A REVIEW OF THE DIFFERENCES BETWEEN NORMAL AND OSTEOARTHRITIS ARTICULAR CARTILAGE IN HUMAN KNEE AND ANKLE JOINTS.

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ABSTRACT

Background

Osteoarthritis (OA) is the most common joint disease yet its pathophysiology is still poorly understood. It is more prevalent in some lower limb joints than others; in particular the knee is more commonly affected than the ankle. Research into articular cartilage and OA has primarily focussed on using animal models. However, it is apparent that articular cartilage differs between species, so more research is concentrating on human cartilage.

Objective

This paper reviews recent studies that have been undertaken to elucidate the reasons for this, and to discover if the findings would alter the conception that articular cartilage is not capable of repair.

Method

Primary research papers into human knee and ankle cartilage published since 1997 have been reviewed.

Results

Differences in the structure, metabolism, physical properties and response to trauma have been found, implying that ankle cartilage may be more resistant to damage.

Conclusions

More research is needed before definitive conclusions can be reached, but the findings so far suggest that OA should not be accepted as the inevitable outcome of joint injury and individuals and practitioners, such as podiatrists, may be able to use simple measures to prevent or delay its onset.

Keywords
Ankle; Articular cartilage; Knee; Osteoarthritis

BACKGROUND

Articular cartilage is no longer considered to be an inert tissue that is inevitably damaged as a result of wear and tear or of aging. Instead it is proving to be a unique, dynamic, specialised tissue. [1] In 1997, an alternative view was beginning to emerge that articular cartilage was capable of restoring and remodelling itself, implying that treatment for degeneration of the cartilage was not confined to removal of the cartilage, but that there were possibilities for maintaining or restoring the joint surface. [1]

The structure of articular cartilage not only differs between species and individuals within that species, but also between joints within that individual. [2; 3] Coupled with the fact that idiopathic OA rarely occurs in some joints such as the ankle, these inter-joint variations may provide some insight into the pathogenesis and progression of OA. [4]

Most of such research published has been carried out by one team in the USA – the Rush Department of Biochemistry, Rush University, Chicago. [5] They have focused on comparing ankle and knee cartilage from human cadavers and identified distinct differences in composition and metabolism. They conclude that anatomical and biomechanical differences alone do not explain why the knee joint is more susceptible to OA than the ankle joint and suggest that there are numerous subtle differences between the cartilage and bone from the two joints that may protect the ankle cartilage from progressive degeneration. [6]

This review aims to highlight differences that have been found between ankle and knee articular cartilage and their significance to the development of OA within these joints in the few studies that have been carried out on *human* articular cartilage since 1997.

METHOD

The number of suitable papers available for review was likely to be limited mainly because the study of the *human* ankle and knee is relatively new, the availability of suitable donors for research is limited, and the topic is a restricted area of interest. It was anticipated that relevant literature might be elusive.

The following method was used to search the literature:

- Search terms used: ankle, knee, cartilage, osteoarthritis – singly and in combination. These broad terms were chosen as it was anticipated that relevant literature may be hard to locate.
- Post 1997. Huch, Kuettner and Dieppe [4] had published a comprehensive paper on this subject in 1997.
- Electronic databases searched: Medline, AMED, Web of Knowledge, Zetoc, Biomed Central, Infotrac, Swetswise, Science Direct, Pubmed Central, Highwire, Google Scholar.
- Hand-searched journals: American Journal of Physiology, Annals of Rheumatic Diseases, Arthritis Research and Therapy, BMC Cell Biology, British Journal of Podiatry, Canadian Medical Association Journal, Foot and Ankle International, Journal of American Podiatric Medical Association, Journal of Bone and Joint Surgery (US and UK), Journal of Biomedical Discovery and Collaboration, Journal of Foot and Ankle Surgery, Journal of Histochemistry and Cytochemistry, Journal of Orthopaedic Surgery and

Research, Molecular and Cell Biology, Molecular Biology of the Cell, Osteoarthritis and Cartilage, Rheumatology, The Foot.

- Papers studying only the ankle or knee cartilage were included to support evidence from the studies comparing the cartilage from the two joints.

REVIEW OF THE DIFFERENCES

Articular cartilage and osteoarthritis

In order to appreciate the differences between knee and ankle articular cartilage, it is important to understand the general concepts of its properties and its involvement in OA.

