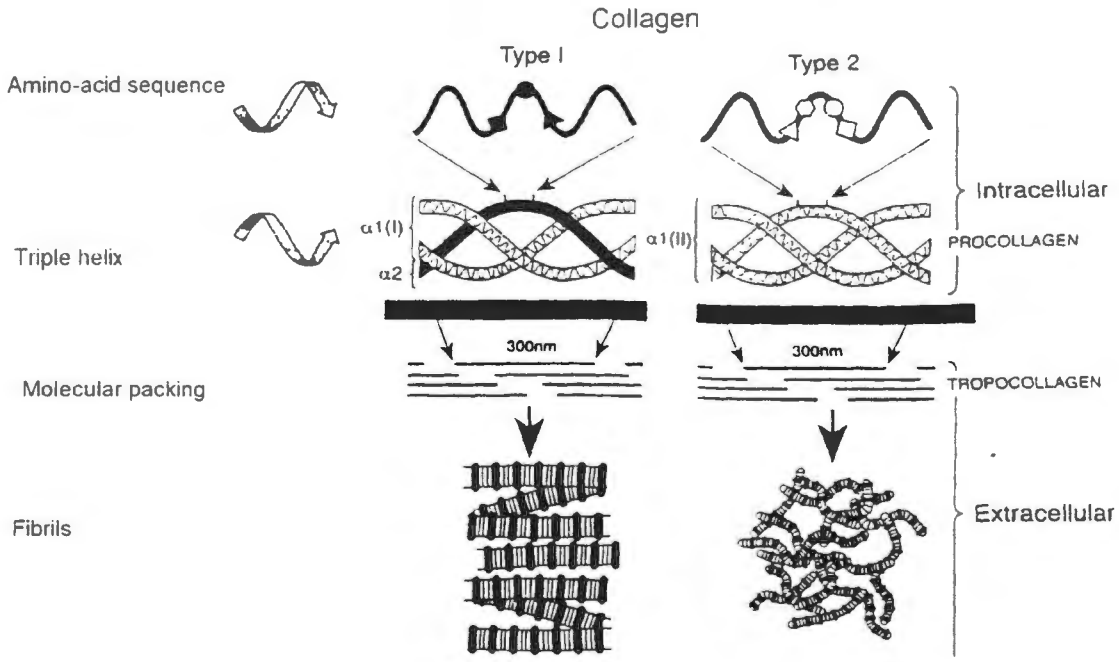


Fig. 2.2 A diagrammatic representation of the differing structure of Type I and Type II collagen (Jeffrey 1, 1994)

The description of the collagen organisation differs depending on the method of analysing it. Its ionizotropic properties are due to a three-dimensional manner in which the collagen is laid down (Hamerman 1989; Jeffery 1 1994). Collagen, therefore, provides the main strength of articular cartilage. However, the mechanical properties of articular cartilage are influenced by the interaction of collagen and proteoglycans. Relevant aspects of the

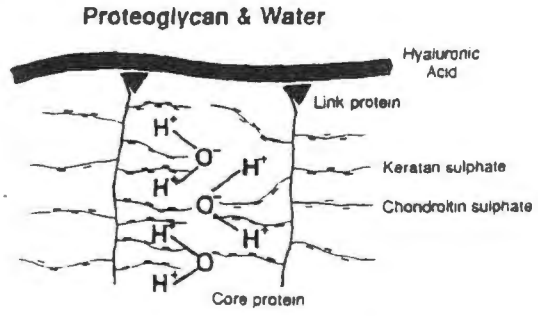
biochemistry of proteoglycans will now be discussed.

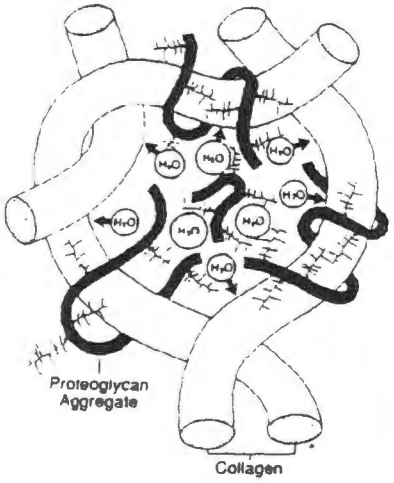
2.2.2.2 Biochemistry of Proteoglycans (PG)

Proteoglycans are large complex protein-polysaccharide molecules. The proteoglycan monomer is composed of keratan sulphate and chondroitin sulphate which are bound covalently to a protein core. They are synthesised in the endoplasmic reticulum of the chondrocyte and are modified by the Golgi apparatus. They are then packed in secretory vesicles and secreted into the cartilage matrix. The chondrocyte also synthesises and extrudes smaller linked proteins which stabilise the covalently joined proteins. One of these proteins is dermatin sulphate (Jeffery 1 1994; Greenwald et al 1978).

Proteoglycan has a "bottle brush" structural arrangement and the keratan sulphate and chondroitin sulphate are attached to, and radiate perpendicularly, from the protein core (Jeffrey 1 1994). In articular cartilage, most proteoglycan monomers are associated with hyaluronate in that they form large proteoglycan-hyaluronate aggregates. Proteoglycan has a gel-like structure. The sulphated sugars repel each other and thereby attract water. The collagen fibrils form a honeycomb-like structure compressing the proteoglycan molecules to half their potential size. The mechanical properties of articular cartilage depend on the relationship between collagen and proteoglycan. The proteoglycan-water gel gives the cartilage matrix a high osmotic pressure and low water permeability. If the matrix is compressed by mechanical loading, the amount of fluid loss is limited. As soon as the cartilage is unloaded, it returns to its original shape (Figure 2.3). The proteoglycan bound with water creates a tendency to swell which pre-stresses the collagen and gives cartilage its characteristic elasticity. Thus, water content of cartilage is essential to maintain the normal mechanical function of cartilage (Jeffery 1 1994; Mankin et al 1975), and it has implications on the ability of articular cartilage to withstand repetitive impact

loading such as during distance running.





(a) (b)

Fig. 2.3a **A diagrammatic representation of the Proteoglycan aggregate and its interaction with water.**

Fig. 2.3b **A diagrammatic representation of the meshwork of Type II collagen fibrils constraining and interacting with the proteoglycan aggregates. (Jeffrey 1, 1994).**

Other proteins are also present in cartilage. These are chondronectin, which is thought to be responsible for establishing a relationship between the collagen fibres and the chondrocytes and fibronectin, which has been found in increased concentrations in the cartilage of osteoarthritic joints (Hamerman 1989). The exact roles of these proteins in the development of OA have not been determined.

The structure and biochemical interaction of collagen and proteoglycans influences the biomechanical properties of articular cartilage. The biomechanical properties of articular

cartilage will now be reviewed

2.2.3 The Biomechanics of Articular Cartilage

Biomechanics is the science that investigates the effects of forces on the living oganism, especially forces applied to the skeleton by gravity and the system of muscles (World Book Dictionary 1981).

In articular cartilage there is a high water content and this distinguishes it from other connective tissues. The fluid of articular cartilage is extracellular, therefore its organisation and behaviour depends on its interaction with articular cartilage matrix molecules (Woo et al 1992). The ability of proteoglycans to interact with tissue fluid gives articular cartilage its unique mechanical properties (Hamerman et al 1970). Any alteration in the relationship between collagen and proteoglycans will influence the biomechanical properties of articular cartilage.

During running and walking, forces on the joint may vary from zero to several times body weight (Seirig et al 1975). It is thus important to consider how collagen fibres and proteoglycans in the articular cartilage interact, under high loading conditions, with water and interstitial fluid. Articular cartilage exhibits viscoelastic behaviour when it is compressed. Viscoelastic behaviour is the time dependent mechanical behaviour of tissues that is characterised by continuous changes in stress or strain (Woo et al 1992). Mechanical loading causes the flow of interstitial fluid and macromolecular motion in the tissue matrix. Frictional forces generated by the solid and fluid phases prevent the articular cartilage from deforming instantaneously (Hayes et al 1978).

Creep, which is the viscoelastic behaviour characterised by the increase in strain with time under a constant stress, and stress relaxation response, which is a viscoelastic behaviour represented

by a decrease in stress with time under a constant strain of articular cartilage in response to load application, is illustrated in Figure 2.4 (Woo et al 1992).

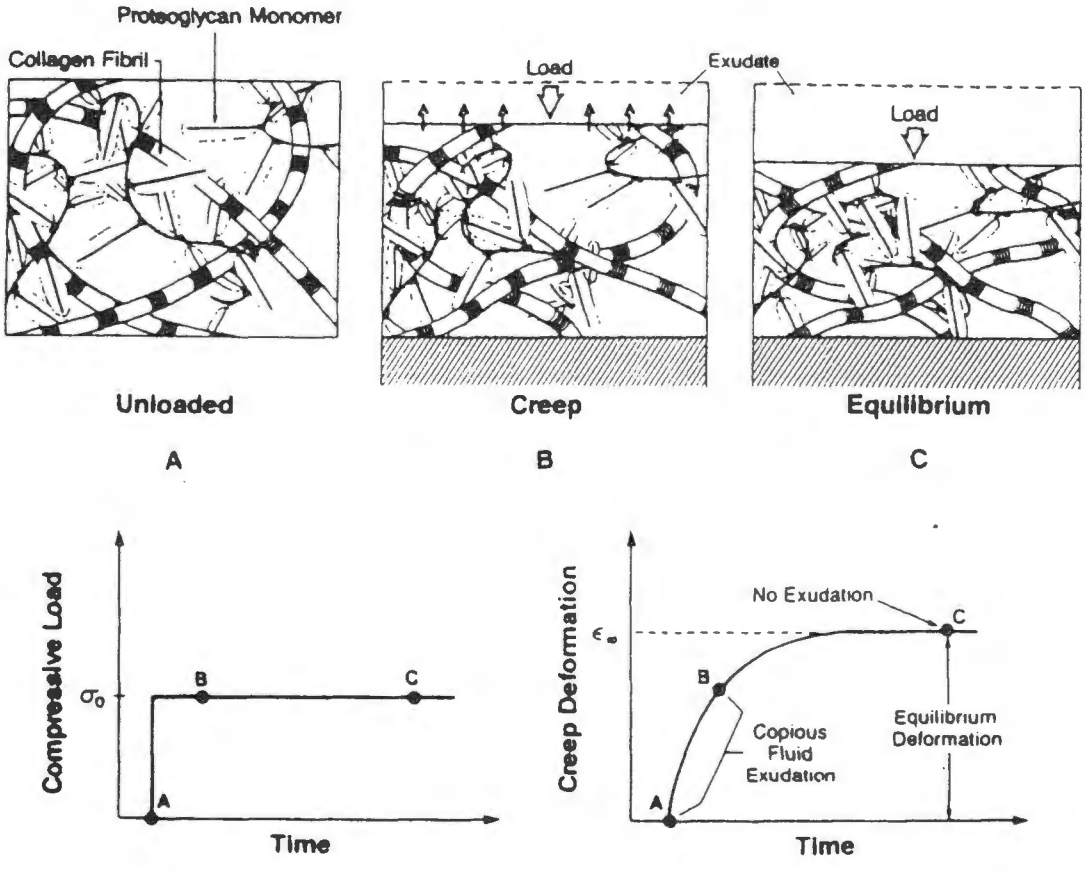


Fig. 2.4 The flow-dependent creep response of articular cartilage under uniaxial compression. (Mow et al 1988 in Woo et al 1992)

After load application, articular cartilage deforms as fluid is exuded. During creep the load that is applied is balanced by the compressive stress within the proteoglycan-collagen matrix and the frictional drag generated by the flow of interstitial fluid in articular cartilage (Mow et al 1984). Once unloaded, the tissue relaxes rapidly and fluid is redistributed within the matrix.

Therefore, stress-relaxation ceases when the compressive stress developed within the matrix reaches the stress generated by the compressive load. High stress levels are not maintained in

cartilage. This leads to rapid spreading of the contact area in the joint. The aggregate modulus of cartilage is the ability of the tissue to resist a compressive load and this relies on the proteoglycan structure and its interaction with collagen. If this interaction is disrupted, the normal properties of articular cartilage are changed (Woo et al 1992).

An important property of articular cartilage is that it has a low permeability to water. This allows nutrients to diffuse through the matrix and to influence the biomechanical properties of articular cartilage as noted above. The superficial zone of articular cartilage is more permeable to water than the deeper zone (Woo et al 1992). The proteoglycan-collagen combination provides most of the stiffness of cartilage (Muir et al 1970). The random organisation of collagen in the intermediate zone of cartilage contributes significantly to withstand shear forces placed on it. A shear force is the force causing two parts to slide on each other in opposite directions. Cartilage also resists tensile stresses that result from joint loading. This is because the superficial zone is stiffer than the intermediate and deep zones (Roth et al 1980).

Thus, the unique biochemical structure of articular cartilage directly influences its biomechanical properties which adapt according to the loads placed on the articular surface. The biomechanical properties are also influenced by the structure and function of the tide mark and the subchondral bone. These aspects will now be discussed.

2.3 The Tide Mark and Subchondral Bone

The calcification of articular cartilage is limited to a small area which is characterised by a wavy line referred to as the tide mark. This serves as an anchor for the collagen fibres of the non-calcified areas of the cartilage to the subchondral bone. This calcification front is a layer of osseous tissue of variable thickness beneath the cartilage. Although it is vascular, it acts as a barrier that blocks any blood supply or nutritional transports from bone to cartilage thus

preventing calcification of articular cartilage. It is stiffer than cancellous bone but slightly more compliant than cortical bone. The compliance of cancellous bone together with that of the subchondral plate is responsible for the optimal joint congruency when the joint is placed under mechanical high loads. The formation of subchondral bone thus contributes to the more even distribution of stresses on the joint surface (Woo et al 1992, Resnick et al 1981). Repetitive impact loading causes changes in the subchondral bone by decreasing its compliance and hence its deformability. These changes produce abnormal load distribution on the joint and are believed to be early initiating events in the development of osteoarthritis (Radin et al 1972). The thickness of articular cartilage is not static and is constantly remodelled according to the stresses placed on it. This regulation process is thought to occur at the tide mark area, where it has been shown that there is increased adenosine tri-phosphotase (ATPase) activity. Histochemical staining of the calcification front has shown calcium phosphate lipid complex, as well as alkaline phosphotase. In this region there is a marked change in the proteoglycan content of the matrix. Calcification is an active process which is dependent on chondrocyte activity. It is initiated in extra-cellular membrane-bound vesicles which are in close proximity to the chondrocytes. The calcification front is thus in a state of dynamic equilibrium balanced by factors promoting calcification (enzymes that promote deposition of calcium and phosphate) and inhibiting substances such as proteoglycans and nucleotide triphosphate (Woo et al 1992; Resnick et al 1981).

2.4 The Synovium, Synovial Fluid, and Joint Lubrication

The synovium is responsible for the formation of synovial fluid which serves to lubricate the joint space. An analysis of the structure and function of these entities is important so as to understand their role in the pathogenesis of OA.

2.4.1 The Synovium

The synovium is a delicate highly vascularised membrane that lines most intra-articular surfaces apart from the central cartilagenous tissue and intra-articular discs (Davies et al (eds) 1962; Resnick et al 1981). It is pink in colour and has villous projections which are vascular and vary in size. Adipose tissue accumulates in some villae thereby enhancing the cushioning effect in the joint space (Palmer 1967).

The synovial membrane has two layers; the intima and the sub-intima. The intima consists of two cell types. Type A cells resemble macrophages and appear to be important in phagocytic function, whereas Type B cells may be responsible for hyaluronic acid secretion. There is an elastic component in the synovium which prevents the formation of redundant synovial folds. The main function of the synovial membrane is to secrete synovial fluid in to the joint space thereby acting as a lubricant. Other functions and the site where they occur in the synovium are listed in Table 2.1. (Resnick et al 1981).

Table 2.1 THE FUNCTIONS AND SITE OF ACTIVITIES IN THE SYNOVIAL MEMBRANE.

FUNCTION	SITE
Mucin component of synovial fluid	?Type B cells
Dialysate component of synovial fluids	Capillaries
Phagocytosis	Type A cells
Drainage of wastes from cavity	Lymphatic Capillaries
Regulation of entry of nutrients	Entire synovial membrane

(Resnick et al 1981)

Synovial fluid is a clear, colourless, and highly viscid fluid. It is a dialysate of plasma to which hyaluronidate is added. There are small groups of nucleated white blood cells, macrophages, and free synovial cells in the synovial fluid. It acts as a lubricant to the joint and supplies nutrition to the adjacent articular cartilage and discs. Intermittent compression and release of cartilage forces fluid into the matrix to provide nutrition to articular cartilage. Repetitive loading in the form of exercise enhances this process, whereas joint immobility is thought to be associated with abnormal changes in cartilage (Jeffery 1 1994).

2.4.3 Joint Lubrication

Diarthrodial joint surfaces have a low coefficient of friction. However, the precise mechanism of joint lubrication is unclear. Three mechanisms of joint lubrication are proposed. These are fluid film lubrication, boundary lubrication, and mixed lubrication.

2.4.3.1 Fluid film lubrication

Fluid film lubrication occurs when there is a film of lubrication between two sliding surfaces. This film separates two articulating surfaces which then allows smooth movement between each joint surface. A modification of fluid film lubrication is elasto-hydrodynamic lubrication where the bearing surfaces are elastic so that the pressure of the wedge of lubricant deforms the surfaces and forms a more effective fluid film separating the two surfaces. A weeping hydrostatic lubricating mechanism occurs when fluid is squeezed from the articular cartilage on to the surface of the cartilage when load is applied. When the pressure is released fluid flows back into the cartilage (Jeffery 1 1994; McCutchen 1959) (Figure 2.5).

