Cartilage – can it repair?

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Cartilage is a connective tissue made up of specialised cells called chondrocytes which produce an extracellular matrix of collagen fibres, proteoglycan, and elastin fibres. This article focuses on joint cartilage, specifically in the knee. It will discuss how damaged cartilage affects pain and the latest research into cartilage repair.

LEARNING OUTCOMES
TO SUPPORT PHYSIO FIRST QAP

1 Revisit and familiarise ourselves with cartilage anatomy and physiology.
2 Gain a deeper understanding of pain mechanisms associated with cartilage damage.
3 Reflect on latest clinical evidence for surgical and non-surgical intervention on cartilage repair.
4 Reflect on a new physiotherapy modality MRT and its role in cartilage repair.

A refresher of structure

Cartilage is a connective tissue made up of specialised cells called chondrocytes. The extracellular matrix is classified into three types: elastic, hyaline and fibrocartilage, which differ in amounts of collagen and proteoglycan.

The surface area of cartilage condyle is negatively charged and composed of collagen, embedded with a proteinaceous matrix. Young cartilage is around 85% water and, as we age, that figure gradually declines to 70%, and the negative charges and sialic acids reduce – a factor that is believed to be a possible link to early osteoarthritis (Laver-Rudich & Silbermann 1985). Cartilage can be divided into zones, all of which have three regions:

- The superficial zone communicates directly with synovial fluid to obtain nutrients. Being avascular, aneural and with no lymphatic system, the nutrients needed for the chondrocytes are obtained by diffusion and this fluid flow occurs with the compressive forces of movement (exercise). Dense collagen fibres are parallel to the articular surface, while the chondrocytes lie flat. This layer has a tensile strength that can withstand the articulation of the joint surfaces on each other, and protects the deeper structures.
- The mid zones have oblique, thicker collagen fibres and larger amounts of proteoglycans that act like a bridge between the superficial and deep cartilage. Here the chondrocytes are less dense and more rounded in shape but are more numerous. The collagen is not arranged parallel to the joint surface. This zone functions to resist compressive forces.
- The deep zone has the thickest collagen fibres with a lessening density of columns of chondrocytes, perpendicular to surface of the joint. It provides the greatest resistance to compressive forces and, through a calcified layer of cartilage, anchors it to the bone. Its function is to adhere the articular cartilage matrix to the subchondral bone and provide a barrier between this zone and the bone. It is the primary site of articular cartilage pathology.

The three regions in each zone are:
Area 1: The pericellular matrix that is a thin layer made up mostly of glycoproteins that cover the chondrocytes, and may play a role on load bearing (Eggli *et al* 1985).
Area 2: The territorial matrix made up of a fine "basket weave" of collagen fibres. It is suggested that these may protect the cartilage cells against mechanical stresses and heavy loads (Guilak & Mow 2000; Muir 1995; Poole 1993; Szirmai 1969).
Area 3: Made up of proteoglycans and random bundles of collagen, the orientation of which is determined by which zone they are located (Mow & Guo 2002).

The relationship between glycogen aggregates in the matrix and the interstitial fluid provides a compressive resilience to cartilage through negative repulse forces. This gives it biphasic viscoelastic behaviour that lessens as we age, and the changes in the chondrocyte distribution through the zones reduce their ability to reverse any damage (Fox *et al* 2009; Buckwalter *et al* 1990; Mow *et al* 1980).

Cartilage is found in joints, intervertebral discs, bronchial airways, the nose, the ear and ribcage. As physiotherapists, we are most interested in the musculoskeletal aspects of cartilage, so this article will focus on the cartilage present in joints specifically in relation to the knee, owing to the similarities of the purpose of cartilage. This is because it tends to be common for the knee joint to be affected by osteoarthritis, a problem

"DEEPER DAMAGE OF ARTICULAR CARTILAGE DOES NOT NECESSARILY RESULT IN A WORSENING OF PAIN"

associated with the wear and tear of cartilage.

The character of cartilage is one of strong resilience and, in varying amounts, smooth and flexible movement. Hyaline cartilage is found in joints at the end of bones and, when bathed in synovial fluid, provides a shock absorbing and low friction surface for ease and range of movement. The menisci in the knee joints consist of fibrocartilage that offers more strength.