The structure and arrangement of the cartilage components enables it to resist deformation under stress, be resilient and distribute loads, thus protecting the underlying bone. Although relatively thin, it has great durability and can provide normal joint function throughout an entire lifetime. [7]

It is a highly organized connective tissue, comprising a single type specialized cell – the chondrocyte – within an extracellular matrix (ECM). The cartilage is avascular, aneural, and alymphatic so nutrients and hormones need to diffuse from the synovial fluid through the matrix to reach the cells. Individual chondrocytes are very metabolically active, but the low cell density means a low overall metabolic rate within the articular cartilage. [7]

A variety of complex interactions between the matrix and the chondrocytes maintains a fine balance between synthesis and degradation of articular cartilage. Matrix-degrading molecules including matrix metalloproteinases (MMPs) and enzymes such

as aggrecanase, plus cytokines and growth factors are produced by chondrocytes under normal and pathological conditions. [8]

The ECM consists of tissue fluid and a macromolecular framework of collagen in which proteoglycans (PG) and other molecules are embedded. Up to 80% wet weight is water with gases, small proteins, metabolites, and a high concentration of cations to balance the negatively-charged proteoglycans which attract water molecules and are responsible for the high osmotic swelling pressure. [7]

Collagen forms 60% of the dry weight of the cartilage with the various types functioning in different ways throughout the cartilage. The collagen fibres provide stability and prevent shear and flow of tissue fluid. The fibres are firmly embedded in the subchondral bone and pass perpendicularly from the bone to the superficial zone of the cartilage, where they lie parallel to the articulating surface thus forming an arch-like structure. [7; 9]

There are 3 distinct zones within the articular cartilage, the size and appearance of which vary within species, and in different joints within the same species. The superficial zone has flat, disc shaped chondrocytes; the middle and deep zones have more spherical chondrocytes. [6] Matrix variations are also seen within the zones. [7]

Osteoarthritis is the most prevalent joint disorder in the world, with primary OA being generally more common than secondary OA. [1; 10] OA most commonly affects the knee, hip, hand and spine; the ankle, wrist and shoulder are less frequently involved, with the cause of knee OA being mainly idiopathic, and ankle OA, trauma. [11]

The progress of OA is not relentless; the condition can remain stable for several years. [10] The rate of progression varies with species and joint location [12] and can be divided into three overlapping stages. [1]

1) Disruption or alteration of matrix

2) Chondrocyte response to tissue damage

3) Decline of the synthesis response and progressive loss of tissue

Even in 2006, the pathophysiology of joint degeneration leading to the clinical syndrome of OA was poorly understood. [10; 13]

Differences between ankle and knee cartilage

Similar and dissimilar characteristics can be seen in knee and ankle joints. Each comprises three bones that form a synovial hinge joint, stabilised by muscles and ligaments. The articular surfaces of the ankle joint are more congruent than those of the knee; however the knee menisci help to increase the contacting surface area. Ankle and knee cartilage vary macroscopically and microscopically in structure, material properties and metabolism, both in normal and damaged tissues.

Cartilage thickness

Researchers have measured cartilage thickness (Table 1) by determining the thickness of slices or plugs of cartilage from a destroyed joint. Each method had its own limitations. [14] Although measurements varied depending on the method used, the mean thickness of the ankle cartilage was found to be less than that of the knee by two

researchers [14; 15]. The findings of Sugimoto *et al*. and Millington *et al*. supported the ankle cartilage measurements. [16; 17]

The maximum cartilage thickness and homogeneity varied within the joints, with the knee having more variation than the ankle. [14; 15]

Cellularity of articular cartilage

It had been discovered that the chondrocytes are not scattered at random and that their number and arrangement vary significantly between the ankle and knee cartilage, and within the zones. [3; 18] Rolauffs *et al*. (2008) have identified four distinct arrangements of chondrocytes: strings, clusters, pairs and single chondrocytes, oriented parallel to the articular surface. In addition, they suggested that the pattern correlates with the diarthrodial joint type of articular surface in which they occur. [18]

Horizontal sections of the superficial zone from the ankle contained chondrocytes organised into clusters or chondrons of 2 to 6 cells, lying horizontal to the surface. There was no difference in the occurrence of clusters taken from different sites of the articular surface of the ankle. Chondrocytes in the deep zone of the ankle were found either singly or as doubles. [19]

In the knee, however, the chondrocytes in the superficial zone existed as singles or doubles, isolated from each other. Clusters were not identified in any site examined in the knee. Within the knee, 90% chondrocytes were present as single cells, compared to 3.8% in the ankle. [19]

Extracellular matrix components

Differences within the content of the ECM of the knee and ankle cartilage were also found to exist.