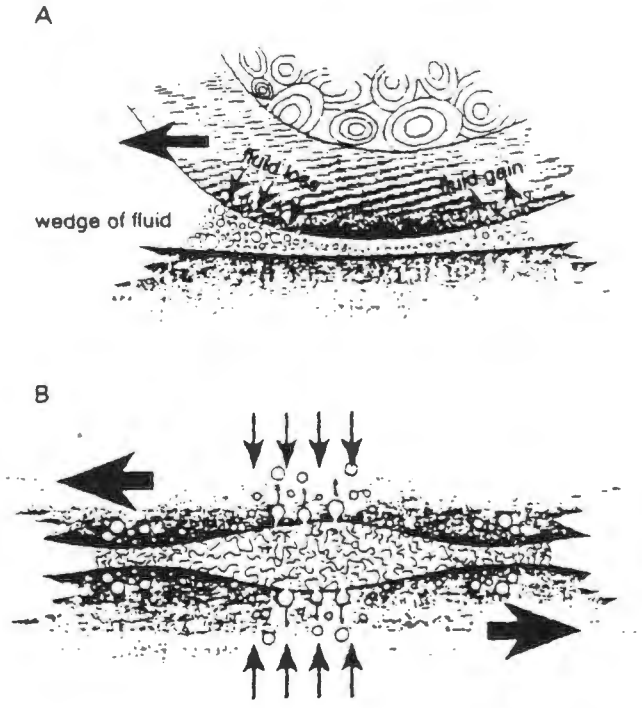


Fig. 2.5a A diagrammatic representation of weeping hydrostatic lubrication.

(Jeffrey 1 1994 adapted from Radin et al 1979 after McCutchen 1959)

Fig. 2.5b A diagrammatic representation of boosted lubrication.(Walker 1968)

2.4.3.2 Boundary lubrication

Boundary lubrication refers to a specific glycoprotein called "lubricant" which forms a monolayer of molecules that are absorbed on to each weight-bearing surface. These are able to carry loads and hence reduce friction. A modification of this process occurs when the solvent component of the synovial fluid is squeezed into articular cartilage when loaded. This leaves the hyaluronidate protein complex to act as a lubricant (Walker et al 1968; Jeffery 1 1994; Swann et al 1979).

2.4.3.3 Mixed lubrication

Mixed lubrication refers to the process whereby fluid film and boundary lubrication take place in the same joint under different conditions. Boundary lubrication occurs when the load is high and is of long duration, whereas fluid film lubrication occurs when the loads are relatively low and when the contact surfaces are moving at high relative speeds (Jeffery 1 1994; Armstrong et al 1982). In osteoarthritis, changes in the properties of articular cartilage diminish the effective lubricating ability of the joint resulting in further wear and tear of the articular cartilage (Woo et al 1992).

2.4.3.4. Cartilage nutrition

Articular cartilage is avascular and thus it can only obtain its' nutrition from the blood supply in the subchondral bone or by diffusion from synovial fluid. It appears that limited subchondral nutrition occurs in a few of the larger human joints such as the hip and knee as well as the first metatarsophalangeal joint (McKibbin and Maroudas 1979).

In the adult the bone-cartilage interface is impermeable to water and solutes whereas in the child the bone-cartilage interface is permeable to water and solutes (Maroudas et al 1968).

A study using dyes, resins and scanning electron microscopy suggested the existence of a canal

system in the meniscus (Bird 1989).They consist of a series of "receptive cisterns" surrounding or attached to the blood vessels in the peripheral area of the meniscus. These canals or cisterns vary in size and shape. The cells of the meniscus appear to be nourished by a transudate that leaves the blood stream through the vessels in the peripheral edge of the meniscus and perfuses through the canal system. The chondrocytes in the superficial zone of articular cartilage derive their nutrition from synovial fluid whereas those in the lower zones obtain nutrients from the subchondral bone through channels in the tide mark (Hamerman 1989).

2.5 Physiology of the normal joint

Maintenance of cartilage and joint shape is important in the prevention of osteoarthritis. Although joint shape is genetically determined, the maintenance of the functional shape is governed by Wolff's Law (Wolff 1986). Wolff's Law states that the bone density and organisation is determined by the forces placed on it. This means that the self-regulating bone modelling process occurs at articular ends of subchondral bone (Bullough 1992). Growth and modelling occur by endochondral ossification. This is characterised by calcified cartilage in the epiphyseal growth plate which is invaded by blood vessels from subchondral bone and is then replaced by tissue synthesised by osteoblasts. The thickness of calcified cartilage is maintained because, as the calcification front advances into the non-calcified cartilage, calcified cartilage is absorbed by subchondral bone. The number of blood vessels entering calcified articular cartilage and the rate of endochondral calcification changes with age. The number of blood vessels decline up to the age of 60 years and then increase again with older age. It is not clear how cartilage remains avascular. An explanation might be that there are protease and endothelial cell growth inhibitors which inhibit vascular proliferation (Hamerman 1989).

Growing cartilage receives its nutrition by diffusion through the subchondral bone, before the tide mark is formed. During adulthood, most nutrition of articular cartilage occurs via the synovial

fluid. It has been shown that if a joint is immobilised there is some impairment of nutrition. Regular loading in the form of exercise, however, enhances the nutrition of cartilage. This is because there is increased penetration of cartilage by solutes in synovial fluid (Maroudas et al 1968; Jeffery 1 1994).

The change in modelling activity of the joint could be as a result of a change of ligamentous laxity and joint stability caused by neuromuscular degeneration (Bullough 1992). Immobilisation of the joint results in decreased synthesis of glycosaminoglycans whereas repetitive loading as in exercise increases this. Anabolic activity in articular cartilage is determined by the load placed on it. Too little loading results in an alteration in the proteoglycan and an accumulation of water resulting in a softening of articular cartilage (chondromalacia). Excess load produces cell death and matrix degeneration. Cyclic adenosine monophosphate (AMP) and prostoglandin E2 (PGE2) have been implicated in the transduction of these mechanical stimuli (Hamerman et al 1970).

2.6 Summary

The diarthrodial joint is a highly specialised structure. The intra-articular entities (articular cartilage, synovium, synovial fluid, tide mark and subchondral bone) are adapted to withstand loads up to four times body weight (Rydell1966). It is important to have an understanding of their unique structure and function, particularly how they adapt to mechanical loading. The extra-articular structures (ligaments, joint capsule, and surrounding muscles) stabilise the joint and augment the ability of the intra-articular structures to withstand mechanical loading. Any alteration in the structure and function of these entities could lead to the development of OA.

CHAPTER 3

OSTEOARTHRITIS (OA): A REVIEW

3.1 Introduction and Definition

Osteoarthritis is considered to be a pathological process arising in response to a variety of different initiating entities. Thus, defining OA is difficult. However, the following definition of osteoarthritis was formulated at a workshop in 1994 (Huch et al 1997). *Osteoarthritis is a result of both mechanical and biological events that destabilise the normal coupling of degradation and synthesis of articular cartilage, chondrocytes, extracellular matrix and subchondral bone. Although they may be initiated by multiple factors including genetic, developmental, metabolic and traumatic, OA involves all of the tissues of the diathrodial joint. Ultimately, OA is manifested by morphologic, biochemical, molecular, and biomechanical changes of both cells and matrix which lead to a softening, fibrillation, ulceration, loss of articular cartilage, sclerosis, and eburnation of subchondral bone, osteophytes, and subchondral cysts. When clinically evident, OA is characterised by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of inflammation without systemic effects.*

It is thus considered to be a pathological entity with many aetiological factors resulting in a degenerative process. These are intrinsic entities within the joint and extrinsic factors relating to loading and stresses placed on the joint.

In this chapter the following will be reviewed: 1) the effects of mechanical loading on articular cartilage and relevant animal studies relating to this; 2) the aging joint; 3) the pathology of OA, and 4) the diagnosis of OA.

3.2 Mechanical Loading, Damage, Healing, and Disuse of Articular Cartilage

3.2.1 Mechanical Loading and Damage of Articular Cartilage

Distance running causes a significant amount of mechanical loading on the joint surface. It is thus important to have an understanding of mechanical loading on the articular surface as any damage that might ensue could be a predisposing factor in the development of OA. Articular cartilage is the weight-bearing surface in a mechanically loaded joint. However, it is too thin to function as a shock absorber; it simply transmits loads to the subchondral bone (Radin 1987). Articular cartilage will deteriorate if loads are excessive. This depends on the magnitude, type, and frequency of the load (Radin 1987).

Articular cartilage is damaged by a combination of shearing and impact loading, which do not have to be extreme if these are delivered at a very high rate (Radin 1987). When loading occurs at a high rate, there is loss and/or alteration of proteoglycans which decreases compliance of the cartilage and increases its permeability to water. Impact loading may also damage and disrupt the collagen fibril network and disturb its relationship with proteoglycans. The effects of loading on chondrocytes is poorly understood. However, in an *in vitro* study, chondrocytes responded to cyclical loads within the physiological range of between 5 and 15mPa, by increasing

proteoglycan synthesis. Proteoglycan synthesis was inhibited when a high intensity cyclic or static load was applied (Buckwalter et al 1994).

Areas of disintegration and erosion develop on articular cartilage in adulthood. This is known as fibrillation (Meachim 1969). The cartilage loses its smooth and glistening surface (Radin 1987). Vertical tears develop in the cartilage as a result of tensile stresses being applied to it (Figure 3.1).

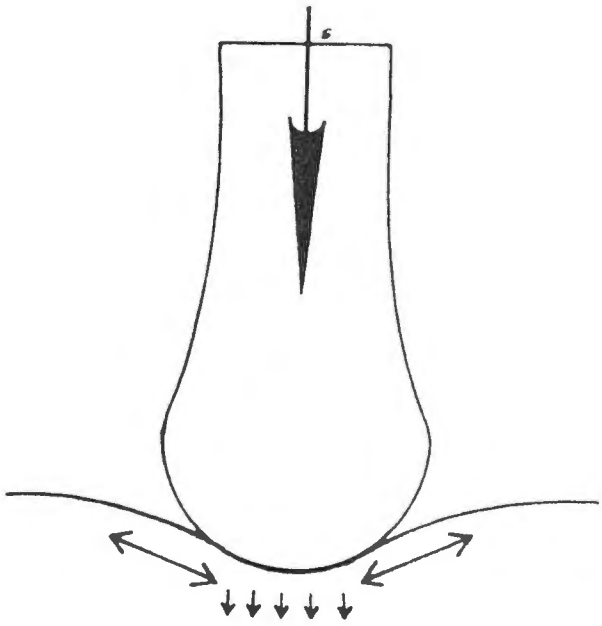


Figure 3.1 Diagrammatic representation of the tensile stresses developing on edges of zone of contact of articular cartilage under load.

(Radin 1987)

The degree of disintegration and erosion depends on the compliance of the underlying subchondral bone. Bone remodels itself according to the load placed on it. Subchondral bone becomes less compliant as the load placed on it increases. When subchondral bone stiffens, the difference in compliance between it and overlying cartilage increases. Thus, profound tensile

stresses are placed on the cartilage and this is thought to predispose to the formation of vertical cracks in the cartilage (Radin 1987). Fibrillation also occurs when the area of cartilage outside the zone of habitual contact becomes frail (Radin 1987). The fibrillation that results is reversed when that area of articular cartilage is loaded. Remodelling occurs throughout adult life and if this process is not balanced, destructive lesions occur in the cartilage (Radin 1987).

3.2.2 Disuse of Articular Cartilage

A joint that is immobilised undergoes certain deleterious effects. It has been demonstrated that there is a 41% decrease in proteoglycan content when a canine knee is immobilized for six weeks (Palmoski et al 1981). Prolonged joint disuse increases cartilage water content and decreases cartilage compliance and thickness. Articular cartilage is thus made more vulnerable to injury from impact loading. This is of relevance in the pathogenesis of osteoarthritis when, after a period of immobilisation, strenuous exercise is started before the articular cartilage has had time to adapt to impact loading (Buckwalter 1996).

3.2.3 Cartilage Healing

When articular cartilage is injured, there is a release of blood clotting factors and inflammatory mediators. The defect is initially filled with fibrous tissue and un-differentiated mesenchymal cells. Growth factors are responsible for differentiating these cells and chondrocytes which form collagen and proteoglycan. This occurs 6 to 8 weeks after the injury. The bony portion is usually repaired from immature bone, fibrous tissue, and hyaline cartilage matrix. The chondral portion, however, is not fully repaired to its original state (Buckwalter et al 1992). It is not known why repaired cartilage functions normally on some occasions, whereas in most cases there is evidence of fibrillation. It appears that the cells in the repair process produce different macro-

molecular substances and this might be influenced by mechanical factors (Campbell 1969; Radin 1987).

Articular cartilage that has been repaired differs from undamaged cartilage in that more Type I collagen fibres are laid down in repaired cartilage. These fibres are laid down in a haphazard way and there is a relatively greater proportion of proteoglycan which is more hydroscopic and thus swells more than normal cartilage. In repaired cartilage, the structural relationship between proteoglycan and collagen is also disrupted. A matrix that is more permeable to water cannot withstand the loading forces placed on it and this may lead to increased damage, resulting in macro-molecular fractures of articular cartilage (Campbell 1969).

3.2.3 The effects of Mechanical Loading on Articular Cartilage in Animals

3.2.3.1 Introduction

Animal models offer distinct advantages in documenting the pathogenesis of a disease process because a number of factors can be controlled. In researching the causes of OA, animals can act as their own controls and this is a distinct advantage. A temporal sequence of biochemical or biomechanical changes in the joints can also be documented with less difficulty. However, the choice of animal models is crucial. Larger animals are useful for Magnetic Resonance Imaging (MRI) analyses of joints, whereas smaller animals are useful where biochemical and biomechanical factors are analysed (Pritzker 1994). A brief review of some relevant animal studies will now be presented.

3.2.3.2 Animal Studies

The structure and the nature of the collagen fibres in articular cartilage has been investigated as early as the beginning of this century. One of the first scientific studies of this kind investigated the effects of increased load bearing on the articular cartilage (Retterer 1908). In this study, guinea-pig forelimbs that had been loaded were amputated, and were found to have an increased thickness of articular cartilage compared with the limbs that had not been loaded. Furthermore, the superficial cells (chondrocytes) altered their shape and the subchondral bone was thickened in the loaded forelimbs.

In 1941, a study using a motor driven treadmill to exercise guinea pigs was carried out (Saaf 1941). The running distance was 1000 metres/day for 20-100 days. The articular cartilage of the loaded femoral heads revealed more and enlarged chondrocytes than controls. The intercellular matrix in the running group was also thickened compared to the control group. Lanier (1946) subjected mice from the age of 6 weeks for 12.5 months of forced exercise (not defined) and concluded that the control group who did not exercise had more lesions (not defined) on the articular cartilage than the mice that were exercised. Krause (1969) was the first investigator to document the potential negative effects of exercise on cartilage. In his study, mice performed strenuous running on a treadmill at approximately 6000-12000 metres a day with a total running distance of 450-800km in 63 days. In the running group, acid-mucopolysaccharide stainability was reduced in the articular cartilage. In this study, excessive mechanical stress was postulated as a risk factor for the development of OA.

Radin (1987), using sheep, compared exercising sheep on hard surfaces and a control group exercising on softer surfaces. Running on a hard surface induced degenerative changes in articular cartilage and subchondral bone. In this study, the pathological changes of osteoarthritis, including fibrillation which is considered to be microfractures of cartilage, were simulated. It was

concluded that rapid loading presents the stress relaxation curve which occurs when water in cartilage flows away from high pressure areas. This results in transmission of greater forces onto the bone with subsequent stiffening of the subchondral bone leading to osseous microfractures.

In 1978 Radin investigated repetitive intermittent loading on knee joints of rabbits (Radin et al 1978). The results were consistent with what had been observed previously, namely the early changes in articular cartilage in response to repetitive impact loading involved an increase in cellular metabolism. Specifically there was 1) an increase in glycosamine sulphate, 2) an increase in the number of chondrocytes, 3) an increase in thymidene uptake, 4) a decrease in hexosamine content, and 5) hydroxyproline content remained constant. Cellular proliferation occurred which preceded an increase of metabolic activity of the chondrocytes. There was an increase in stiffness of subchondral bone and because bone stiffness under these circumstances results from healing of microfractures, it is possible that microfracturing of the subchondral bone preceded the metabolic changes in the articular cartilage. When the animals were not exposed to intermittent loading for four additional weeks after an interrupted series of intermittent loading periods, there was continued low content of hexosamine which possibly might indicate that degradative enzymes were released.

3.2.3.3 Conclusion

Although many of the animal experiments have demonstrated structural, histochemical and biomechanical changes when articular cartilage is loaded, it is difficult to extrapolate these studies to the human model. Firstly, humans are bipedal and animals quadripedal. Secondly, there are certain variations in how the articular cartilage of different species respond to impact loading. Thirdly, a major flaw in experimental design is that the exercise intensity, duration, and frequency, was not always standardised (Pritzker 1994).