Cartilage damage and pain

The International Cartilage Repair Society has set up an arthroscopic grading system by which cartilage defects can be ranked:

- grade 0: (normal) healthy cartilage
- grade 1: the cartilage has a soft spot, blisters, or superficial wear
- grade 2: minor tears less than one-half the thickness of cartilage layer
- grade 3: lesions have deep crevices of more than one-half thickness of cartilage layer
- grade 4: the cartilage tear is full thickness and exposes the underlying (subchondral) bone.

Being avascular and aneural, articular cartilage has a very limited capacity for self-repair so even small incidences of damage can get worse over time.

When shallow damage deepens, however, it does not necessarily result in a worsening of pain and the chondral defect can reach the subchondral bone undetected. Wang *et al* (2006) found that these seemingly harmless small defects in the cartilage could progress to osteoarthritis.

When a defect in cartilage does go through the healing process, it is instigated by the blood supply in the bone. The scar tissue in this process is made up of a type of fibrocartilage; a denser cartilage that is unable to withstand the demands of everyday activities in the way that hyaline cartilage does. Fibrocartilage is, therefore, at a higher risk of breaking down.

Acute injuries to articular cartilage can be caused by overuse through impact loading and weight bearing forces that lead to mechanical disruption of both the chondrocytes and extracellular matrix, or through joint immobilisation, i.e. lack of use that can cause loss of matrix macromolecules without mechanical damage to the chondrocytes or the collagen fibril meshwork. In the case of impact loading injuries, if the process of the injury is repeated, the subsequent degeneration of matrix macromolecules, such as proteoglycans can lead to irreversible mechanical disruption of the articular cartilage surface.

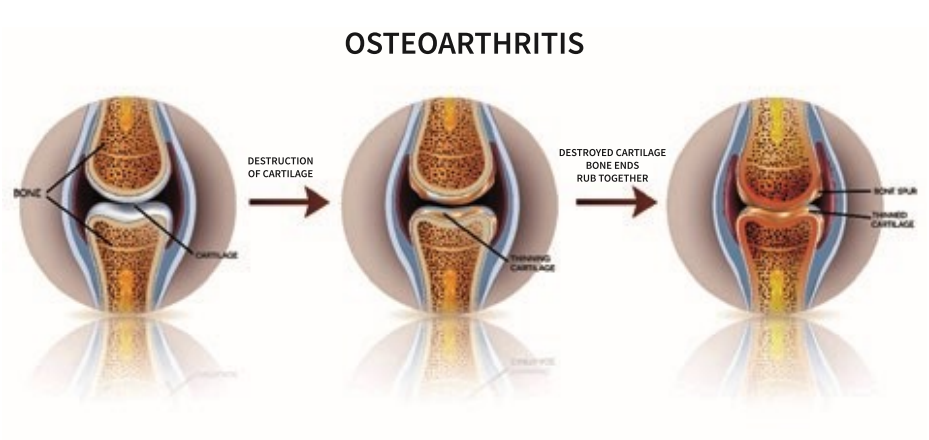

FIGURE 1: Destroyed cartilage

The response of articular cartilage to an injury is determined by a number of factors:

- the extent and severity of the injury
- the state of the cartilage
- age
- structure
- composition
- function
- durability of the repair tissue.

For repaired tissue to fulfill the demands of a joint surface, it must return normal, pain-free motion for an extended period to prohibit further degeneration of the joint (James & Uhl 2001).

So, can we feel pain from cartilage wear? Given that cartilage lacks any nerves, it makes sense that pain wouldn't be felt in any severity of wear (Felson *et al* 1990). This view continues to be supported by two very large, ongoing USA studies: the Osteoarthritis Initiative and the Framingham Osteoarthritis Study that are currently tracking a combined total of almost 1,200 patients with knee arthritis, and results show that loss of cartilage is not strongly linked to pain (**www.semarthritisrheumatism.com**).

These findings seem to fly in the face of common orthopaedic thinking which constantly drums into patients that the appearance on x-ray of narrower joint space equates to more pain – clearly a view that is not based on current scientific evidence. There is a need to move beyond this "cartilage-centric" approach to osteoarthritis pain and its joint replacement strategy to focusing instead on finding out what is causing pain. It is clearly a myth to suggest that cartilage thinning is the root cause.