The glycosaminoglycan (GAG) content was significantly higher in the ankle than the knee cartilage. It was also higher in the middle and deep zones of normal knee and ankle cartilage than in the superficial zone. The GAG content was reduced in OA cartilage, but this may be due to the PGs being released from the damaged matrix. [20; 21]

Physical properties

Together the equilibrium modulus, dynamic stiffness and hydraulic permeability define the ability of the ECM to withstand compressive loads and their values were higher in the ankle cartilage than in the knee. [2] The ankle had the stiffest cartilage and a significantly greater mean compressive modulus. [22]

The lower response of ankle chondrocytes to inflammatory molecules may be the result of differences between the transport properties within the ankle and knee cartilage. Molecules diffuse through the avascular cartilage and the rate of this is determined by the diffusion and partition coefficients. The diffusion coefficients did not vary significantly between joint or zone, whereas the partition coefficient was 47% lower in the ankle than knee. [23]

Metabolism and response to injury and trauma

As new undifferentiated cells are unable to enter the avascular cartilage and there is no clotting mechanism to signal the need for repair process, chondrocytes are responsible for the maintenance of the ECM i.e. the synthesis and degradation of the

matrix components in normal situations and in response to injury and/or abnormal forces on the joint. [7]

Mechanical stress is believed to initiate alterations in the chondrocyte–matrix interactions and metabolic responses within the chondrocytes causing an imbalance between synthesis and degradation. [24] Marked differences in the relative levels of the aggrecan gene mRNA have been seen in the response of ankle chondrocytes to 20 minutes mechanical stimulation at 0.33 Hz within a sealed pressure chamber, compared to the response of knee joint chondrocytes. [25] (See figure 1.)

Ankle chondrocytes were found to be more metabolically active than those from the knee [25; 26]; variations were also seen in the different zones within the cartilage. Deep zone chondrocytes were found to synthesize more PG and collagen than those in the superficial zones in both joints. [2; 3; 23]

There appears to be a net anabolic response to injury in the ankle cartilage and a net catabolic response in the knee. These metabolic differences in the ankle and knee in response to injury and stress are summarized in Table 2.

Marked differences were also found between chondrocytes from ankle and knee cartilage, even when the cells were removed from their native matrix and allowed to regenerate a matrix, suggesting that there are inherent differences in the phenotypes of chondrocytes from different joints. [27]

DISCUSSION

The number of papers published on the subject of knee and ankle articular cartilage proved to be limited, with many stemming from the same research group - the Rush Department of Biochemistry. [5] Their studies however were consistent in both their methods and source of donor material.

Access to living cartilage is obviously restricted so cadaveric specimens must be used, bringing into question – is this a true reflection of the properties of the articular cartilage? Previously, much research had been carried out on animal cartilage, but now it is apparent that the cartilage differs between species, the relevance of these studies is limited.

The actual number of donors used in the studies was, on the whole, small. In several cases ipsilateral knee and ankle joints were used to give plausible results on the assumption that the knee and ankle joint from the same limb would have been subjected to similar stresses during the individual's lifetime. These results were confirmed with findings from single knee or ankle joints.

Most of the studies used recognised OA grading scales [2; 6; 10; 19; 20; 23; 25; 26; 27; 29] and identified any modifications they may have made to them. However, since these grading systems are subjective, the differentiation between 'normal' and 'osteoarthritic' cartilage could be debatable.

Other variables in the research included the sampling sites, the number of samples used, preservation of the samples, orientation of the samples (vertical or horizontal slices), but even with these variables the results did tend to follow the same trends. Future research will, hopefully, incorporate more consistent measuring and sampling methods.

The differences between the ankle and knee cartilage were found to be present not only in the averaged values, but also in the individual ankle–knee pairs. [2] The general consensus appears to be that ankle cartilage is better adapted to deal with cartilage lesions and the ensuing development of OA.