The experimental evidence from animal studies thus indicates that if the joints are exposed to moderate loading such as in running, there is no accelerated damage to articular cartilage. Therefore moderate loading does not lead to the development of OA. However, excessive high impact loading might predispose to the development of OA. In this section, one of the important extrinsic factors viz. mechanical loading, which might under certain circumstances be one of the predisposing causes in OA, was discussed. In the next section, one of the intrinsic factors which might predispose to OA will be reviewed. This is the effect of the aging process on articular cartilage.

3.3 The Aging Joint

3.3.1 Introduction

The aging process in joints is not uniform and various factors can modify it. Two important questions are (1) whether OA is an inevitable consequence of aging, and (2) whether exercise (in particular, regular repetitive loading) plays a role in accelerating aging in joints.

Epidemiological studies indicate an increased frequency of OA with age (Figure 3.2). These studies also indicate that OA appears earlier on in age in the hip and knee joints compared with other non-weight-bearing joints. It has also been shown that joint shape changes with age. Genetic factors probably determine the original shape of a joint, and this original shape becomes modified according to the mechanical stresses placed on it (Peyron et al 1992). In articular cartilage, structural changes related to age occur mostly in the superficial layer. Electron-microscopy has demonstrated that aging is associated with uncovering of superficial collagen fibres and fibrils floating in the joint cavity (Longmore et al 1975). Magnetic resonance imaging (MRI) studies showed a thinning of articular cartilage with age (Karvonen et al 1994).

It is well documented that joint remodelling occurs throughout life. Destructive lesions develop in cartilage as a result of an imbalance in the remodelling process because of an inability of the articular surfaces to remain congruent (Meachim 1969). Therefore, the joint surfaces do not maintain their same shape and size. This is probably a result of the decreased shock-absorbing properties of the surrounding muscles and ligaments with age.

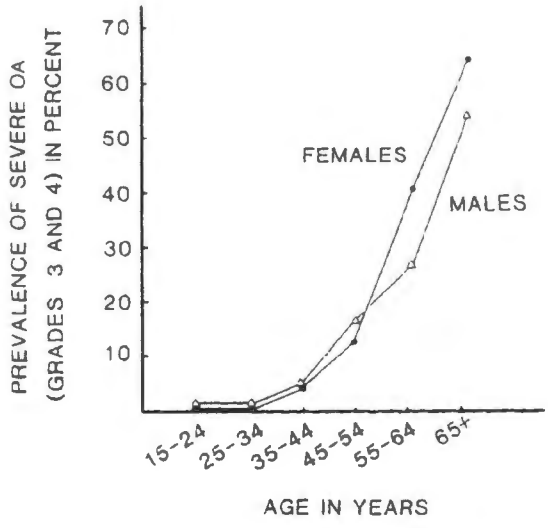


Figure 3.2 The prevalence of OA in at least one joint in males and females from two English population samples. (Steinbrocker's functional grade 3 (limited capacities : can only partly perform usual occupations and self-caring tasks) and 4 (chair or bedridden)

(Peyron et al 1992, using data from Lawrence (1977))

3.3.2 Biochemical and Biomechanical Changes with Age

The main biochemical changes in articular cartilage with age are depicted in Table 3.1 (Hamerman 1989). As articular cartilage ages, it changes colour from bluish to yellow-brown. In

adults, the water content of articular cartilage decreases from 75% to 70% over a period of thirty years and this is particularly evident in the deeper layers of articular cartilage (Venn 1978). The glycosaminoglycan content increases due to an increase in keratan sulphate. Hyaluronic acid content is also increased and the length of the proteoglycan monomer is decreased (Heinegaard et al 1977). Type 2 collagen content does not change with age although it becomes less compliant. This might be due the changes in proteoglycans that occur with aging (Karvonen et al 1994).

Table 3.1 COMPARISON OF CHANGES IN ARTICULAR CARTILAGE IN AGING AND OSTEOARTHRITIS

Criterion	Aging	Osteoarthritis
Water content	Decreased	Increased
Glycosaminoglycans		
Chondroitin sulfate	Normal or slightly less	Decreased
Chondroitin sulfate 4/6 ratio*	Decreased	Increased
Keratan sulfate	Increased	Decreased
Hyaluronate	Increased	Decreased
Proteoglycans		
Aggregation	Normal	Diminished
Monomer size	Decreased	Decreased
Link Protein	Fragmented	Normal
Proteases	"Normal"	Increased

* The ratio of chondroitin sulfate on the fourth to chondroitin sulfate on the sixth carbon atom.

(Hamerman 1989)

Biochemical changes in articular cartilage, caused by aging, are largely a result of the inability of the chondrocytes to replicate deoxyribonucleic acid (DNA). There is also decreased cellularity in

articular cartilage with aging. Furthermore, altered joint congruity changes compressive loading of the cartilage and this alters the ionic environment of chondrocytes. Proteoglycan synthesis is then inhibited (Karvonen et al 1994).

Biomechanical behaviour of articular cartilage under weak compressive and tensile forces does not vary with age. However, in response to high magnitude forces, the tensile stiffness decreases with age (Kempson 1975). The compression strain and low stress-tensile properties are related to proteoglycan concentration, whereas high stress-tensile properties are related to the collagen content (Peyron et al 1992). Increased compliance of articular cartilage with age results in an increased contact area of articular surfaces under load (Peyron et al 1992). There is increased stiffness in the ligaments due to increased cross-linking of the collagen fibres. This is thought to be due to a maturational process which is normal. Aging is also associated with altered locomotor control of the opposing muscle groups which surround the major joints (Karvonen et al 1994). These muscles act as shock-absorbers that protect the joints from every day trauma. A decreased function of the peripheral nervous system with age might impair the shock absorbing function of these muscles.

Although decreased compliance of subchondral bone, together with increased impact loading, are important factors in the aging process, there are also chemical factors contributing to this process. As previously mentioned, proteoglycans may play a pivotal role in the maintenance of cartilage. Type II collagen does not alter with age but its structure might be influenced by proteoglycans (Karvonen et al 1994). Abnormal chemical mediators from proteolytic degradation and from free radical degradation are released when articular cartilage is loaded. It is thought that these factors play a role in the degeneration process of articular cartilage.

It is difficult to relate the aging process in articular cartilage to the development of OA as the biochemical changes that occur with aging and OA differ. Also, although the biomechanical

properties of articular cartilage alter with age, it is uncertain whether symptomatic OA will develop in the aging joint. However, it can be hypothesised that the superficial fraying that occurs in aging cartilage might inhibit chondrocyte function. This, together with the decreased water content that occurs in aging cartilage, could precipitate the development of vertical cracks in articular cartilage. The ensuing release of inflammatory mediators and the altered load distribution on the articular surfaces could precipitate the development of OA (Buckwalter et al 1993). The influence of impact loading in the form of exercise on the aging process needs to be discussed.

3.3.3 Exercise and aging: animal models

There are only a few animal studies that have documented the relationship between exercise and the aging of joints. It is not clear whether exercise retards or enhances the aging process in joints. One study in which canine articular cartilage was loaded, demonstrated that the load-bearing joints showed a 19.4% increase in hexosamine and a 50% increase in glycosamine (Kostensky et al 1972). These substances are markers for chondroitin sulphate and keratan sulphate which are part of the collagen in articular cartilage. In this study, it was concluded that load bearing led to an accumulation of keratan sulphate and thus accelerated the aging process.

In another study, the influence of exercise on aging in rat joints was examined. Animals between the ages of 6 and 24 months were exercised at moderate intensity (75% of heart rate maximum) on a level treadmill 5 days a week, for periods of 6-12 months (Walker 1986). Histochemical methods were used to examine the changes in articular cartilage in the exercised group and compared to a control (sedentary) group of rats. The results showed that more structural defects were found in articular cartilage of the exercised group. However, there was no significant difference in the incidence of defects in the groups that were exercised for 6 months compared with 12 months. These defects were located in the uncalcified cartilage and were superficial to

the tide mark. Control animals of all ages had similar defects but these defects were fewer and smaller in size than those in the exercise group. The findings of this study were in contrast to another study where exercise contributed to the frequency but not the severity of the defects that occured in the uncalcified cartilage (Williams et al 1982).

Osteophyte formation is thought to be associated with aging. In a study investigating the effects of exercise on osteophyte formation, guinea-pigs were divided into four groups. Group 1 had the left knee injected with sodium iodoacetate (IO) and were sacrificed after one week. Group 2 had the left knee injected and were then exercised before being sacrificed after one and three weeks only. Group 3 were exercised only, and Group 4 were sacrificed at the beginning of the study. The exercise consisted of running on a treadmill for 15-20 minutes covering a distance of 750-1000 feet. In the group whose knees were injected with IO and exercised, the articular cartilage that was damaged showed reduced chondrocyte depletion, and reduced fibrillation compared with the non-exercised group. However, there was accellerated osteophyte formation in the group that was exercised. The conclusion was that osteophyte formation might not be a consequence of aging alone and that exercise might influence osteophyte formation particularly in previously damaged articular cartilage (Williams et.al 1984).

It is difficult to extrapolate the findings derived from animal studies to humans. However, the results from these animal studies appear to indicate that exercise may influence the aging process in articular cartilage by increasing the frequency of defects in uncalcified cartilage. It is not clear whether this predisposes to the development of OA and this still needs to be determined. Non-invasive methods are needed to examine the interaction between exercise and aging in human joints. Longitudinal studies using Magnetic Resonance Imaging are a possibility.

3.3.4 Summary and Conclusions

It is not clear whether the changes that occur in the musculo-skeletal system with age predispose to the development of OA. Any reduction in synthetic activity of chondrocytes can compromise the structure of cartilage. A reduction in synthetic activity of chondrocytes may occur with aging and thereby cause thinning of the cartilage, resulting in a loss of congruency of the joint. The loss of congruency might alter the environment of the chondrocytes which, in turn, might inhibit the synthesis of proteoglycans. This destabilisation of joint mechanics then might lead to osteoarthritis.

Osteoarthritis is a process characterised by a decrease in proteoglycan concentration in articular cartilage. This results in more water absorption. There is then increased load on the subchondral bone (Cooper et al 1994). Cellular and biochemical factors together with biomechanical factors could result in the aging joint which may predispose to the development of osteoarthritis.

3.4 Pathology Of Osteoarthritis

3.4.1 Definitions and Introduction

Pathology is the branch of medicine concerned with the cause, origin, and nature of disease; it is the explanation of disease (Collins Pocket Dictionary 1989: Bullough 1992).

The function of a joint depends on the shape of the joint surfaces, the mechanical properties of the bone, cartilage, and supportive tissues, together with the integrity of the peri-articular ligaments and the normal function of the neuromuscular systems. Disturbance in any one of

these factors could predispose to the development of osteoarthritis. Some aspects of the pathology of OA will now be discussed.

3.4.2 Anatomical Pathology of Osteoarthritis

3.4.2.1 Gross Pathology

Osteoarthritis is a non-inflammatory disease characterised by the formation of new bone in the form of osteophytes and loss of bone and cartilage in some regions of the joint where there is mechanical overloading. Osteophytes are formed by endochondral ossification which occurs as a result of vascular penetration into existing cartilage or cartilagenous metaplasia at the joint margins, ultimately resulting in a larger joint by increasing the surface area of the joint surface and thus spreading the mechanical load over a larger surface area (Solomon 1976). Foci of metaplasia also occur at the capsular and ligamentous insertions (Bullough 1992). Tissue injury invariably results in an inflammatory response followed by a repair process. This is evident at the bone-cartilage interface where "tongues" of subchondral bone extend into the calcified cartilage (Bullough 1992).

In osteoarthritis, there are three patterns of macroscopic alterations involving the cartilage surface. These are fibrillation, erosion, and cracking. These patterns cause a loss of the glistening surface of articular cartilage, which becomes yellow, granular, and dull. Fibrillation is described as a replacement of the smooth appearance of cartilage by a velvety surface. It occurs in all joints and has been described as a consequence of underloading the joint (Bullough 1992). Erosion is a characteristic process of the degenerative joint. Cracking of the cartilage extends vertically and horizontally. This process can eventually denude the joint surface in certain areas, thereby exposing the underlying bone (eburnation).

3.4.2.2 Histopatholgy

The effect of injury to the articular surface is reflected in the histologic response of both the matrix and the cells. There is focal cellular proliferation of chondrocytes resulting in clumping which occurs adjacent to the fissures.

Denuded bone has small pits from which small nodules of fibro-cartilage protrude. When the cartilage has been eroded, there is a proliferation of osteoblasts to form new bone. This occurs as a result of microfractures which develop because of abnormal loading in that area. An additional result of localised loading is that localised pressure necrosis can occur (Bullough 1992). This results in the formation of subchondral bone. Cysts can regress if cartilage regenerates over the surface. Bodies of cartilage can become fragmented. These can increase in size, particularly if they re-attach to the synovium (Bullough 1992). Microscopic tears occur in ligaments around arthritic joints. It is not known whether these are a consequence or a cause of osteoarthritis.

Mechanical loading results in the breakdown of cartilage and the fragments are removed by phagocytic cells of the synovium. An inflammatory response in the synovium follows. The synovium becomes hyperplastic and eventually extends into the synovial cavity to form a pannus. This response is not nearly as marked as in rheumatoid arthritis which is a destructive process. As the nutritional functions of the synovium are compromised, the arthritic process is perpetuated (Bullough 1992).

3.4.3 The Biochemical Changes In the Cartilage iIn Osteoarthritis

The main biochemical changes in articular cartilage in response to OA are: 1) a loss of proteoglycan, 2) increased water content, and 3) a significant change in the arrangement and

size of the collagen fibres (Mankin et al 1975). The increase in water content in the cartilage in osteoarthritis is due to a reduction in the amount of proteoglycan in cartilage. Proteoglycan is hydrophylic, and a reduction in proteoglycan would result in a reduction of water content. However, in the early stages of OA, cartilage swells because of the increased water. The explanations for this are: 1) that the remaining proteoglycan uncoils itself thereby exposing more hydro-negative charges on itself, or 2) the collagen itself is more likely to attract water (Mankin et al 1992).

There are inter-polypeptide cross-links that join adjacent fibrils within the collagen fibres. Collagen may fail by breakage of cross-links between adjacent fibrils or separation of fibres where they cross each other in the network. Proteoglycan aggregates are disrupted at the binding site with the hyaluronate molecule and along the core protein. If these cross-links are destabilised when, for example, articular cartilage is traumatised, collagen weakens and fragments (Figure 3.3.). This allows water to enter its intermolecular space resulting in a swelling and softening of articular cartilage (Jeffery 2 1994).

Changes in proteoglycan structure are also associated with aging but it is not clear whether these changes ultimately lead to the development of OA. In the early stages of OA, there appears to be increased activity of the chondrocytes which synthesise proteoglycan. However, the proteoglycan that is synthesised appears to be immature because there is a decreased amount of keratan sulphate and an increased amount of chondroitin sulphate (Muir et al 1970). There is the possibility that there is an asymmetric degradation of proteoglycan by keratonase (Erhlich 1975). Changes in proteoglycan structure could result in altered electro-chemical binding to collagen. This contributes to a softened and more fragile articular cartilage.

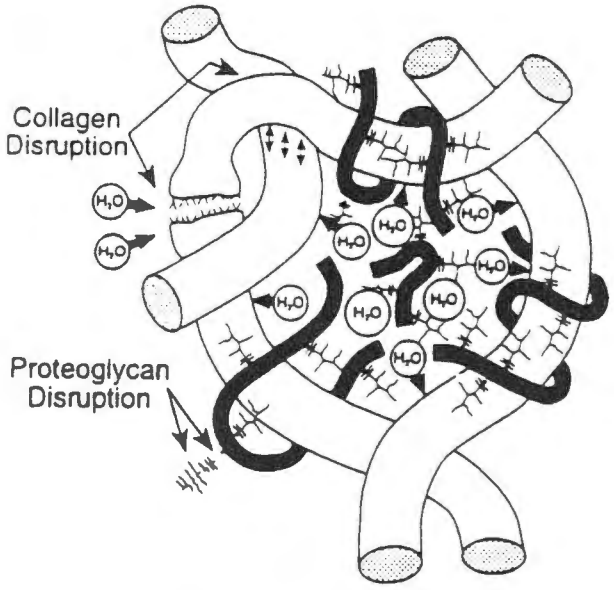


Fig 3.3 **A diagrammatic representation of osteoarthritic changes in cartilage matrix (cf Fig 2.3).** **(Jeffrey 2, 1994)**

It is now thought that an important event in the breakdown of cartilage in osteoarthritis is due to degradative enzymes. The principal mediator in this system is thought to be Interleukin 1 (IL-1) which is produced by mononuclear cells, including synovial lining cells and chondrocytes. IL-1 stimulates the synthesis and the secretion of a number of degradative enzymes which digest cartilage. Tissue inhibitor of metalloproteinase (TIMP) and plasminogen activator inhibitor 1 (PAI)) that can limit this process have been identified (Mankin et al 1992). It appears therefore that there is a balance of repair and degradation of cartilage. This maintains the integrity of cartilage until the degradative process outstrips the repair process, thereby resulting in OA.

3.4.5 Biomechanical Changes in the Osteoarthritic Joint

The biochemical changes in the articular structures in OA directly influence the biomechanical properties of articular cartilage, ligaments, menisci, subchondral bone, and the synovial fluid.