This raises the obvious question of why do we feel pain when the cartilage wears? Here are some facts that may have an impact:

- Inflammatory chemicals in the joint cause swelling, structural breakdown and pain.
- Cartilage breakdown leads to bone damage (figure 1), swelling, osteophytes and bone pain-associated brain changes, and the centralisation

> "REGULAR MOVEMENT AND DYNAMIC LOADING IS NECESSARY TO MAINTAIN FUNCTIONING ARTICULAR CARTILAGE"

phenomenon. Recent studies analysed the brain in chronic osteoarthritic joint pain states and found modifications in grey matter that did not regenerate until six to nine months after surgery (Gwylim 2010).

- Neuropathic pain is a less understood part of joint pain. Studies suggest that patients with joint pain may exhibit degrees of neuropathic pain (Cedraschi *et al* 2013; Hochman *et al* 2014) and that neuropathic pain is more frequent and underdiagnosed (Jespersen *et al* 2010).
- A knee with cartilage erosion leads to sensitisation peripheral nociceptors in the inflamed synovium and damaged subchondral bone (Mapp 1995).
- Continuous nociceptive input drives chronic pain central sensitisation. Interactions between central and peripheral systems suggest a general plasticity of the nociceptive system in osteoarthritic pain (Imamura *et al* 2008).
- This plasticity includes emotional factors, hence the therapist / patient relationship and the patient's mind state may impact their response to treatment.
- Some studies have analysed brain activation and have demonstrated that chronic joint pain is associated with brain modifications. Central sensitisation (Graven-Nielsen & Arendt-Nielsen 2002) in osteoarthritis has been confirmed both by quantitative sensory testing (QST) analysis and functional MRI (Suokas *et al* 2012; Arendt-Nielsen *et al* 2010).

All of these factors underpin the complexity of pain and could explain failures of traditional therapeutic approaches, including physiotherapy and joint replacement surgery.

When it comes to treating cartilage wear, there are currently three available options:

- conservative treatment and management
- surgical repair
- joint replacement.

Non-surgical approaches to cartilage treatment

Clearly, the most attractive treatment option in terms of risk and cost is the conservative route. Even though science progresses at an unbelievable pace, the fact remains that we are better off with the joints we are born with than any artificial modification, and thus it makes total sense to pursue this vigorously before considering other options.

Conservative treatment typically consists of exercise and medication to reduce pain and control inflammation. However, this falls short of addressing some of the issues mentioned earlier. For example, neuropathic overlay from the spine not only compounds the pain problem, but can have long-term consequences for the deterioration of the condition due to the interference in nerve feedback to the brain. Therefore, the neuropathic condition should always be investigated as part of the clinical assessment. Similarly, the inclusion of a biomechanical assessment makes total sense.

Joints need to move to remain healthy. Inactivity leads to an increased risk of cartilage damage and makes the progression of osteoarthritis far more likely, so regular motion and dynamic loading is necessary in order to keep the normal articular cartilage functioning. The prescription of appropriate exercise for range of movement such as Tai Chi or yoga, walking, and swimming, is essential to ensure sufficient nutrient supply that will assist in retaining healthy cartilage. Additional muscle strengthening work such as Nordic Pole walking, Pilates and weight training to improve joint support is also vital. Exercise / movement will fire the piezoelectric currents in collagen, which is essential to cartilage repair (Fernandez 2012).

Unfortunately, long-term prescription of medication is overused, despite the fact that it makes no logical sense to promote a daily dose of pills with the potential multitude of side effects. Further, Shield (1993) suggests that local anaesthetics and medications such as ibuprofen can have adverse effects on the functioning of cartilage cells.

Where these conservative options fall short, however, is in addressing some of the consequences of cartilage thinning such as osteophyte growth, as they don't necessarily offer longer-term solutions that might help reduce the need to consider invasive procedures. There is an option that enables the treatment of such conditions conservatively and this will be discussed later in this article.

Non-conservative interventions

It is not within the scope of this article to review in detail all of the available invasive options for treating loss of cartilage. Instead, this is a brief overview of some of the clinical evidence.