But is the ankle cartilage more resistant to progressive tissue degeneration or does it have increased potential for repair? A variety of suggestions for the differences between knee and ankle cartilage and their response to OA were proposed:

- The interaction between joint injury and cytokines. [29]
- Cellular differentiation rather than environmental effects. [28]
- Amount of PG content. [23]
- Biomechanical forces. [18]

The biomechanical differences between the two joints may also contribute to the variations between the articular cartilage in the ankle and knee. Dynamic loading may influence the thickness of articular cartilage which may help explain why knee cartilage is thicker than the ankle. [18] The type of joint may determine arrangement of chondrocytes [18] and the congruity of the joint, which may be affected by abnormal

biomechanical forces, may affect the forces within the joints and influence the development of cartilage. [30]

The thickness of cartilage has been shown to affect the response to stress and strain. Thinner cartilage is better adapted to transmit stress across the whole articulating surface, whereas where there is greater variation in thickness, stress will be concentrated in the thicker areas. The cartilage becomes adapted to dealing with those stresses so when an abnormal stress is applied to a previously under-loaded area, the cartilage cannot cope and the degeneration process starts. [31]

Topographical variation in the distribution of cartilage is greater in the knee, suggesting that there is more scope for degeneration due to stresses on previously under-loaded areas of cartilage, as may happen following injury that alters the alignment of the joint surfaces. But is this thickness the result of the arthritic changes or is OA the result of the thickness?

Muldrew [9] presented a hypothesis on the evolutionary adaptation of articular cartilage to enable it to perform at its optimal level. He suggested that the higher the number of chondrocytes within the tissue, the less amount of space would be available for the matrix components. These chondrocytes, therefore, would be responsible for less matrix maintenance and better able to respond to other stimuli. In less dense tissue, as seen in the knee, each chondrocytes has more matrix to maintain, and conflicts arise between normal maintenance and response to trauma.

In addition to this, the arrangement of most of the ankle chondrocytes into chondrons may help with the response to trauma. Chondrons are rich in PG and collagen types II, VI, and IX. Type VI collagen has been shown to be resistant to degradation by MMPs so continues to offer a protective surrounding to the chondrocytes. [20] Furthermore, the proximity of chondrocytes within the chondrons would presumably enhance intercellular signalling, enabling responses to be more co-ordinated.

The higher number of cells and PGs within the ankle cartilage means cartilage is less able to swell should water enter via a lesion and is thus better able to maintain its stiffness and resilience. This increased density may also impede the movement and flow of fluid and macromolecules through the tissue when the cartilage is compressed, thus restricting the exposure of ankle chondrocytes to catabolic factors. In addition, the horizontal arrangement of chondrons within the parallel collagen fibres in the superficial zone of the ankle cartilage may provide a barrier to full-thickness defects of the cartilage. [19]

The amount of movement at the joint has a bearing on the cartilage properties. The highest range of motion for normal walking and running is found at the knee, followed by the hip with the lowest range at the ankle, suggesting that the thickness of cartilage may be determined by the degree of dynamic loading of the joints during normal activity. [15]

The cartilage response to sudden or slowly applied loads differs. Usually, compression causes movement of fluid within the cartilage, distributing the load and decreasing the load on the subchondral bone. But when sudden loading is applied as

in acute joint trauma, fluid is unable to move. The matrix is damaged and the chondrocytes experience mechanical stress. [32] Perhaps, therefore, the ankle is better able to cope with gradual increases in stress such as obesity and is more likely to develop severe degeneration following acute trauma.

Contrasting responses to stress and injury have been seen, i.e. anabolism in the ankle and catabolism in the knee. Interestingly, the ankle response appears to be widespread across the whole surface, rather than confined to the lesion and the immediate surrounding area. [21] This may be the result of better communication between the chondrocytes within the chondrons.

The thinner middle and deep zones seen in the ankle would imply that the superficial zone is in closer proximity to the more metabolically active deep zone and thus could benefit from the actions of the chondrocytes within the deep zone more quickly than the knee. Ankle chondrocytes also respond earlier to smaller lesions i.e. are pro-active [21].

Ankle chondrocytes appear to be more resistant to the effects of IL-1 and Fn-f, and to be able to reverse their effects under the influence of OP-1. This may be due to the lack of receptors on the chondrocytes or to the phenotype of the chondrocyte. It has been shown that ankle chondrocytes when removed from their native matrix and allowed to reform the ECM, retain their restricted response to IL-1 suggesting that this response is inherent [26].