3.4.5.1 Articular Cartilage

In damaged articular cartilage, the collagen network is disrupted, proteoglycan molecules expand, and the water content of articular cartilage increases. The proteoglycan molecules are smaller and thus migrate from the extracellular matrix. The biomechanical properties of articular cartilage therefore change. The chondrocytes are responsible for the synthesis of matrix; the amount and quality of which is thought to be dependant on the loads placed on the chondrocytes (De Witt et al 1984). The matrix transmits mechano-electrical signals through the chondrocyte cell membrane. In damaged cartilage such as in OA, the chondrocytes act as immature cells and thus synthesise immature collagen. This leads to tissue failure under repeated loading.

In walking or running, the forces placed on the joint surfaces can vary from zero to several times the body weight within one second. It is important to understand how articular cartilage responds to these conditions, particularly the manner in which the fluid phase interacts with the solid phase.

3.4.5.1.1 Creep

Creep is defined as a viscoelastic behavior characterised by the increase in strain with time under a constant stress (Woo et al 1992), as discussed in greater detail in Section 2.2.3. When a unidirectional load is placed on articular cartilage, fluid is gradually exuded from the solid phase as the stress on the cartilage increases. When equilibrium is reached, the fluid ceases to exude. The internal stress then drops when equilibrium is reached, i.e. when there is no further fluid exude from the solid phase.

3.4.5.1.2 Aggregate Modulus

The aggregate modulus is the ability of the solid phase of articular cartilage or meniscus to resist compressive loads. It depends on: 1) the proteoglycan structure, 2) the proteoglycan interaction with collagen and, 3) how porous the matrix is to the fluid flow. In the early stages of OA, the water content of cartilage increases. This reduces the aggregate modulus of the matrix and increases the permeability of the extracellular matrix (Armstrong et al 1982). Thus, the articular cartilage is more compliant in OA which results in an increased load being placed on the underlying subchondral bone.

3.4.5.2 The ligaments

Ligaments can control the joint kinematics by virtue of their large collagen content. They are able to withstand large tensile forces, and prevent shear axial movements of the external components making up the joint. Should the collagen matrix in the ligaments become disrupted, the ligaments become more lax resulting in a decrease in stability of the joint. This would result in abnormal loads being placed on the underlying cartilage (Woo et al 1992).

3.4.5.3 The Meniscus

The meniscus plays a vital role in the distribution of the load on the tibial plateau at the tibio-femoral joint. The load distribution of the meniscus varies; at least 50% of the compressive load is transmitted in extension, and up to 85% is transmitted in 90° flexion of the knee. The wedge shape of the meniscus accounts for the differential compressive load pattern of the femoral side compared to the tibial side. Loads on the meniscus result in the meniscus being pushed out radially. Most of this radial displacement is stabilised by attachments of the anterior/posterior horns. Structurally, the meniscus is similar to articular cartilage. The collagen fibres are

distributed circumferentially and radially. Removal of the meniscus will alter the compressive load distribution in the joint because the joint space becomes narrowed. This leads to abnormal distribution of the forces in the knee joint and thus to increased damage of the underlying articular cartilage which then results in OA (Woo et al 1992).

3.4.5.4 The Subchondral Bone

Subchondral bone separates the articular cartilage from cancellous bone. It is more compliant than cortical bone, thereby complementing the shock-absorbing properties of articular cartilage. There is some incongruity between subchondral bone and the joint surfaces which allows a more even distribution of the forces when the joints are placed under compressive loads. Repetitive loading can result in a decreased compliance of subchondral bone. This is due to increased vascularisation of subchondral bone leading to increased ossification which is a fundamental predisposing mechanism to the development of osteoarthritis (Radin 1987).

3.4.5.5 Synovial Fluid

It is postulated that synovial fluid becomes more viscous in osteoarthritis. Therefore, the lubricating properties of synovial fluid are modified and this may decrease the lubrication of the joint (Woo et al 1992).

3.4.6 The Aetio-pathogenesis of Osteoarthritis

Aetiologic entities refer to primary inciting factors. There is often an overlap between these factors and pathogenic pathways. Among these factors are aging and repetitive mechanical loading on articular cartilage. In the early stages of osteoarthritis, there appears to be a failure of the collagenous network and an auto-degradation of proteoglycan aggregates within the matrix.

This results in a failure of cross-linking between the collagen fibres. Proteoglycan molecules are also damaged which results in more water being absorbed into the collagenous matrix resulting in softening of the cartilage. Repetitive mechanical loading on this damaged cartilge, particularly when the congruity of the joint surface is disturbed, can potentially damage the chondrocytes thereby releasing enzymes which will also enhance collagen damage. The repair process to the damage is confined to cartilage. There is a transient tissue response which has a limited capacity to fully repair itself. However, it is thought that the continuous joint movement limits further damage to the cartilage and remodelling can occur at the edges of the lesion. When subchondral bone is damaged, the normal inflammatory healing process ensues (Meachim 1969).

Synovial fluid is a dialycate of plasma to which hyaluronic acid is added by the beta cells. In OA this becomes more viscid due to the increased concentration of hyaluronic acid. This will result in an impaired lubricating process thereby adding to the pain and stiffness of the joint (Howell et al 1992).

3.4.7 Summary and Conclusions.

The two major factors involved in the aetiology and pathology of OA are 1) intrinsic factors such as the aging process and failure of articular cartilage, and 2) extrinsic factors i.e. physical forces placed on the joint such as mechanical loading (Figures 3.4 and 3.5).

Articular cartilage degenerates if abnormal stresses are placed on it and its capacity to repair is limited (Howell et al 1992). The distribution of the load on the joint surface is influenced by joint contour, congruity, and rapid loading.

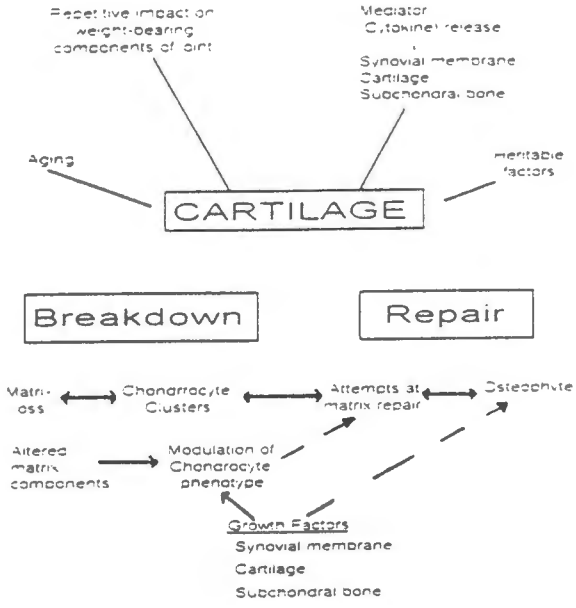


Fig. 3.4 A diagrammatic representation of the interaction of factors contributing to the evolution of osteoarthritis.

(Hamerman, 1989)

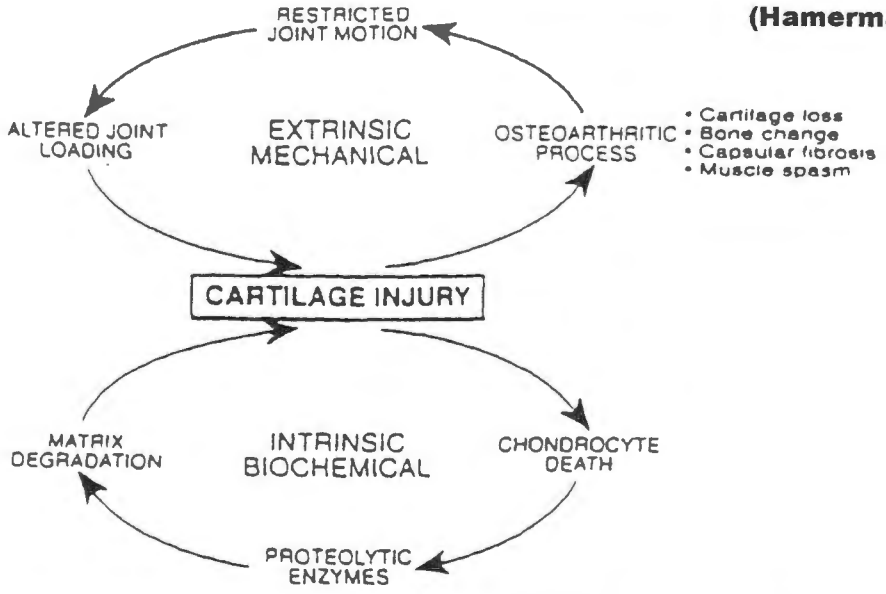


Fig. 3.5 A diagrammatic representation of the self-perpetuating cycles of cartilage destruction resulting from extrinsic mechanical stress on degenerating cartilage and intrinsic changes in the cartilage itself.

(Jeffrey 2, 1994).

If there is failure in any of the joint structures such as in the aging process, OA might well develop, even when subjected to normal loads as in every-day life. However, should the joint be subjected to abnormal loads, the ability of the joint surface to regenerate and repair might well be impaired.

3.5 The Diagnosis of Osteoarthritis

3.5.1 Introduction

The diagnosis of OA is not clear and a variety of clinical and radiological criteria have been proposed. The reason for this is that there is no single definition of OA. The diagnostic criteria for OA will thus depend on the type of study being carried out. This dissertation is an epidemiologic study and thus symptomatic criteria relating to OA were used. Some aspects of the difficulties in diagnosing OA will now be discussed.

3.5.2 Clinical Criteria

Criteria for the clinical diagnosis of OA have been developed using the "Delphi" technique of opinion sampling. This is a procedure designed to generate a consensus of expert opinion in situations of uncertainty. The characteristics include anonymity, feedback, and iteration. The cycle is repeated three times to provide consensus on the sensitivity and specificity (Altman et al 1986; Altman et al 1983). Clinical criteria are sensitive but not specific. In order to identify patients with OA, sensitive methods must initially be used.

The ranking of clinical criteria for the diagnosis of OA using the "Delphi" technique are shown in Table 3.2. Joint pain is the most sensitive symptom of OA. However, as it is subjective, the sensitivity is dependent on the pain threshold of the patient. OA may be a phasic condition with

diagnosis of OA, using clinical criteria, increases when there is associated swelling and stiffness. This is because swelling and stiffness are usually consequences of an arthritic process whereas pain can be a symptom of non-arthritic conditions.

Table 3.2 Relative ranking of clinical parameters for OA of the knee.
Ratings in order of importance by consensus of committee.

History			
1	Pain	1	Crepitus
2	Age > 50 yr	2	Bony enlargement
3	Decreased function	3	Limitation of motion
4	Swelling	4	Instability
5	Stiffness for > 30 min	5	Tenderness

Laboratory Findings	
1	Normal Erythrocyte sedimentation rate (ESR)
2	Non-inflammatory synovial fluid
3	Negative or very low titer rheumatoid factor

Altman et al 1983

A number of studies investigating the relationship between pathologic signs, radiographic signs, and clinical signs and symptoms of OA have been reported. An autopsy study of persons younger than 40 showed that 90% of the joints examined had pathologic evidence of degenerative disease and yet there was a lack of related clinical symptoms (Lowman 1955). In another study, only 30% of persons with radiological evidence of OA had clinical symptoms of OA (Cobb et al 1957). Other studies have shown an association between radiological signs and the predisposition to develop clinical signs of OA (Lawrence et al 1966; Gresham et al 1975). The disparity in these reports may be due to the use of different radiological criteria for the diagnosis of OA. In summary, the clinical crteria used in this dissertation in ranking order are: 1) joint pain, 2) stiffness, and 3) swelling. Other symptoms such as limitation of movement, giving way, and

muscle weakness are a consequence of OA and thus would not increase sensitivity and specificity.

3.5.3 Radiological Criteria

The first radiological criteria for diagnosing osteoarthritis were developed by Kellgren et al (1957) (Table 3.3.). In this classification, there was an overemphasis on osteophyte formation relative to joint space narrowing (Huch et al 1997). Relating to OA of the knee, it was concluded that radiological grading of skyline patellofemoral views was a more reasonable method of assessment than using the lateral view (Jones et al 1993). However, further validation of this method is required. Regarding radiological changes of OA of the knee, discrepancies in the standard techniques, i.e. anterior-posterior and lateral views with the patient bearing weight and with fully extended knees, were emphasised by Blackburn et al (1994). Plain radiographs underestimate the extent of cartilage damage compared to arthroscopic assessments. Furthermore, joint space narrowing on plain radiographs was not always associated with cartilage damage (Fife 1992). Hernborg et al (1977) and Danielsson et al (1970) mentioned in their reviews that osteophytes without joint space narrowing were simply a manifestation of aging. Changes in beam positioning on radiological assessments can modify the extent of the joint space narrowing. In assessing the progression of OA, radiographs were found not to be that sensitive.

Table 3.3 Osteoarthritis Classification Criteria

Joint	Clinical and Laboratory			Clinical, Laboratory, and Roentgenographic		
Knee	1	Knee pain		1	Knee pain	
			And			And
	2a	Crepitus		2	Osteophytes	
			And			Or
	2b	Morning stiffness <= 30 minutes				
			And			
	2c	Age =>38 years				
			Or			
	3a	Crepitus		3a	Synovial fluid: two thirds clear, viscous (age >= 40 if no synovial fluid available). White blood cell count <2000	
			And			And
	3b	Morning stiffness > 30 minutes		3b	Morning stiffness > 30 minutes	
			And			and
	3c	Bony enlargement		3c	Crepitis	
			Or			
	4a	No crepitus				
			And			
	4b	Bony enlargement				
Sensitivity			89%			94%
Specificity			88%			88%
Hip	1	Hip pain		1	Hip pain	
			And			And
	2a	Hard internal rotation equal toor less than 14°		2	At least two of the following: ESR less than 20mm per hour Roentgenographic femoral or acetabular osteophytes Roentgenographic joint space narrowing (superior, axial, or medial	
			And			
	2b	ESR equal or less than 45mm per hour (hip flexion equal or less than 115° if no ESR available				
			or			
	3a	Range of motion equal to or greater then 15° internal rotation				
			and			
	3b	Morning stiffness of the hip of 60 minutes or less				
			and			
	3c	Age > 50 years				
Sensitivity			87%			89%
Specificity			75%			91%

ESR = Erythrocyte sedimentation rate (Kellgren et al 1957)

The proportion of radiological disease which is symptomatic is between 40 to 80%, and about 50% of subjects with symptomatic OA of the knees have an associated disability. In an attempt to define OA of the knee, Spector et al (1993) examined a large population to determine the association between different radiological features and knee pain.

In this study, 977 women aged 45 to 64 were selected from a general practice in Chingford, UK. One thousand nine hundred and fifty four standardised anterior/posterior weight-bearing radiographs of both knees of these women were analysed. Intra- and inter-observer reproducibility was tested. Most clinicians agree that knee pain must be associated with a radiological sign. In this study, the presence of osteophyte formation had the strongest association with OA of the knee. However, the role of the osteophyte in osteoarthritis is controversial and that role is probably different at different sites (Croft et al 1994). Although hip pain is a sensitive method of defining hip osteoarthritis, patients do vary in their threshold for reporting the symptoms and there are causes of hip pain other than osteoarthritis (Croft et al 1994). The American College of Rheumatology (ACR) recommended that osteophytosis is a sensitive method for defining hip osteoarthritis (Altman et al 1986) in contrast to a British study which recommended joint space narrowing as a sensitive criteria (Croft et al 1994). The difference between the two studies is that the ACR investigation recruited symptomatic patients. It has been shown that 30 to 40% of people with radiological signs of OA do not complain of pain (Croft et al 1994). This group would have been excluded in the ACR study had the radiological criteria been used at the beginning. In cases where a control group has a large number of people with other joint disease such as rheumatoid arthritis, joint space narrowing may be present and thus this criteria would reduce the specificity to diagnose OA and osteophytosis would be a better discriminant. Thus to diagnose OA radiologically, the criteria to choose between are either the presence of osteophytes with joint space narrowing, or joint space narrowing alone (Nevitt 1996). This choice would be determined by the purpose of the study. These studies indicate the importance of selecting the control group of people in such a way as

to avoid bias, but to exclude persons who have other joint diseases with radiological features which would decrease the specificity of defining a population with osteoarthritis (Croft et al 1994). The standard choice for the radiological diagnosis of osteoarthritis would depend on the purpose of the study.

3.5.4 Magnetic Resonance Imaging (MRI) and Athroscopy

A discussion on the diagnostic difficulties in OA would not be complete without reference to the use of MRI and arthroscopy. A study was undertaken where 33 patients with OA of the knee were evaluated by means of plain weight-bearing radiographs of the knee and arthroscopy under local anaesthetic. Sixteen of these patients had MRI views of their knees (Blackburn et al 1994). Plain radiographs and MRI largely underestimated the arthroscopically determined cartilage abnormalities. Blackburn et al (1994) thus concluded that outpatient arthroscopy, performed under local anaesthetic, had a high degree of patient acceptability compared to MRI and was more accurate in estimating cartilage damage than other techniques. However, arthroscopy is an invasive procedure and thus MRI is a more promising and appropriate method of estimating articular cartilage damage in the hip and knee joints.

3.5.5 Conclusion

In order to diagnose OA, arthroscopic examination appears to be the most specific method. However, when conducting epidemiological studies in OA, clinical criteria would be the most appropriate. The most specific combination of clinical symptoms are pain, together with stiffness and swelling.