CARTILAGE CELL INJECTIONS

Cartilage cells can be cloned and reproduced in a laboratory. However, the real problem comes in placing those cells in a particular joint and in getting them to function effectively.

New cartilage must somehow adhere to the surface of the joint in the right place. It must then be able to support the weight of the body and glide smoothly to allow normal movement. Research into the use of growth factors and genetic engineering will in future be directed at manipulating the body to repair the damage before arthritis destroys the joint.

As previously discussed, cartilage is much more than just chondrocyte cells. It is a scaffolding tissue made up mostly of non-cellular material, mainly water, with collagen and other proteins. Injecting cartilage cells into the knee doesn't mean the body can make up the other components of cartilage. As knee arthritis progresses, the joint can become further damaged which, over time, may include the formation of osteophytes – changes that make restoring a joint impossible, even if cartilage repair were a possibility.

ARTHROSCOPIC LAVAGE / DEBRIDEMENT

This is a palliative treatment, rather than a restorative one. Its aim is to resolve mechanical restriction by removing small flaps of cartilage or fibrous tissue.

MICROFRACTURE SURGERY

Damaged cartilage is drilled to expose subchondral bone of the joint in order to access the bleed underneath. At eight weeks the body makes a fibrous patch and, at four months, a fibrocartilage one that wears out after a year (Knutsen *et al* 2007).

The next stage of the process of microfracture surgery is the implantation of a collagen membrane inserted at the fracture site to aid mesenchyme stem cells (MSCs). Known as autologous matrix-induced chondrogenesis (AMICs), these techniques are aimed more at the most severe levels of osteoarthritis. In their paper on a five patient case study, Saw *et al* (2011) injected blood progenitor cells and hyaluronic acid into the surgically prepared fracture sites. The fact that this resulted in some hyaline cartilage growth led this Malaysian team to look into future, larger randomised trials.

OSTEOCHONDRAL AUTOGRAPHS AND ALLOGRAPHS

Briefly, this technique involves a dowel of bone being "punched" out of a strong bit of the joint and placed into the weak part, altering the overall stresses across the joint surface (Solheim *et al* 2010). The donor site can be from a deceased person. Rejection drugs are not needed in this procedure, but the repair is difficult to secure as cartilage takes two years to achieve 75% adaption and needs a lengthy, structured rehabilitation programme.

AUTOLOGOUS CHONDROCYTE IMPLANTATION (ACI)

This now requires two surgical procedures; chondrocytes are harvested through an arthroscope from the patient, grown in a laboratory for six weeks then replaced with a matrix or membrane structure (Knutsen *et al* 2007). The chondrocytes can, however, only be inserted into small spaces and are not suitable for "resurfacing" the whole joint. As this process only helps in tiny areas of damage, it is unsuitable for arthritic knees.

AUTOLOGOUS MSC TRANSPLANT

This is still an experimental, minimally invasive arthroscopic technique. In this procedure MSCs are derived from bone marrow, placed in a gel matrix and implanted at the site where new cartilage would develop (Behrens 2005). It is a relatively safe procedure as it uses the patient's own cells and, at three years post treatment, there has been no evidence of cancer cells developing at the repair site (Centeno *et al* 2010).

In a 2008 study, Robert Litchfield concluded that routine knee surgery is ineffective at improving joint function or pain in knee osteoarthritis (Kirkley *et al* 2008). Arthroscopic surgery helped only with a minority of milder symptoms, such as meniscal pad tears. However, even meniscal surgery, when compared to sham treatment, proved ineffective (Sihvonen *et al* 2013). I would conclude that, while there is tentative evidence for surgical procedures for cartilage repair in patients with limited areas of damage, there is no proven procedure as yet for cartilage repair in more advanced knee arthritis.

Magnetic resonance treatment

In the earlier discussion on non-surgical treatment options, I mentioned that there might be a treatment in our toolbox that offers a solution for the complexity of pain and loss of function that we currently associate with cartilage wear in the knee. We may never have the luxury of a complete toolbox, but one item that I believe should be considered as an important option is magnetic resonance treatment (MRT).