The expression of MMP-3 and -8 by the ankle chondrocytes is more controlled with levels only being detected in the presence of factors such as IL-1. This may imply that as MMPs are present in normal knee cartilage, degradation of matrix components could occur more easily than in the ankle [20].

CONCLUSIONS

Although the number of samples studied in these review papers was, on the whole, small, the consensus appears to be that ankle cartilage is more resistant to OA development, even though disruptions to the cartilage surface may appear. This may be for a number of reasons:

- the structural arrangement of the cartilage – thinner, more concentrated cellularity.
- stiffer, higher equilibrium and compressive moduli.
- better intercellular communications – cells grouped into chondrons so signals can pass between them more easily via cilia, rather than having to pass through the ECM to the next cell.
- increased resistance to inflammatory molecules such as IL-1 and Fn-fs.
- increased metabolic activity seen in the ankle chondrocytes.

The physical differences are probably of more relevance to podiatrists although the biochemical variations are an interesting consideration.

Joint instability in particular is known to be a precursor to OA. As OA can develop insidiously, perhaps more preventative treatments can be offered to patients seen by podiatrists rather than accepting the development of OA as inevitable. Podiatrists may consider earlier preventative treatment of conditions, such as: ligamentous laxity, abnormal foot function/ position, sports trauma. Even ‘simple’ remedies such as aerobic exercising, specific muscle strengthening, shock absorption, may help delay or prevent the progression to symptomatic OA.

Degeneration has been found to occur in areas not used to periods of stress. One possible cause for this pattern of degeneration is lack of use or stress in these areas of the joint. Just as unused bone or unused muscle atrophy leading to degeneration so can unused cartilage. [32] If these unloaded areas were never subjected to mechanical stress, degeneration at these sites may not be important. However, bone and joint cartilage, are in a constant state of change through the process of remodeling. [33] Age-related changes in the remodeling process can lead to increasing joint congruity in old age. [34] These changes may result in an alteration of load in the joint such that increased stress on formerly unloaded atrophic cartilage occurs. Arthritis always results in a change in joint shape. [35] It is suggested that a change in shape caused by a disturbance in the remodeling process may itself be an important contributing cause of osteoarthritis. [31] It may therefore prove useful to evaluate the accurate position of the articulating surfaces – even the smallest amount of incongruity can increase stresses on the cartilage leading to degeneration.

Cartilage response to sudden (acute joint trauma) or slowly applied loads differs. If sudden loading is applied fluid is unable to move, the matrix is damaged and the chondrocytes experience mechanical stress. [36] It is possible the ankle is better able to cope with gradual increases in stress such as obesity but more likely to develop severe degeneration following acute trauma.

Traumatic joint injury has been linked to OA in later life. Little is known about the cellular changes between the time of injury and the presentation of OA. More research is indicated, ideally with longitudinal studies, to track the progress of OA. The use of

joints such as the 1st MTPJ that presents with OA at an earlier age might prove valuable and help to identify potential factors in the progression of this disease.

LIST OF ABBREVIATIONS

CII	Collagen type 2
ECM	Extracellular matrix
Fn-f	Fibronectin fragments
GAG	Glycosaminogen
Il	Interleukin
MMPs	Matrix metalloproteinases
MTPJ	Metatarsophalangeal joint
OA	Osteoarthritis
OP-1	Osteogenic protein-1
PG	Proteoglycan
TNF	Tumour necrosis factor

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FIGURES

Figure 1 - Representation of the effect of .33Hz stimulation on aggrecan gene expression on human ankle and knee chondrocytes. (Adapted from Orazizadeh et al. [22])

TABLES

Table 1 - Methods used to measure the thickness of ankle and knee cartilage

Legend: N/K - Not known; N/A – Not applicable

Table 2: Summary of metabolic differences in ankle and knee cartilage in response to injury and stress.

Legend:

CII - Collagen Type II;

Fn-f - Fibronectin fragments;

GAG – Glycosaminoglycans;

IL – Interleukin;

MMP - Matrix Metalloproteinases;

OP-1 - Osteogenic Protein-1;

PG –Proteoglycan; TNF - Tumour Necrosis Factor