3.6 Summary

OA is a complex pathological entity which has many predisposing factors. These are intrinsic factors within the joint, and extrinsic factors that occur outside the joint. Two of these factors were reviewed. These were the aging joint and the effect of mechanical loading on the joint. The difficulties in diagnosing OA, particularly correlating clinical criteria with radiological criteria are reviewed. The literature reviewed illustrated the difficulties in designing a research study in OA. This is because of the many confounding variables that can influence the study. The animal and epidemiological studies reviewed indicated that moderate running, as well as marathon running, do not predispose to the development of OA in the hip and knee joints.

The following chapter will review the specific relationships between distance running and its role in the potential development of osteoarthritis in the weight-bearing joints.

CHAPTER 4

DISTANCE RUNNING AND OSTEOARTHRITIS: A REVIEW OF THE LITERATURE

4.1 Introduction

It can be hypothesised that the increased amount of impact loading on the hip and knee joints in ultra-distance running might be a contributing factor in the development of early osteoarthritis in these joints. In this chapter the effects of running on articular cartilage in animals and from epidemiological studies in humans will be reviewed.

4.2 The effects of running on articular cartilage: Animal studies

The effect of running on articular cartilage has been investigated in a number of studies using animal models (Tammi et al 1987). In one of the earlier studies, the effect of vigorous exercise on the reversibility of canine knee cartilage atrophy produced by immobilisation of the leg was studied (Palmoski et al 1981). In this study, the right hind legs of seven dogs were immobilised for six weeks. Two animals were sacrificed immediately and the remaining five were sacrificed three weeks after removal of the cast. During this period two were allowed to walk while the remaining 3 were placed on a vigorous treadmill exercise program. The results of this study showed that articular cartilage in the immobilised knees had an

increase in water content, decreased thickness, and a decrease in proteoglycan synthesis. The articular cartilage in the knees of the walking group showed reversal of these changes, whereas the cartilage in the running group exhibited continuing decreases in thickness. Though the proteoglycan content was increased in the running group, its structure was abnormal. This study indicated that the integrity of the extra-cellular matrix was diminished after immobilisation and that further loading during subsequent exercise might decrease the ability of the chondrocytes to repair the damaged cartilage. This study also indicated that articular cartilage which atrophied because of disuse suffered from running but not from free walking.

Age can also influence the integrity of cartilage when running is commenced (Jurvelin et al 1986). The shear forces between the surface cartilage might be responsible for the surface lesions observed after running (Tammi et al 1987).

The articular cartilage in animals, in particular the proteoglycan content or the glycosaminoglycan content, can be analysed (glycosaminoglycan is part of the proteoglycan structure) to determine the effects of repetitive loading on cartilage. Glycosaminoglycan content in articular cartilage has been reported to decrease after running in dogs, guinea pigs, and mice but was unchanged in rabbits. The glycosaminoglycan content is dependent on the age of the animals (Tammi et al 1987).

In one study, it has been shown that gradual low intensity training in young rabbits increased proteoglycan content in articular cartilage (Saamanen et al 1986). However, when the rabbits ran without a conditioning period (not defined) there was no significant increase in glycosaminoglycan content (Videman et al 1984). In another study, a reduction in proteoglycan in the femoral-head cartilage in adult dogs was demonstrated after an eight-month running programme (Vassan 1983). These lesions were aggravated if the joints were immobilised prior to exercise (Palmoski et al 1981).

The effects of different training volumes on healthy cartilage were studied in response to strenuous (20 km a day) and non-strenuous (4 km a day) running for 15 weeks in beagle dogs. The results of this study showed that glycosaminoglycan levels were increased in non-strenuous running while strenuous running decreased the proteoglycan at the same location (Saamanen 1986). However, there were no macroscopic or microscopic changes, although fibrillation of articular cartilage has been demonstrated after long periods of high intensity running (Helminen et al 1986).

The effects of running on the femoral-head joint surfaces of rabbits has been studied by scanning electron microscope (Candolin et al 1986). In this study, sudden maximal running caused more irregularities on joint surfaces than prolonged submaximal running. However, the authors did not define sub-maximal or maximal exercise.

The influence of strenuous running (20 km/day 5 times a week, for 25 weeks) on articular cartilage in young (15 week old) beagle dogs was compared to a control group of beagle dogs that did not exercise. Histological analysis of articular cartilage of the humeral heads of beagles showed a decrease in the volume and volume density of the chondrocytes in the running group (Helminen et al 1986).

The effects of strenuous running (20 km/day at 6.1km/hour for 15 weeks) and moderate running (one hour a day at 4 km/hour, 5 days a week for 15 weeks) on the articular cartilage in the knee joints of beagles was also studied. There was slight increase in thickness and an increased proteoglycan content in the articular cartilage in the moderate running group. Strenuous running had the opposite effect (Kiviranta et al 1986).

Biochemical changes in articular cartilage composition have also been demonstrated with enhanced weight-bearing and running training in young rabbits. In one study, running enhanced the glycosaminoglycan content but decreased the hyaluronic acid. The ability of hyaluronic acid to interact with proteoglycans is important to maintain proteoglycan integrity

(Palmoski et al 1981). In another study, the collagen content did not significantly change in rabbits or dogs in response to non-strenuous running (not defined) (Tammi et al 1983; Saamanen et al 1986).

In another series of studies, the effects of running on articular cartilage in dogs has been investigated (Arokoski 1993). Moderate running (4 km./day, 5 days/week for 40 weeks) increased articular thickness, stiffness, and proteoglycan content whereas more strenuous running (20 km/day, 5 days /week 15 weeks) decreased cartilage thickness and proteoglycan content. Longer-term running (40 km/day for up to a year) decreased proteoglycan content and cartilage stiffness and stimulated remodelling of subchondral bone but did not lead to degenerative joint disease. These changes were correlated with the biomechanical properties in articular cartilage. The shear modulus in the articular cartilage was decreased after prolonged distance running (40 km/day for one year) and this was restricted to prominent weight-bearing areas of the joint (Arokoski et al 1993; Arokoski et al 1994).

The effects of life long running with added weight has also been investigated in beagles. The animals were divided into two groups. The exercised group ran 4 km/day with jackets weighing 11.5kg five days a week for 550 weeks. The control group were caged for the same period. There was no difference in the gross and microscopic appearance in the joints in both groups. There was no evidence of increase of joint degeneration in life-long moderate exercise in this study (Buckwalter 1996).

As previously mentioned, matrix synthesis is dependant on chondrocyte activity, and this is defined by the amount of proteoglycan in the matrix. It is difficult to demonsrate whether chondrocytes respond to loading such as running. In one study, chondrocytes became enlarged in the articular cartilage of rabbits in response to running but there was no increase in cell number (Paukkonnen et al 1985). The pathway to cartilage damage may be joint movement in cartilage depleted of proteoglycan.

Shay et al (1995) divided hamsters into two groups; one housed in standard cages and one given free access to running wheels. Half of each group were injected with lipo-polysaccharide (LPS) to cause an inflammatory response in the joint. Only the LPS-injected running joints showed cartilage fraying over large areas of the articular surface, as well as areas in which the villus projections had been flattened. The damage done to the synovium could stimulate an increased inflammatory response due to the release of enzymes and cytokines.

Two hundred and ninety four inbred C57BL male mice, which express a high incidence of spontaneous OA of the knee joints, were divided into two groups comprising of runners and controls. The runners were trained daily between 2 and 18 months of age by running on a treadmill at 13.3 metres/minute for 1,000 metres/day. The mice were sacrificed at 2, 6, 10, 14, and 18 months of age and their knee joints were examined histologically. It was found that the incidence of OA in the medial tibial condyles at the age of 18 months increased from 72% in controls to 88% of the runners. Similar histologic changes were present in other areas of articular cartilage of the knee joints (Lapveteläinen et al 1995).

The influence of excessive running load on the development of knee OA was investigated in male Wistar rats (Pap et al 1998). Intracranial self stimulation (not defined) was used to motivate the rats to run daily distances of 500m, 5 days a week. Ten rats ran a distance of 15 km within three weeks. Another group of ten rats ran 30 km within six weeks. Histologic examination of the knee joints was performed on all rats together with a immunoreactivity test of the chondrocytes to MMP-3, a cartilage degrading enzyme in OA. Moderate OA was present in the rats that ran 30 km while mild OA was present in the group that ran 15 km. There was increased immunoreactivity to MMP-3 in the rats that ran 30 km compared to those rats that ran 15 km. The investigators concluded that increased running loads lead to an increased production of MMP-3 which could result in increased histologic changes of OA. However, when conducting animal studies in OA, certain species or breeds of the animals studied may have a primary genetic predisposition to develop OA (Holderbaum et al 1999).

This must be accounted for before concluding the exercise is a significant factor in the development of OA in certain species of animals.

A study in Germany was carried out using beagle dogs (Oettmeier et al 1992). The investigators examined the histological changes of articular cartilage and subchondral bone in a group of running dogs and a control group. The running group ran on a treadmill for 25 weeks up to 40 km/day, starting at 15 weeks of age. In all the articular cartilage in the running group, the calcified and uncalcified regions showed slight thickening. The thickness of the subchondral bone plate was also thicker in the running group.

A recent study in dogs was undertaken to determine whether an increased level of life-long exercise caused degeneration or changes that may lead to degeneration of articular cartilage (Newton et al 1997). Eleven dogs were exercised on a treadmill at 3 km/hr for 75 minutes, 5 days a week for 527 weeks while carrying jackets weighing 130% of their body masses. Ten control dogs were allowed unrestricted activity in cages for 550 weeks. At the end of the study, articular cartilage of the medial tibial plateau was examined by light microscopy. The thickness and biomechanical properties of the artcular cartilage were also examined. There were no differences in all these parameters in both groups of dogs. It was concluded that a lifetime of regular weight-bearing exercise in dogs with normal joints did not cause alterations in the structure and mechanical properties of articular cartilage that might lead to joint degeneration. However, the lateral tibial plateau was not examined in the same manner.

4.2.1 Conclusions

Results from studies in experimental animals suggest that joint loading plays an important role in the physiology of articular cartilage. The proteoglycan (PG) content in articular cartilage is a major factor influencing its compliance. When loaded, there is an increase in PG content and stiffness. However, when cartilage is not loaded, the PG content decreases and hence its stiffness decreases. It appears that moderate and possibly strenuous life-long

joint use does not predispose to cartilage damage. However, disuse followed by sudden high impact loading may result in cartilage damage which can lead to the development of premature OA. Moreover, when the weight-bearing joints are loaded, there are adaptive changes in the articular cartilage and subchondral bone (Oettmeier et al 1992).

4.3 Running and Osteoarthritis: A Review of Epidemiological Studies In Humans

4.3.1 Introduction

Epidemiology can be defined as the study of the distribution and determinacy of disease in the human population (Walter et al 1990). Epidemiology is a powerful tool that can be used to study the predisposing factors in OA. However, it does have many pitfalls such as case definition and bias in terms of the study population. Some aspects of epidemiologic studies will now be discussed.

4.3.1.1 Case Definition

Epidemiological studies require a clear, concise, and reliable case definition, which has to be reproducible, accurate, non-invasive, consistent, and relatively inexpensive (Spector et al 1994). There is, however, little consensus in defining osteoarthritis. Kellgren et al (1957) produced a radiological classification which is sensitive. However, many cases of osteoarthritis are defined radiologically as asymptomatic (Spector et al 1993; Croft et al 1994).

The American College of Rheumatology (ACR) recommended clinical criteria to define OA, where subjects are required to have specific current joint pain on most days for at least a month (Spector et al 1994). However, studies have indicated that this method lacks

specificity (Spector et al 1994).

4.3.1.2 Case Control Studies

A case control study can be defined as a study where cases with the disease and controls without the disease are identified. The data on exposure to the existing risk factors can be usually be determined by self-administered questionnaires. An odds ratio is calculated to express the association between those cases exposed to the risk factor and the control cases that were not exposed to the risk factor (Spector et al, 1994).

Problems with case control studies are firstly, to obtain a correct definition of disease, and secondly, to choose a suitable control group. Finally, it is imperative that confounding variables are excluded.

4.3.1.3 Cohort Studies

Cohort studies are defined as those studies involving groups of individuals. They are important to determine the temporal sequence of exposure of the disease. Cohort studies are characterised by a group of individuals who are defined as having a risk to develop OA. The exposure to the risk factor occurred before and not as a consequence of the disease. This requires some estimate of the timing of the onset of the condition (Spector et al 1994). The validity of these studies are affected by loss to follow-up.

The ideal studies would include contributions from orthopaedics, rheumatology, biomechanics, biochemistry, radiology and possibly other disciplines. They would carefully define and quantify physical stress, include appropriate study and control populations, be of sufficient duration and sample size to provide definitive information, use standardised clinical and radiological assessment of joint degeneration, quantify functional status, and assess contributions of other risk factors. These would be difficult studies to conduct and probably

will never be achieved. However, better information is required so that physicians may responsibly advise the millions of participants about the beneficial and deleterious effects of regular exercise (Panush et al 1987).

There are numerous epidemiological studies relating occupational and sports activities to osteoarthritis of the hip and knee joints. Relevant studies will now be discussed.

4.3.2.1 Epidemiological Studies in Occupational Activity and Sports other than Distance Running

An increased incidence of degenerative hip disease in a group of athletes with different sports backgrounds was first documented in 1971 (Murray et al 1971). In this case control study, three groups of males aged seventeen to twenty-one completed a questionnaire concerning their personal and athletic history. A single antero-posterior radiograph of the pelvis was obtained to identify "tilt" deformities of the hip. This consists of a medial angulation of the femoral head in relation to the femoral neck. This is thought to be a consequence of a slipped capital epiphysis. The athletes were then divided into two groups according to whether they had participated in a highly athletic regime or a more scholarly programme. The findings were that "tilt" deformities were identified more in those who participated in more active regimes. This was related symptomatically to "growing pains" which, retrospectively, was thought to be because of epiphysiolysis which can predispose to the development of OA.

In another study, no difference in the prevalence of osteoarthritis of the cervical or lumbar spine in young active parachutists or other ex-military parachutists was documented (Murray-Leslie et al 1977b). In this study, spinal injuries and symptoms were studied in 109 ex-military parachutists and 112 sport parachutists by means of questionnaires. Forty-six ex-military parachutists aged 50 years or over had x-rays of the lumbar spine and 58 sport parachutists had x-rays of the cervical spine. This was a cross-sectional study which did not

that of the general population. This study did not implicate parachuting as a cause of intervertebral disc degeneration.

A similar study was undertaken using the same cohort which showed that there was no increased prevalence of OA in the ankles and knees (Murray-Leslie et al 1977a).

A number of studies have described an increased incidence in joint degeneration relating to other sports, indicating that repetitive high stress resulting from impact loading might be the cause of osteoarthritis (Table 4.1).

Table 4.1 The increased incidence of joint degeneration relating to various sports.

Sport	Site (Joint)	Risk of Osteoarthritis
Baseball	Elbow, shoulder	Probably increased
Football	Ankle, foot, knee	Possibly increased
Rugby	Knee	Possibly increased
Soccer	Ankle, foot, hip, knee, cervical spine, talus	Possibly increased
Weight lifting	Spine	Possibly increased
Wrestling	Cervical spine, elbow, knee	Possibly increased

(Lane et al (1993) adapted from Panush et al (1987))

A study was carried out to determine the relationship between different physical loading conditions and findings of knee OA (Kujala et al 1995). One hundred and seventeen male former top-level athletes aged between 45-68 years were assessed. Twenty-eight had been former long distance runners (not defined), 31 had been soccer players, 29 weight lifters, and 29 shottists. Histories of lifetime occupational and athletic knee-loading i.e. training intensity,

29 shottists. Histories of lifetime occupational and athletic knee-loading i.e. training intensity, knee injuries, and knee symptoms (pain) were obtained. The subjects were examined clinically and radiologically. The results showed an increased risk of developing knee OA in soccer players and weight lifters. The increased risk was explained in part by knee injuries in soccer players and by high body mass in weight lifters. The long distance runners showed least risk of developing knee OA.

To emphasise the need to correct for occupational status, Cooper et al (1994) carried out a small population-based case control study on 109 men and women with osteoarthritis characterised by: 1) painful knee joints, and 2) radiological evidence of OA. This was compared with 218 age-matched controls who did not complain of knee pain. The information included an occupational history with details of whether the main job entailed squatting, kneeling, stair-climbing, heavy lifting, walking, standing, sitting, or driving. The investigators concluded that their data indicated that prolonged repetitive knee-bending (>30 minutes a day) is a risk factor. The risk was higher because of the increased mechanical loading with the bending movement of the knee.

4.3.2.2 Epidemiological Studies in Distance Running

One of the first studies to relate distance running and OA showed a reduced incidence of osteoarthritis in Finnish long distance runners (Puranen et al 1975). Hip joints of 74 former elite runners were radiologically examined. Sixty subjects responded to a questionnaire. The mean age of respondents was 55 years and the mean duration of competitive running was 21 years. The distances run were unspecified. The results of this study showed that 9% more respondents in the control group showed radiological evidence of OA of the hip compared with runners. The selection of the top runners was not clear and the X-rays were read without knowledge of the running volume of the participants. The hip x rays of 115 age matched male patients admitted to Oulu University Central Hospital for complaints that did not affect the hip joints, were studied. The study implies that improved nutrition of the

clinically and radiologically. Musculoskeletal symptoms (pain and swelling) of hip, knees, ankles, and feet were not significantly different between the two groups. Radiological examination for osteophytes and cartilage thickness also did not show significant differences between the two groups.