As its name implies, MRT utilises the same scientific principles as MRI. In fact, the development of MRT or MBST resulted from the repeated observation that some patients gained therapeutic benefit from MRI (Frobose 2000). MRI science relies on the ability to focus energy into targeted body tissue by spinning hydrogen ions from a high to low energy state. While this concept is used in MRI to create an image, in MRT it is used as a treatment tool. Cartilage tissue is subjected to a multidimensional polar axis of electromagnetic fields, the spin axis of the hydrogen nuclei or protons align parallel to the magnetic field precess at their larmor frequency. This field then transfers the energy to the proton and inverts its spin direction. When the field is switched off, the proton gives out energy as it returns to its original position; it is the resonance between proton spin and precession frequency that gives the therapeutic signal that, it is proposed, regenerates cartilage.

Although MRT is relatively unheard of in the UK and is not, as yet, NICE approved for the NHS, it's a technique that has been used for more than 20 years in Germany and, with the number of treatments approaching 200,000 and zero incidences of side-effects, it is increasingly being recognised for use around the world (Frobrose *et al* 2000).

While the exact mechanism of how MRT works is still not fully understood, there are a number of promising double blind trials. For example, a study on osteoarthritic fingers (Kullich & Außerwinkler 2008) clearly shows encouraging results. An in-vitro study of cell proliferation in petri dishes showed a 270% rate above control for

> "MRT IS A TECHNIQUE THAT HAS BEEN USED IN GERMANY FOR THE TREATMENT OF CARTILAGE REPAIR FOR MORE THAN 20 YEARS"

chondroblasts, and 290% osteoblasts (Temiz-Artmann *et al* 2005).

I have treated hundreds of patients with this method in my own practice and have observed inspirational anecdotal evidence, with a 75% success rate of significant change. Surgeries have been cancelled, painkillers reduced, exercise adhered to, significant reductions in pain on the VAS scale, and significant improvements in function and quality of life.

In order to evaluate how MRT could work in conjunction with physiotherapy I, together with my in-house orthopaedic surgeon, visited the scientists at Medtec in Germany. A comment that my colleague made with regard to the lack of risk in using MRT treatment has stuck with me ever since: *"The worst thing that can happen is that it doesn't work, and that's not something I can say about anything else I offer."*

As helpful as medication is, it is stated elsewhere that prescriptions kill thousands every year (Bates 2003). More than six million British patients suffer hip and knee osteoarthritis and, in a 2015 UK study of mortality rates 30 days post total knee and total hip replacement, the mortality rates were 0.8%, i.e. 4,800 individuals (Smith *et al* 2015).

Conclusion

Articular cartilage is a highly specialised bit of kit. Its lubricated action copes with large loads, but its complexity makes treating, healing and researching it a significant challenge. There is strong evidence to show that a healthy cartilage is dependent on nutrition, exercise, and safe mechanical loading, as well as internal factors such as piezoelectric and hydrostatic effects. Aging causes a reduction in its viscoelastic state, stiffness and fragmentation. The jury is still out on the clinical evidence for effectiveness of surgical repair. However, it is encouraging that there is some promising evidence emerging from the use of developing technology, such as MRT, that suggests a future where damaged or aging cartilage may be repaired successfully and safely.

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About the author

Nicky graduated in biological sciences in 1988 and then physiotherapy in 1991. During the following 25-year search to find better methods to treat pain, she studied Gunn Intermuscular Stimulation (IMS) and qualified at the highest level. She has taught and presented on health and pain internationally and is the founder and owner of three health companies. She treats and teaches her painkiller methods at her Stafford, Harrogate, Norwich and Harley Street clinics. Nicky embraces holistic, hands-on physiotherapy and recognises the importance of the mind and health in improving treatment outcomes. She has travelled internationally to evaluate new technologies.

Nicky is an Honorary Fellow of the Institute for the Study and Treatment of Pain (iSTOP) and was awarded the Acupuncture Association of Chartered Physiotherapists (AACP) 2016 award for excellence in patient care, and the 2017 Best UK Pain Relief Clinic in recognition of her unrelenting commitment, and her outstanding cutting edge approach to treating patients, presenting internationally at seminars, on radio, and in writing for books for the public on how to improve their health.

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Useful websites

www.mrtcentre.co.uk

www.semarthritisrheumatism.com