The effects of regular long-distance running (97 km/week) on the hips in later life was studied in 59 men, made up of 27 former long-distance runners, 9 former bob-sleigh riders, and 23 healthy untrained men (Marti et al 1989). The subjects completed detailed questionnaires relating to exercise habits, sports injuries, and medical history. Fifteen years after the initial assessment, radiographs of the hips of these men were analysed. There was a significant increase in radiological signs of osteoarthritis in runners compared with those who did not participate in long distance running. Multiple variable regression analysis was performed to correct for age, because the controls were younger than the athletes. However, there were other limitations to the study. These included: 1) that no initial radiographs were available, 2) the study sample size was small, and 3) there were no data relating to the actual prevalence of osteoarthritis in this population. Furthermore, the athletes had run much higher weekly distances than in other studies. The radiographs showed that runners had a hypertrophic type of osteoarthritis in the form of osteophyte formation as opposed to a destructive form of OA; (Osteophytes are considered to be a compensating entity by which the surface area of the joint is increased). More importantly, only four of the runners complained of pain.

More recently, a study relating long-distance running and OA was reported (Konradsen et al 1990). This study was a small case-control study, analysing 27 runners with an average age of 50 years and who had run an average of 40 km a week. There were no differences in joint alignment, range of motion or joint pain, and radiological signs of osteoarthritis of the hips, knees, and ankles, between runners and an age- and weight-matched control group. The weekly distances run in this study were much lower than those of ultra-distance runners.

An epidemiologic study investigating sports participation and prevalence of OA of the hip was reported (Vingard et al 1993). This study was a case-control study comprising all Swedish men aged 50 to 70 year who lived in the referral areas of 4 hospitals in Stockholm. The subjects were recruited from patients who received hip joint replacements. The control subjects were randomly selected from the hospital population. All the subjects were interviewed telephonically for details regarding their sports participation, hours of exposure to the sport, and the length of time exposed to other sports. Confounding factors such as weight, smoking, and body mass index (BMI) were controlled and only those subjects with primary OA were questioned. The participants were grouped according to age and the length of time they were exposed to various sports. Different sports with the same type of loading were grouped together. The results of this study, expressed as relative risk using logistic regression analysis, showed a higher risk of osteoarthritis in long distance running (1.7), and track, field, and racket sports (2.4), compared with sports where there was less impact loading on the joints, e.g. ice hockey (0.4) and handball (0.5). Golf, swimming, and biking showed results similar to long distance running (1.5). This study as well as that of Marti et al (1989) were the first to indicate a probable increased risk of osteoarthritis related to excessive stress on the joint when participating in sports, including distance running.

The cumulative 21-year incidence of admission to hospital for OA of the hip, knee, and ankle in former elite athletes and control subjects who were age-matched males, was conducted by researchers in Finland (Kujala et al 1994). This study was a national population-based study comprising 2049 male athletes who had represented Finland during 1920-1965. The control group of 1403 men was selected from the public archives of the register of men liable for military service. A questionnaire was posted to surviving former athletes and controls. In this study, 120 athletes and 36 controls were admitted to hospital for osteoarthritis of the hip, knee, or ankle during the 21-year follow-up. The mean age for the first hospital admission was higher in endurance athletes (long-distance running and cross-country skiing) compared with mixed sports (soccer, ice hockey, and track and field sports) and power sports (boxing, wrestling, weight-lifting, and throwing). The age distribution varied with the different sports

and some sports were not controlled for age. Corrections for BMI and occupation were made. Athletes for all types of competitive sports are slightly more likely to need hospital care for osteoarthritis of the weight-bearing joints of the lower limbs. However, the need for hospitalisation occurred at an older age in those athletes who participated in long distance running. This could be coincidental,as no mention was made of injuries to weight bearing joints. Injuries incurred in mixed sports such as soccer and ice hockey could involve internal injuries of the knee, which are more likely develop into OA. These are confounding variables in relating OA to exercise.

The implication is that long distance running was not a precipitating factor to the development of premature OA of the weight-bearing joints. Mixed and power sports (as defined) might predispose to premature OA of these joints.

A radiological survey of the hips and knees in female ex-athletes and a population control was undertaken to determine the risk of OA associated with long-term weight-bearing sports (Spector et al 1996). It was a retrospective cohort study comprising 81 ex-elite athletes (67 middle- and long-distance runners and 14 tennis players) aged between 40-65. The control group was obtained from a register of a general practice in Chingford, U.K. The ex-runners were participating in an average of 3.1 hours of vigorous weight-bearing sports (undefined) per week and running an average of 14.6 miles per week. There was a two- to three-fold increase in the risk of developing radiological OA of the knees and hips (particularly the presence of osteophytes) in the ex-athletes. However, the reported knee and hip pain were similar in both groups. The pain thresholds were markedly higher in the ex-athletes and may explain the lack of increase in knee pain in this group. The radiological presence of osteophytes in the knee, in the absence of symptoms, has been found to be related to subsequent (10 years later) disability and physical functioning (Davis et al 1991). The author concluded that long-term, weight-bearing sports activity can not be dismissed as a factor in the development of OA in the knee in females.

In recent years, investigators at Stanford University carried out two case-control studies on the relationship between running and OA (Lane et al 1986) and running and musculo-skeletal disability (Lane et al 1987). The subjects were aged 50 to 72 years and approximately 60% were male with a minimum of a high school education in all groups. In the first study, a detailed validated questionnaire was sent to 1360 runners and 1300 controls. Care was taken to eliminate self selection by: 1) noting exaggerated differences in the results, 2) healthy community controls were unlikely to have osteoarthritis, 3) the groups were carefully matched for confounding variables, 4) the groups were assessed objectively using Computerised Axial Tomography (CT) and X-rays. From this group, 41 runners from the 50+ age group and 57 control subjects from the Lipid Clinic in Stanford were randomly selected. X-rays of the hands, knees, and lateral lumbar spine, and CT of the first lumbar vertebra (L1) were obtained from all the subjects. X ray findings were graded from 0 to 3 according to the degree of joint space narrowing, scoliosis, and spur formation. The results from the first study were that there were no differences between the running and control groups with respect to joint space narrowing, crepitus, joint stability, or symptomatic osteoarthritis. Running was associated with increased bone mineral density but not clinical OA.

In the second study, the same groups of runners and controls were also used to study the effects of running on musculo-skeletal disability and the rate of the development of such a disability (Lane et al 1987). The health status of the groups were compared using "the Disability 30" index, which compares the present ability to perform specific tasks with ability to perform the same task at the age of 30. The number of times the two groups visited a doctor was also compared. Bias was decreased by separating the study population group into 4 groups. These were: 1) "serious runners" defined as those who had run significant (as defined) distances; 2) "runners" defined as those subjects who had run any distance; 3) "community controls" who were all subjects recruited from the community control population, and 4) "non-runners" who were those subjects who had never run. Self selection of runners, who were generally healthier than controls, was controlled by: 1) analysing matched pairs, 2) re-analysing the data, excluding pairs of runners and control subjects who had major

medical problems, 3) analysing reasons for stopping running, 4) comparing groups, including all subjects who had ever run, in either group, 5) performing separate validation studies on runners and control groups, 6) comparing precursor factors, such as ligament laxity and family history of arthritis, and 7) choosing a serious running group for comparison so that a very large difference in activity would exist between the two groups. The prevalence of musculo-skeletal disability was lower in runners, as was the rate of development of the problems associated with these symptoms (Lane et al 1987).

The first prospective cohort study which investigated the effect of running on the development of OA and bone density was published in 1990 (Lane et al 1990). The subjects of the study came from the same group of subjects who were assessed in the previous studies described in this review (Lane et al 1986). X-rays of the hands, lateral lumber spine, and knees of the running group and control group were assessed. The results of this study reported that running did not appear to influence the development of OA diagnosed by radiological criteria in that there was a significant increase in X-ray features of OA in all groups during the two-year period. However, there was increased spur formation in the knees of female runners. The clinical significance of this is not clear. There was a significant decrease in the bone density for nearly all subjects, but especially in women runners who ceased running compared to those who continued running. At the two-year follow-up, runners maintained a greater bone density.

In a longitudinal study lasting five years, the effects of running and aging on the development of radiographic and clinical osteoarthritis of the knees, hands, and lumbar spine was reported (Lane et al 1993). In this study, 35 running subjects and 38 controls with a mean age of 63, were matched for age, education, and occupation. They all underwent rheumatological examination, completed questionnaires, and had radiographs taken of their hands, lateral lumbar spine, and knees in 1984 and 1989. The five-year follow-up radiographic results of both runner and control groups showed progression of osteoarthritis in the knees, hands, and lumbar spine as determined by the ACR criteria for diagnosing OA. The conclusion of the

study was that recreational running did not accelerate the development of radiographic or clinical osteoarthritis of the knees. However, with aging, 13% of all subjects developed osteoarthritis of the hands and 12% of all subjects developed osteoarthritis of the knees.

A longitudinal study lasting nine years investigating the relationship of running to OA of the knee and hip and bone mineral density (BMD) of the lumbar spine was published recently (Lane et al 1998). The cohort comprised 28 runners and 27 controls (with a mean age of 66 years) from the original group that was studied in 1984 (Lane et al 1986). All subjects underwent rheumatologic examination, completed annual questionnaires, and had X-rays taken of the knees in 1984, 1986, 1989, and 1993. In 1993, the knees were assessed in pairs (1984 and 1993). The hips were X-rayed in 1993. BMD assessments were obtained in 36 subjects using CT in 1984, 1986, 1989, and 1993. The results showed a significant increase in osteophyte formation in the knees in both groups over the 9-year period. X-ray evidence of hip OA was not different in both groups. The BMD of the lumbar spine remained 20% higher in the running group. Although the numbers were small in this study, there were no differences in the age, exercise histories, running status, or disability in the 55 study subjects who returned for the 9-year follow-up visit and the 43 subjects who chose not to attend. Moreover, being a longitudinal study, the subjects studied acted as their own controls.

4.4 Summary and Conclusions

The results from animal studies indicate that exercise is an important factor in maintaining the structure and function of articular cartilage. It is difficult to determine whether exercise is a risk factor for OA partly because it is difficult to define OA. In low impact activities such as recreational running, cycling, and swimming, the risk of developing OA in normal joints does not appear to be increased. However, individuals who participate in sports with abnormal or injured joints, or at a highly competitive level, appear to have an increased risk for developing osteoarthritis (Buckwalter et al 1997). Well-controlled longitudinal studies of

young elite athletes who developed joint injuries will have to be conducted to substantiate this hypothesis.

The epidemiological studies suggest that long-distance running and specifically marathon running does not increase the risk of the development of premature OA of the weight-bearing joints.

CHAPTER 5

A STUDY INVESTIGATING THE RELATIONSHIP BETWEEN ULTRA-DISTANCE MARATHON RUNNING AND OSTEOARTHRITIS.

5.1 Introduction

Exercise, particularly distance running, is a popular recreational and competitive activity. It has been well documented that regular exercise training can improve the quality of life and increase longevity (Booth et al 1995, Paffenbarger 1986). However, there has also been concern that weight bearing exercise, such as distance running, could predispose to damage of the musculo-skeletal system (Panush et al 1994). Osteoarthritis (OA) is the most common joint disease in the middle aged and elderly (Moskowitz 1992). It is thus important to investigate whether distance running is a risk factor for development of OA. Studies using an animal model, as well as epidemiological studies in humans indicate that "moderate" distance running is not a predisposing factor to the development of OA (Newton et al 1997; Lane et al 1998). However, ultra-distance marathon running, defined as running distances greater than 42 km, requires greater volumes of training which results in more repetitive impact loading on the joint surface of the weight bearing joints. At present, it is not known whether this amount of impact loading is a risk factor for the development of OA.

5.2 Aim of the Study

The aim of this study is to document the prevalence and risk of OA in the weight bearing and non-weight bearing joints of male distance runners who have accumulated low, medium and high lifetime training volumes.

5.3 Methodology

A case control study was designed to determine the prevalence and risk of OA in different joints (weight-bearing and non-weight-bearing) in a group of ultra-distance marathon runners compared with a non-running control group. For the purposes of the study, OA was defined as pain and/or swelling and/or stiffness in a joint.

5.3.1 Subjects

The subjects for this study were selected from previous and current runners of the Two Oceans Ultra-marathon (56km) in Cape Town (South Africa). The database of all the runners who participated in this race between 1970 and 1983 was supplied by Unidata, Cape Town, South Africa, which is the company that computerises all the results of the Two Oceans Ultra-marathon. The entire database from the Two Oceans Marathon was used to obtain the postal addresses including local postal codes from all the runners. All female runners were excluded from the runner population because a suitable control group of non-runners was obtainable from the alumni of a boys-only school. The individual ages of all the male runners was calculated as the age on the 1st January 1995. The total number of male runners in the data-base was 1356. The male runners were then divided into six age groups ranging from 18 to 79 years of age. A random sample of 25 runners in each 10-year age group was then selected from the population of male runners (Table 5.1). Runners were age matched with past pupils of Rondebosch Boys' High School, Cape Town, drawn from a list supplied by the

alumni society of that school (Table 5.2). The ages of subjects in this control group were calculated by assuming that they were 18 years of age during their final year at school (Table 5.2).

Table 5.1 The selection and response rates of the running group.

Age Groups	Number of Runners selected	Number of Respondents	Response rate (%)
18-29	25	7	28
30-39	25	13	52
40-49	25	17	68
50-59	25	22	88
60-69	25	17	68
70-79	3	0	0
TOTAL	128	76	59

Table 5.2 The selection and response rate of the control group.

Age groups	The final year of schoolboys	Number of selected controls	Number of responses	Response rate (%)
18-29	1994-1983	39	17	44
30-39	1982-1971	35	16	46
40-49	1970-1959	41	18	44
50-59	1958-1947	38	20	53
60-69	1946-1935	29	21	72
70-79	1934-1923	22	22	100
TOTAL		204	114	56

A total of 128 runners and 204 controls were randomly selected to participate in the study. More controls were selected initially as it was anticipated that some controls would turn out to be runners. Completed information was obtained from 76 ultra-distance marathon runners and 114 controls. Eleven subjects in the control group had in fact participated in ultra-distance marathon races. They were thus transferred to the running group. However, there were a further 43 subjects in the control group who had running volumes, (although they had not competed in any ultra-distance running events) similar to those of the ultra-distance runners (Table 5.3.). These subjects were also transferred to the running group. The final number of subjects in the control group was therefore 60 and in the running group 130 (Table 5.3.).

Table 5.3 The Return Rate of Mailings.

Total number of respondents **190**

Category	**Runners**	**Controls**
First Mailing	39	70
Ultra-distance runners	11	-11
	50	59
Second Mailing	26	33
Third Mailing	11	11
Total Replies	87	103
Runners transferred from controls	43	-43
Total numbers	130	60
Sub-category of runners		
Low Volume	43	
Medium Volume	43	
High Volume	44	

The runners (n=130) were then divided into three groups according to the total running volume. The total running volume was calculated by the following formula; years involved in

running x months/year running x 4 x hours/week running. The running volume had a skewed distribution. This was transformed by taking the logarithmic value of the running volume to the power e. The running volume was categorised by taking tertiles of the original distribution. The cut points corresponded to 840 hours and 2690 hours. The subjects were then divided into four groups: 1) controls (non-runners) (n=60), 2) low volume runners (0-840 hours) (n=43), 3) medium volume runners (842- 2690 hours) (n=43) and 4) high volume runners (> 2691 hours) (n=43). The prevalence (%) of OA in all groups was compared.

The running group was further divided into two groups; i.e. those who were currently running at the time of the study, and those who had stopped running. The significance of these two groupings are discussed below and are represented in Tables 5.9 and 5.10 respectively.

5.3.2 Questionnaire

5.3.2. Questionnaire Development

A questionnaire (Appendix 1) was developed and comprised of eight sections; 1) Personal details i.e. name address age and telephone number; 2) Educational status, 3) Occupation category (professional, artisan, student, clerical, retired, unskilled, or unemployed), 4) Anthropometric data, i.e. height and weight, 5) Past medical, surgical and orthopaedic histories, including hospitalisation, current medication and history of intra-articular corticosteroid injections, 6) Histories of past and present running for the calculation of running volume, 7) Past and present participation in other sports, the time participated in that sport and whether any injuries had been incurred, 8) Physical occupational activities (walking, standing, carrying, and climbing stairs), and 9) Symptoms indicative of osteoarthritis in joints, namely pain, swelling and/or stiffness of the hip, knee, and ankle joints.

5.3.2.2 Questionnaire validation (Appendix 2)

Prior to the questionnaire being sent, it was validated by assessing 29 questionnaires which had been sent to patients with known OA and controls without 0A. The diagnosis of OA was made by a family practitioner or an orthopaedic surgeon using: 1) clinical criteria (pain and/or stiffness and/or swelling in the hip and/or knee joints (Altman et al 1986), 2) radiological criteria (joint space narrowing osteophytes and subchondral cysts (Altman et al 1986), and 3) arthroscopic criteria (Blackburn et al 1994). The clinical criteria in the questionnaire were validated against either radiological or arthroscopic criteria as the gold standard to diagnose OA. The sensitivity of the questionnaire to diagnose OA was calculated as 92% and its specificity as 71%.

5.3.2.3. Questionnaire administration

In order to improve the return rate of the questionnaires, two mailings were sent out, each about a month apart (Table 5.3). Incentive prizes were offered to a candidate from each group who returned questionnaires. Ten non-responders from each group were also contacted telephonically and asked to give their reasons for not replying to the questionnaire. The reasons given were that the questionnaire was either not received (old address list) or that it was not considered necessary to fill in the questionnaire. This applied particularly in the control group where it was interpreted that the questionnaire only applied to individuals who participated in running. The third reason was disinterest in the study. The subjects were questioned telephonically about their running history and symptoms of pain, stiffness and swelling. None of them indicated that they had the clinical criteria to diagnose OA.

5.3.3 Analysis of results

Information about the ages (years), heights (cm) and weights (kg) of runners and controls were obtained from the questionnaire. The age of each respondent was rounded to the nearest year at the time of completing the questionnaire. The heights of the participants

were reported to the nearest centimetre and weights were reported to the first decimal in kg.

The occupations of respondents, as indicated on the questionnaire, were divided into seven groups. These groups were: professional, artisan, student, clerical, retired, unskilled, and unemployed. The highest education level attained was divided into the following groups: primary school, high school, technikon, university, and other.

The medical history of the respondents consisted of four main entities: 1) Hospital admission and the reason (medical, surgical or orthopaedic) for being admitted, 2) Use of long-term medication, in the form of non-steroidal anti-inflammatory drugs, analgesics or other forms of medication, and 3) A history of oral systemic steroids use, or intra-articular injections of steroids, including the name of the joint that was injected.

The running history of the sub-categories of runners was expressed by comparing the number of hours per week, months per year and the total number of running years. The number of marathons and ultra-distance marathons in which the respondents participated were also compared. Sub-categories of respondents that were currently running or had stopped running were reported. The reasons for having stopped running were reported. The reasons included: i) injures, ii) changed sport, iii) stopped because of medical reasons, or iv) boredom.

The number of respondents who were currently participating and having previously participated in other sports were compared between groups. Injuries of the weight-bearing joints (viz. hip, knee, or ankle) while participating in other sports activities was also reported. These values were expressed as frequencies of injuries (%) in different groups.

The physical activity while carrying out their profession was compared in the runner and control groups. The activities were expressed as hours per day for: i) walking, ii) standing, iii) carrying heavy objects, and iv) climbing stairs (expressed as flights per day).

The prevalence of (i.e. percentage of subjects with) joint pain, and/or swelling and/or stiffness in the different weight-bearing joints of the respondents was compared. In this initial analysis, no adjustment for age and previous injuries were made. The prevalence of symptoms in weight-bearing joints and non-weight-bearing joints among the respondents of the groups was also compared. The wrist and fingers were included in the study to account for the effect of aging on joints. The shoulder and elbow joints were not analysed as OA of these joints is unusual unless there is a history of occupational or accidental trauma (Chandnani and Resnick 1992). It was thus considered not to be relevant to include these joints in a study of this nature. Moreover, not being weight bearing joints thereby not being affected to impact loading as in ultra-distance marathon running was another reason for not including them in the study.

Finally, the odds ratio for the risk of developing pain and/or swelling and/or stiffness, of weight-bearing and non-weight-bearing joints, adjusting for age and previous injuries, was compared between groups.

5.3.3.1 Statistical Analysis

Statistical analysis of all data was performed by the Biostatistics Division of the Medical Research Council of South Africa.

5.3.3.1.1 Analysis of Individual Weight-bearing Joints

An analysis of OA of individual weight-bearing joints of the respondents was performed using generalised estimating equations (GEE) (Laing et al 1986). The probability of the presence of OA in an individual joint was modelled on the following subject co-variables;

1) log (running volume) categorised into three groups as described,
2) age
3) previous injuries due to other sports, and

4) the co-variant type of joint (ankle, hip, and knee) at the joint level. (Table 5.4)

The estimation of the odds ratio for running volume was performed with the control group (non-runners) as the reference category.

Table 5.4 Analysis of GEE Parameter Estimates

Empirical Standard Error Estimates

Parameter	Estimate	Empirical Standard Error	95% Confidence Limits			
			Lower	Upper	Z	Pr>|Z|
Intercept	-5.9314	1.2414	-8.3644	-3.4984	-4.788	0.0000
Low Run Volume	1.1672	0.5930	0.0049	2.3294	1.9683	0.0490
Medium Run Volume	0.5293	0.5300	-0.5094	1.5681	0.9988	0.3179
High Run Volume	0.1166	0.5105	-0.8841	1.1172	0.2283	0.8194
L Knee	1.4021	0.5203	0.3824	2.4218	2.6950	0.0070
R Knee	-1.4086	1.1328	-3.6288	0.8116	-1.243	0.2137
L Ankle	0.5813	0.5877	-.05705	1.7332	0.9892	0.3226
R Ankle	-0.0000	0.6304	-1.2355	1.2355	-0.0000	1.0000
L Hip	0.5813	0.5877	-0.5705	1.7322	0.9892	0.3226
R Hip	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Age	0.0262	0.0135	-0.0003	0.0527	1.9369	0.0528
Sportoth*	0.3387	0.8796	-1.3853	2.0627	0.3850	0.7002
Scale	0.9539	-	-	-	-	-

Sportoth* Injuries caused by other sports

The method of GEE takes account of the dependency of joints within a subject and allows the

inclusion of variables from the subject and joint level into the regression model. An exchangeable correlation structure was used in the model.

5.3.3.1.2 Other Statistical Tests

Categorical data were analysed using the Chi-square tests or Fisher' exact test. For continuous variables, a one-way analysis of variance was done. As an alternative, the Krushat-Wallis test which is a rank basal anova was performed.

5.4 Results

The physical characteristics of the three running groups and non-running control group are presented in Table 5.5. There were significant differences in the mean ages in the groups. The mean age of the control group was significantly higher than that of the three running groups. The mean height and weight also varied significantly. The mean height and weight of the medium volume group was significantly higher than that of the other groups.

Table 5.5 Physical characteristics of the runner and control groups.

Values are mean and (SD).

Category	**Controls (n=60)**	**Low Volume Runners (n=43)**	**Medium Volume Runners (n=43)**	**High Volume Runners (n=44)**	**P value**
Age (years)	59 (17) *	39 (15)	46 (13)	52 (12)	0.0001
Height (cm)	177 (8)	179 (15)	181 (6) *	176 (7.2)	0.008
Weight (kg)	77.7 (10.3)	78.5 (9.2)	80.4 (10.6) *	72.3 (11)	0.003
BMI (kg/m^2)	24.9 (3.2)	24.4 (2.9)	24.6 (2.7)	23.4 (2.9)*	0.033

* Indicates a significant difference between groups

There was a significant difference in BMI between the controls and the high volume running

group. However, when adjusted for age, there was no significant difference between all groups (p= 0.069).

The occupational and educational categories of the respondents are represented in Table 5.6. The frequency of retired people was significantly greater in the control group than in the other groups. University graduates represented the most frequent level of education in all the groups. There was no significant difference in the educational status between any of the groups (p = 0.55).

Table 5.6 Occupational and educational categories of the runner and control groups.

Values are expressed as percentages (%) in the groups.

Category	Sub-category	Controls (n=53)#	Low Volume Runners (n=43)	Medium Volume Runners (n=43)	High Volume Runners (n=44)
Occupation	Professional	32.1	44.2	39.5	56.3*
	Artisan	0.0	2.3	2.3	4.6
	Student	3.8	18.6*	7.0	0.0
	Clerk	11.3	18.6	32.6*	20.5
	Retired	50.1*	11.6	18.6	22.7
	Unskilled	0.0	2.3	0.0	0.0
	Unemployed	0.0	2.3	0.0	0.0
Highest level education	Primary	1.9	0.0	2.3	0.0
	High school	24.5	20.9	23.3	29.6
	Technikon	9.4	209	20.9	20.5
	University	60.4	58.1	53.5	50.0
	Other	3.8	0.0	0.0	0.0

* Significant differences between groups.

\# Seven subjects did not respond to this question.

The medical history of the respondents is summarised in Table 5.7. A significantly greater percentage of control subjects had a history of admission to hospital for medical reasons. However, of the high volume group, a greater percentage was admitted for orthopaedic conditions. Significantly, more control subjects were on long term medication. Of this, NSAIDS represented the medication that was used more frequently.

Table 5.7 The medical history of the runner and control groups.

Values are expressed as percentages (%) in the groups.

Category	Sub-category	Controls (n=60)	Low Volume Runners (n=43)	Medium Volume Runners (n=43)	High Volume Runners (n=44)
Hospital admissions	Total	88.0	81.0	73.9	79.1
	Medical	20.0*	5.9	6.5	14.7
	Surgical	77.3	70.5	67.7	70.5
	Orthopaedic	31.8	38.2	45.1	38.2
Long term medication		42.3*	18.6	18.6	20.5
Type of medication	NSAIDS	17.4	14.3	25.0	33.3*
	Analgesics	4.4	14.3	0.0	0.0
	Other	78.3	71.4	75.0	66.7

* indicates a significant difference between groups ($p < 0.05$).

The past history of corticosteroid usage is indicated in Table 5.8. The frequency of corticosteroid ingestion was low in all groups. A total of 34 subjects had a history of corticosteroid injections into their joints. Of these, one non-runner, one low-volume runner, one medium-volume runner, and two high-volume runners had corticosteroid injections in their right knees. Three medium-volume runners received corticosteroid injections into their

right and left hip joints.

Table 5.8 The history of corticosteroid usage.

Values expressed as percentages (%), and n indicates the number of respondents

Past history of cortico-steroid usage	**Controls (n=60)**	**Low-Volume Runners (n=43)**	**Medium-Volume Runners (n=43)**	**High-Volume Runners (n=44)**
Ingested	4.2	9.5	7.0	0.0
Injected	11.5	18.6	26.2	20.5
Injected into knee joint	N=1	n=1	n=1	n=2
Injected into hip joint	N=0	n=0	n=3	n=0
Injected into other joint	N=4	n=7	n=7	n=7

The numbers were too small for statistical analysis.

The running history of the current and past runners is depicted in Tables 5.9 and 5.10 respectively. Two groups of runners are represented i.e. those runners who were currently running (at the time of the study), and those who had stopped running.

Table 5.9 The running history of current runners.

Values are expressed as mean and (SD).

Running variable	Low Volume Runners n=21	Medium Volume Runners n=36	High Volume Runners n=37	p Value
Hours/week	3.4 (2.0)	4.1 (1.7)	8.6 (9.5)*	0.0001
Months/year	8.0 (3.6)	10.6 (2.1)	11.3 (1.3)	0.0004
Years	6.1 (4.0)	13.1 (6.8)	19.8 (10.6)*	0.0001
Marathons #	3.6 (4.7)	17.2 (16.8)	32.4 (30.1)*	0.0001
Ultra-Marathons #	1.9 (3.5)	8.2 (8.5)	13.2 (12.7)*	0.0001

# indicates the number of events participated

* indicates a significant difference between groups

Table 5.10 Running history of past runners.

Values are expressed as mean and (SD).

Running variable	Low Volume Runners n=22	Medium Volume Runners n=7	High Volume Runners n=7	p Value
Hours/week	2.3 (1.5)	5.3 (2.1)	13.5 (18.6)*	0.0001
Months/year	6.3 (3.7)*	10.4 (2.5)	9.1 (2.5)	0.0127
Years	6.6 (6.0)	11.5 (6.7)	22.4 (8.6)*	0.0007
No. Of Marathons #	0.5 (1.7)*	3.3 (3.2)	2.3 (5.6)	0.0227
No. of ultra-marathons #	0.1 (0.5)	1.0 (2.5)	2.0 (5.7)	0.53

# indicates the number of events participated

* indicates a significant difference between groups

The reasons why runners stopped running are depicted in Table 5.11. The most common reason for stopping running in all groups was due to injury.

Table 5.11 The reasons for stopping running as given by the past runners

Values expressed as percentages (%) in the groups.

(Total n = 37)	Low Volume Runners (n=22)	Medium Volume Runners (n=8)	High Volume Runners (n=7)
Injury	31.8	50.0	57.1
Change in sport	18.2	12.5	14.3
Medical reasons	13.6	12.5	14.3
Bored	22.7	25.0	0

The sample numbers (n) represented in this table were too small to calculate a p value.

The frequency with which runners participated in sports other than running, and which joints relevant to this study were injured while participating in these sports is depicted in Tables 5.12 and 5.13. A significant greater number of injuries to weight-bearing joints occurred in the high-running-volume group.

Table 5.12 Respondents participants in sports other than running

Values are expressed as percentages (%).

Controls (n=60)	Low Volume Runners (n=43)	Medium Volume Runners (n=43)	High Volume Runners (n=44)
78.3	88.4	88.4	77.3

Table 5.13 The history of injury to joints in respondents while participating in sports other than running.

Values are expressed as percentages (%) in all groups.

Joints	Controls n=47	Low Volume Runners n=38	Medium Volume Runners n=38	High Volume Runners n=34	p value
All weight-bearing joints	17.0	21.0	39.5	41.2*	0.003
Ankle joint	8.5	2.6	5.3	2.9	0.42
Knee joint	8.5	15.8	26.3	29.4*	0.007
Hip joint	2.1	2.6	5.3	0.0	0.9
Non-weight-bearing joints	19.2	47.4	52.6*	44.1	0.01

* indicates significant differences in the frequency of injury between groups.

Occupational physical activity involved for categories (walking, standing, carrying,) expressed as hours per day and climbing stairs expressed as flights per day is depicted in

Table 5.14. There were no significant differences in the hours spent in different categories of occupational physical activity between the groups.

Table 5.14 The history of occupational physical activity in different categories.

Values expressed as mean and (SD) in all groups. n indicates the number of respondents.

Physical activity	Non-Runners (n=60)	Low Volume Runners (n=43)	Medium Volume Runners (n=43)	High Volume Runners (n=44)
Walking (hours./day)	n=34 1.64 (2.3)	n=37 1.2 (1.3)	n=38 1.0 (1.2)	n=39 1.9 (3.2)
Standing (hours/day)	n=31 1.83 (2.4)	n=33 1.4 (1.8)	n=38 1.0 (1.5)	n=38 1.9 (3.0)
Carrying (hours./day)	n=31 0.1 (0.3)	n=34 0.1 (0.4)	n=37 0.2 (1.0)	n=37 0.3 (0.8)
Climbing stairs (flights/day)	n=33 3.75 (6.7)	n=36 3.7 (8.9)	n=37 1.8 (4.0)	n=39 1.7 (5.2)

n = the number of participants still active in their profession. No significant differences between groups

The prevalence (expressed as a percentage) of subjects with OA in the weight-bearing and non-weight-bearing joints is depicted in Table 5.15. There were no significant differences.

There was a tendency for the prevalence of OA of the ankle joint to be higher in the low-volume running group compared with the other groups.

Table 5.15 The prevalence of OA (joint pain, swelling, or stiffness in the joints) in non- runners and the three runner groups (not adjusted for age and previous injuries to weight-bearing joints).

Values are percentages (%) in the groups.

Type of joint	Joints	Non-runners (n=60)	Low Volume Runners (n=43)	Medium Volume Runners (n=43)	High Volume Runners (n=44)	p value
Weight-bearing	All	15.0	18.6	18.6	15.9	0.95
	Ankle	0.0	7.0*	0.0	2.3	0.07
	Knee	6.7	16.3	16.3	11.4	0.38
	Hip	10.0	2.3	4.7	2.3	0.23
Non-weight-bearing	All	0.0	4.7	0.0	6.8*	0.07
	Wrist	0.0	2.3	0.0	2.3	0.57
	Fingers	0.0	4.7	0.0	4.6	0.17

* $p < 0.1$ indicates a trend towards significance.

The odds ratio for the risk of developing OA (pain and/or stiffness and/or swelling) in the control and the three running groups, adjusted for age and previous injuries, is depicted in Table 5.16. This is graphically represented in Figure 5.1.

Table 5.16 The odds ratio with 95% confidence intervals of OA occurring in the weight-bearing joints in the running groups (adjusted for age, and previous injury to weight-bearing joints).

Group	Odds Ratio	95% Confidence intervals
Low Volume	3.2*	1.01 - 10.27
Medium Volume	1.7	0.60 - 4.80
High Volume	1.1	0.41 - 3.06
Controls	1.0	reference group

* indicates significant difference between the low volume group and the other groups.

There was a significantly higher odds ratio of developing OA in the weight-bearing joints in the low-volume running group compared with the other groups. The high-volume running group had a similar odds ratio of developing OA in the weight-bearing joints as in the control group.

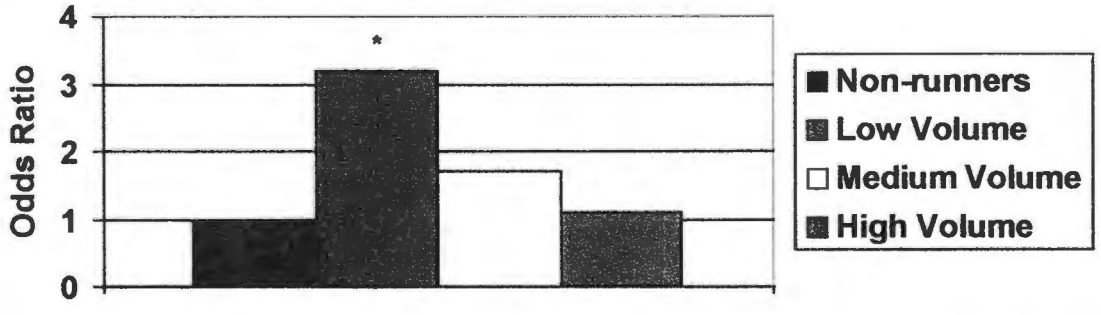


Fig 5.1 The Odds Ratio for risk of pain, swelling, or stiffness in weight-bearing joints in the four groups (adjusted for age, and previous injury to weight bearing joints) (*: p=0.049)

5.5 Discussion

OA is a complex disease which is difficult to define and has many factors that influence its aetiology and pathogenesis. It is considered to be a pathological entity with many inter-related factors influencing its pathogenesis. Among the factors influencing the pathogenesis of OA are impact loading on articular cartilage, such as in distance running and other sports, and the aging process. Moreover, OA has important economic costs, particularly due to loss of work.

This was an epidemiological study, subjective symptoms of pain, stiffness, swelling were used to diagnose OA (Lawrence et al 1989). Although subjective symptoms are not precise, pain, swelling and stiffness are very specific symptoms that a patient can recognise. Care was also taken to test the sensitivity and specificity of the criteria prior to commencing the study. The use of objective clinical criteria using x rays and MRI would have improved the sensitivity and specificity of the diagnosis of OA but this would have resulted in a significantly enlarged study.

This study was designed to compare the prevalence of OA in non-runners to ultra-distance runners. A specific questionnaire was designed to identify individuals who suffer from pain and/ or swelling and/ or stiffness in the weight-bearing (hip, knee, and ankle) joints and non-weight-bearing joints. In the pilot study, this questionnaire was validated and a sensitivity of 92% with a specificity of 71% was calculated. The sensitivity of this questionnaire was similar to the sensitivity of other clinical and radiological methods of identifying OA (Altman et al 1986).

A population of ultra-distance runners was selected for the study to ensure that runners would be those with high running volumes rather than moderate running volumes. In order to determine whether a risk factor (in this case, ultra-distance marathon running) is related to the development of OA, a control group of non-runners was compared with the group of ultra-

distance runners. The control group was selected from the alumni of a school. This control group was included to control for confounding variables such as aging and previous injuries. A problem with such a study is that it is difficult to match the groups due to the difference in the response rates to the questionnaire of the various age groups. This resulted in some bias in the study. It was not anticipated that in the original control group a number of the participants would be regular runners. The running volume of these participants plus the respondents in the original ultra-distance running group was calculated. This running group was then divided into low, medium and high volume running groups. They could then be compared with a group of respondents who had never participated in regular running. The sampling of runners and controls was administered by dividing the groups according to age to ensure that the runners had been running for many years, and that the effect of aging on a joint could be taken into account. Due to the nature of the population that was available for the study, only males and Caucasians were included in the samples (controls and runners). This is a limitation of the study as these data cannot necessarily be extrapolated to female runners and runners of other ethnic groups.

Repeated questionnaires ensured a high response rate of 59% in the runner group and 56% in the control group. This response rate is very high when compared to the response rates to questionnaire studies in general (Lane et al 1986). Non-responders from the runner and control groups were contacted in an attempt to identify any differences between responders and non-responders. Only ten participants could be contacted telephonically. When questioned as whether they had the subjective criteria of OA as defined in this dissertation, there was no difference between the running and control groups.The numbers were too small for statistical analysis.

The mean age of the control group was significantly higher than that of the runner groups. This is a result of a higher response rate in the older age categories of the control group as well as the fact that there were fewer runners that could be selected from the older runners. There were only three runners in the original population that were aged between 70-79 years of age. It was therefore important to calculate the odds ratio for OA in the different groups using age-adjusted data.

The mean weight of the runners in the medium-volume running group was significantly higher than in the other groups. Body weight has been related to the development of OA (Felson 1995) and this might be a factor in the higher risk of OA that was identified in the medium-volume running group. The high-volume running group had the lowest body weight, and this could be attributed to their excercise training programme and associated increased energy expenditure. This study was not designed to undertake an anthropomorphic examination of the participants. The BMI status of the participants was thus calculated. The BMI was less than 25 in all groups. This means that none of the participants were overweight. Thus, even when correcting for age, the differences in BMI could not have influenced the odds ratio for the risk of developing OA in the respondents.

It is interesting to note that that the high-volume running group had the highest frequency of professionals compared with other groups. Significantly, the higher frequencies of clerical workers in the medium-volume running group and the higher frequency of retired males in the control group are interesting observations but probably coincidental and may relate to the pattern of responses to the questionnaire in the different groups.

Although there were no significant differences in the frequency of hospital admissions (total, medical, surgical, and orthopaedic) in any of the groups, the control group had a significantly higher frequency of the use of long term medication (42%). This would be in keeping with the general observation that regular physical activity is associated with a lower incidence of chronic disease such as hypertention, diabetes mellitus, coronary heart disease and osteoporosis (Booth et al 1995).

It is important to note that the frequency of NSAID, analgesic, and corticosteroid (injected and oral) was not significantly different between all groups. However, the moderate-volume running group had a greater frequency of corticosteroid use particularly in the injected form, compared to controls. There was a higher prevalence of NSAID use in the high-volume running group. Although speculative, this was probably due to the higher incidence of running-related overuse injuries. However, other joint or soft tissue pathologies were not

accounted for by the questionnaire. This is a limitation of the study. The number of subjects was too small to analyse the relationship between corticosteroid use (injected or ingested) and the risk of OA. However, an analysis of the data depicted in Table 5.7 shows no obvious difference in the type of joint injected with corticosteroid in the running and control groups.

Running volume was considered to be a more sensitive indicator on the amount of impact loading that occurred on the weight-bearing joints because it represented the total number of times the joint surfaces were exposed to impact loading while running. The running group was divided into the three equal groups as described earlier. Of the high-volume group, 72.7% of participants competed in ultra-distance events compared with 65.1% in the medium-volume group and 25.6% in the low-volume group.

An important aspect of this study was comparing the number of runners who were currently running to those who have stopped running. Fifty percent of low-volume runners had stopped running, compared to 20% in medium-and high-volume groups. Of the 36 runners who had stopped running, 22 were low-volume runners. These runners only participated in three ultra-marathon events, compared to the current runners who participated in an average of 22 ultra-marathon events. Significantly, more runners had stopped running because of injuries, particularly in the low-volume group. These injuries were not specified and this is a limitation of this study as certain mechanisms of injury may predispose to the development of OA. However, when analysing the responses to these questions, the numbers were too small for statistical analysis. It was thus thought to be more relevant to combine these injuries in one group. The reason for doing this was that the odds ratio for risk of OA (as defined) in weight-bearing joints adjusting for age and previous injuries (irrespective of the nature or mechanism thereof) was analysed. Certain injuries may not predispose to OA. However, it was thought that in the final analysis, knowing the nature of these injuries would not influence the final observation of this dissertation.

Participation in sports other than running may be associated with an increased risk of development of OA. In this study, the frequency of sports participation, other than running, in all groups was similar. However, the frequency of injuries sustained while participating in sports other than running was higher for all weight-bearing and non-weight-bearing joints, particularly in the high-volume running group. The knee joint had a significantly greater frequency of injuries. Numerous studies have shown that there is a relationship between the risk of OA of the hip and knees (and ankles) and participation in other sports, particularly soccer (Kujala et al 1995).

The amount of occupational physical activity can also influence the risk of the development of OA (Felson et al 1998). In this study, there was no significant difference in occupational physical activity between the groups. Specifically, respondents in all groups documented similar hours per day walking, standing, and carrying heavy objects, and similar numbers of flights of stairs climbed per day. The activity not taken into account in this study was bending, which has presently been shown to be a factor in the development of OA in the knee joint (Olivieria et al 1995). This is another potential limitation of this study.

The main focus of this study relates to the prevalence of OA in different weight-bearing joints and non-weight-bearing joints in the controls and the groups of runners. The prevalence of OA in all weight-bearing joints was similar in all groups. The knee joint had the highest frequency, particularly in the low- and medium-volume running groups. The questionnaire did not differentiate which joint in the knee was symptomatic as this would involve a clinical examination. Of the weight-bearing joints, the ankle was least affected. It is well known that an ankle joint that has not been previously injured has a low risk of developing OA compared to the hip and knee joints (Huch et al 1997). This is because it is a uniaxial joint which has relatively thick articular cartilage and is adapted to withstanding high impact loads. The tibio-femoral joint has a gliding action with flexion and extension and has a rotating element in it. This makes it more vulnerable to rotational injuries. The hip is a relatively stable joint compared to the knee and it is surrounded by muscles that are adapted to maintain the erect

position of humans. This results in a greater shock absorbing property of the soft tissues, thereby relatively protecting the hip from impact injuries compared to the knee.

The most important finding of this study was that the odds ratio for developing OA in the weight-bearing joints, adjusted for age and previous injuries while participating in other sports, was highest in the low-volume running group. The high-volume group had an odds ratio for developing OA which is similar to that of the non-runners. Moreover, the risk of developing these symptoms decreased linearly from the low-volume group to the high-volume group. The reasons for this finding is speculative but may be related to self selection possibly on a genetic basis of the high-volume running group. However, a genetic study would be difficult to undertake,as families or specific communities would have to studied, particularly taking into account confounding factors that predispose to OA.

The weight bearing joints of the low volume group were exposed to less impact loading than the high volume group. Moreover, the low volume running group had the highest odds ratio to develop OA (as defined) compared to the non-running, medium volume and high volume running groups. The explanation is speculative as this study did not analyse objective clinical criteria for OA. These criteria would have to include a detailed biomechanical and radiological examination of the lower limbs together with a MRI of the knee joints.

Articular cartilage,bone and the soft tissues (muscles,ligaments and tendons) adapt their structures according to the loads placed on them. It could be argued that the greater amount of impact loading in the high volume group could result in a greater strengthening of the soft tissue joint structures than those of the low volume group.This resultants in an increase in the shock absorbing properties of the soft tissues of the high volume group compared to the low volume group. This could result in a more stable joint thereby protecting the joint from developing OA. There is, in fact, a paradigm shift developing as to the initiating factors in OA (Dieppe1999). This is based on a study indicating that quadriceps muscle weakness may precede the development of knee OA (Slemenda et al 1997). It could be hypothesised that the low volume group may not be as well adapted to withstand the impact loading involved in running as the high volume group. The risk of the low volume group developing OA in the

weight bearing joints could thus be increased. The control group was not exposed to significant impact loading compared to the other groups. Although the soft tissues in this group might be weaker (thereby resulting in relatively unstable knee and ankle joints) than the running groups, the relative lack of impact loading on their weight bearing joints could delay the development of OA. Thus impact loading in maladapted joints to exercise could be a risk factor in the development of OA.

The results of this dissertation may stimulate the undertaking of longitudinal study of a cohort of athletes who participate in ultra-distance marathon running. A questionnaire would have to be sent to a cohort of athletes and age matched controls who would be non-runners. A random group of participants would be selected to undergo a detailed clinical biomechanicl and radiological of the lower limbs and a MRI examination of the knee joint (being the most likely weight bearing joint to develop OA). These groups would have to be followed at two to three yearly intervals.

This study will compliment the longitudinal study relating marathon running and OA (Lane et al 1998).

5.6 Summary and Conclusions

A case control study was designed to compare the prevalence of OA in a non-running group and in three groups of runners. The number of subjects was small compared with other studies. More controls responded which might have added some selection bias in the sample. Particularly, there were no matched runners to controls in the oldest group (n=22) which, as discussed, would be prone to develop OA on an age basis. The mechanism of the injuries incurred due to other sports was not accounted for. Other variables that were not accounted for were ethnicity, gender, and genetic factors. However, it is uncertain that this would influence the result of this study.

This study confirms the results of previous studies which showed that distance running does not predispose to the development of OA in weight-bearing joints. It is the first study that

analyses the effect of high running volumes as a factor in the development of OA. However, it is important that a longitudinal study of ultra-distance marathon runners be undertaken to relate the development of OA with objective signs of OA to distance running.

Ultra-marathon distance running is a popular sport and thus it is important to eliminate it as a predisposing factor to the development of early OA of the weight-bearing joints.

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APPENDIX 1

THE QUESTIONNAIRE

APPENDIX 1

HEALTH QUESTIONNAIRE I:

MRC/UCT Bioenergetics of Exercise Research Unit

Department of Physiology

University of Cape Town Medical School

HEALTH QUESTIONNAIRE:

SECTION A

1. PERSONAL DETAILS

1.1 Name: _____ 1.2 Age: _____

1.3 Address: _____ 1.4 Sex: _____

_____ 1.5 Code: _____

1.6 Tel No: (w) _____ (h) _____

2. EDUCATION:

2.1 What is your highest level of education (Please tick)

Primary School__ High School __ Technikon __ University __

Other (specify) _____

3. PRESENT OCCUPATION:

3.1 What is your present occupation? _____

3.2 If you are retired what was the date

of your retirement? _____

4. ANTHROPOMETRY:

4.1 What is your present a) height (cm) _____b) Weight (kg)___

4.2 Over last 20 years has your weight (place tick)

a) Remained the same _____

b) Increased? _____ How much change (kg) _____

c) Decreased? _____ How much change (kg) _____

5. PAST MEDICAL HISTORY: Yes No

5.1 Have you ever been in hospital

in your life? ____ ___

If yes, please state date (year) and the reason:

Date	Reason
_____	_____
_____	_____
_____	_____
_____	_____

5.2 Are you on any long term medication? Yes ____ No ____

If yes, please specify, the reason: _____

date started: _____

type: _____

dose: _____

5.3 Have you ever taken cortisone tablets? Yes ____ No ____

If yes, please specify, the reason: _____

Total number of months used: _____

type: _____

dose: _____

Have you ever had cortisone injections in any of your joints?

If yes, please complete the table

Joint	Side (Right or Left)	Age	N^{o} of injections
_____	_____	_____	_____
_____	_____	_____	_____

6. RUNNING HISTORY:

6.1 Are you currently

a) Running to keep fit (section 6.2) Yes __ No __

b) A competitive runner (section 6.2) Yes __ No __

c) Not running (section 6.3) Yes __ No __

Please complete the appropriate section 6.2 or 6.3

6.2 If you are running currently:

a) How many years have you been running? _____ years

b) How many hours do you run per week? _____ hours

c) How many months do you run per year? _____ months

d) How many marathons (42 km) have you run in your life? _____

e) How many ultra-distance (> 42 km) marathons have you run in your life? _____

6.3 If you are not currently running have you ever

run in the past to - keep fit Yes ____ No ____

- compete Yes ____ No ____

If you answered yes to either of these two questions then complete the rest of question 6.3

a. When did you stop running? (please give your age) _____

b. Why did you stop? (please tick)

due to injury _____

change of sports _____

bored with running _____

medical illness _____

other _____

c. Please complete the following section concerning your running habits before you stopped.

- For how many years were you running? _____ years
- For how many hours were you running per week? _____ hours
- For how many months did you run per year? _____ months
- How many marathons (42 km) have you run in total? _____
- How many ultra-distance marathons (> 42 km) have you run in total? _____

7. OTHER SPORTS HISTORY:

7.1 If you **currently** participate in any other sport besides running please complete the table:

Sport	Years of participation	Months per year	Hours per week
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

7.2 If you have ever injured yourself while playing these sports (question 7.1) please complete the table.

Age of injury	Type of injury (Sprain, fracture, bruise, dis-location, other)	Site of injury (side and body part)	Hospital treatment or Plaster cast
_____	_____	_____	Yes __ No __
_____	_____	_____	Yes __ No __
_____	_____	_____	Yes __ No __

7.3 If you have **participated** in any other sport **in the past**

please complete the following table:

Sport	Years of partici- pation	/ year	Months / week	Hours	Date stopping	Reason for
_____	_____		_____		_____	_____
_____	_____		_____		_____	_____
_____	_____		_____		_____	_____

7.4 If you have ever injured yourself while playing these

sports (question 7.3) please complete the table.

Age of injury	Type of injury (Sprain, fracture, bruise, dis- location, other)	Site of injury (side and body part)	Hospital treatment or Plaster cast
_____	_____	_____	Yes __ No __
_____	_____	_____	Yes __ No __
_____	_____	_____	Yes __ No __

8. OCCUPATIONAL ACTIVITY:

8.1 Does your occupation involve any of the following?

Please indicate the number of hours that you spend per day doing these activities.

- Walking _____ hours/day
- Standing _____ hours/day
- Carrying heavy objects _____ hours/day
- Climbing stairs _____ flights/day

9. OSTEOARTHRITIS

a) Do you suffer from pain, stiffness or swelling in any of the following joints? (Please tick).

Joint	Pain	Swelling	Stiffness
Right knee	_____	____	_____
Left knee	_____	____	_____
Right hip			
Left hip			
Right wrist			
Left wrist			
R/H fingers			
L/H fingers			
Right ankle			
Left ankle			

APPENDIX 2

VALIDATION OF THE QUESTIONNAIRE

APPENDIX 2

VALIDATION OF QUESTIONNAIRE

	Clinical and Radiological Diagnosis of OA		
Questionnaire	OA Present	OA Absent	Number
OA Present	11 (a)	5 (b)	16
OA Absent	1 (c)	12 (d)	13
Number	12	17	29

Sensitivity; = $\frac{a}{a+c} = \frac{11}{12} = 91.7\ \%$

Specificity; = $\frac{d}{b+d} = \frac{12}{17} = 70.6\ \%$