Osteoarthritis 1: physiology, risk factors and causes of pain

In this article...
- How osteoarthritis (OA) is diagnosed
- Pathophysiology and risk factors for OA
- Causes of pain in OA

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Osteoarthritis (OA) is a synovial joint disorder characterised by pain, stiffness, and restricted function. It is often classed as a degenerative disease because the affected joints deteriorate over time.

This article, the first in a three-part series, describes the complex pathophysiology and causes of pain in OA, risk factors, and how it is diagnosed.

OA is often classed as a degenerative disease because the affected joints deteriorate over time. It is also commonly known as a non-inflammatory condition where pain is generated by movement of the diseased joint even though inflammation is a symptom (see below).

Diagnosis of OA
OA can be diagnosed from a persistent history of pain, stiffness and loss of function, and from risk factors (Fig 1 and Box 1). X-ray is the gold standard for diagnosis. OA is diagnosed and graded by severity by the degree of bony changes seen on an X-ray. The most commonly used X-ray tool is the Kellgren-Lawrence scale. This ranges from a score of zero, where no change is seen, to a maximum score of four. A maximum score means the changes are severe, with significant joint space narrowing, bony changes at the joint margins and alteration in the subchondral bone. A number of X-ray views may be needed to diagnose OA, especially in the knee joint.

Pathophysiology and risk factors
OA involves the loss of articular cartilage, the formation of bony spurs at the joint margin (osteophytes), inflammation of the synovial membrane and changes to the subchondral bone (Fig 2). The chronology of alterations in the bone, synovium and cartilage depends on the triggers for OA; changes in each tissue affect surrounding tissues. The pathophysiology of OA is complex as it comes in subtypes including:

1. Osteoarthritis (OA) is a synovial joint disorder involving cartilage, bone and synovial membrane. It can affect small and large joints
2. OA can be diagnosed from a persistent history of pain, stiffness and loss of function. X-ray is the gold standard
3. Risk factors include: age, being female; obesity; metabolic syndrome; repeated kneeling or twisting; or handling heavy weights
4. OA pain is caused by inflammatory mediators, which lead to central sensitisation of the pain processing cells in the dorsal horn of the spinal cord
5. Hip OA affects between 0.9% and 27% of the population, and the rates of knee OA are between 17% and 47%
Inflammatory, to a varying extent;
» Nociceptive (tissue damage) pain;
» Pain at rest, which can have the same characteristics as neuropathic pain.

Bone
The bone just beneath the cartilage in the synovial joint is known as subchondral bone, and has a number of different zones.

The uppermost zone, the subchondral bone plate, is composed of relatively non-porous bone with a limited blood supply. Beneath this is a spongier layer of bone called cancellous or trabecular bone.

In a healthy person, bone is constantly modified by modelling and resorption. This allows it to repair and adapt to changing mechanical requirements.

In some people, the composition or properties of bone are affected by inherited disorders, such as Stickler syndrome, which can lead to a much earlier onset of OA. In most people, the bone changes in OA are seen much later in life, and the triggers are poorly understood.

The subchondral bone plate thickens, the character of the trabecular bone changes, new bone is formed at the joint margins (osteophytes) and subchondral cysts form. These changes are defining features of OA (Goldring and Goldring, 2010).

Cartilage
Cartilage is a relatively vulnerable tissue, and a number of factors, such as age, predispose it to damage.

Pressure (loading) on cartilage causes the cartilage cells (chondrocytes) to produce a collagen and protein matrix. Replacement process of the matrix is normally a slow process, but excessive loading can lead to activation of enzymes (metalloproteases) that digest it, leading to thinning and damage (Goldring and Goldring, 2010). Modifiable factors that contribute to abnormal or excessive loading of the cartilage include:

» Obesity;
» High-level, high-impact sport or occupational activities;
» Repetitive and long-term occupational factors, such as repeated kneeling, twisting and handling heavy weights while standing (Ratzlaff et al, 2011; Yoshimura et al, 2004).

Non-modifiable factors include:

» Being female;
» Congenital joint abnormalities;
» Genetic polymorphisms;
» Ethnicity with susceptibility in particular joints varying between ethnic groups;

Cartilage include:

» Post-traumatic OA, which can lead to activation of enzymes (metalloproteases) that digest it, leading to thinning and damage (Goldring and Goldring, 2010).

Proteases) that digest it, leading to thinning and damage (Goldring and Goldring, 2010).

Once cartilage has been damaged, the products of that damage are engulfed and digested by synovial cells. This leads to the production of inflammatory mediators, such as pro-inflammatory cytokines interleukin IL-1, IL-6 and IL-8, tumour necrosis factor and prostaglandin PGE2. Cartilage damage triggers synovial inflammation, which in turn adds to cartilage damage (Pearle et al, 2007). Low-level (subclinical) synovial inflammation is present in most people with OA and many, even those with no synovial inflammation, will experience intermittent inflammatory flare-ups (Bonnet and Walsh, 2005).

The degree of inflammation is a key difference between OA and rheumatoid arthritis. OA is not always recognised as an inflammatory disease because there are often low levels of leucocytes in the synovial fluid, one of the parameters used to identify an inflammatory condition. Inflammation in OA is usually restricted to a specific area of a joint, but can sometimes be so pronounced that inflammatory chemicals are seen in the circulation as well as the synovial fluid. The degree of inflammation is associated with disease severity and pain. It is likely there are a number of subtypes of OA, some causing a much higher level of synovitis and inflammation than others (Pearle et al, 2007).

Causes of pain in OA
Pain is transmitted from peripheral tissues to the dorsal horn of the spinal cord, and from there to the brain along sensory nerve fibres. The main type of nerve fibre involved in transmission of OA pain is the small unmyelinated slow C-fibre. This carries signals relating to dull and aching pain sensations. There are also A-beta fibres in the joint that transmit information about touch, and A-delta fibres that are responsible for the detection and transmission of signals from pin-prick and heat.

Sensory nerves that travels from the periphery to the spinal cord are called the primary afferent fibres. These connect with nerve fibres in the dorsal horn, carrying pain or touch signals to the brain stem. These dorsal horn nerve fibres are called projection neurons; there are two main types of these:

» Pain-specific projection neurons that only transmit pain, no matter what incoming signal activates them. These are also known as nociceptive specific neurons, and reside mainly in the superficial layers of the dorsal horn;

» Wide dynamic range (WDR) cells, a group of projection neurons that can differentiate between pain signals and touch signals, and can also code the signal’s intensity and location.

Chemical mediators
The process of inflammation in the OA joint leads to the production of a number of chemical mediators. These sensitise the sensory nerve endings (peripheral sensitisation), lowering their threshold and creating the right conditions for other

RISK FACTORS
BOX 1

- Age
- Being female
- Obesity
- Metabolic syndrome
- Developmental dysplasia
- Ethnicity/genetic factors
- Socioeconomic background
- High-level, high-impact sporting activities

Fig 1

A number of factors contribute to an increased risk of cartilage damage and progression of OA, which can be segregated into genetic, biomechanical and environmental. There is some cross-over within these categories.

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玛丽afferent纤维，the more likely it is the transmitters released by the incoming primary afferent fibre to the brain stem. The more neurotransmitters produced by cartilage cells called chondrocytes. Articular (or hyaline) cartilage covers articulating bone surfaces. Chemical mediator: a molecule or compound produced that initiates a chemical reaction when it combines with another substance or a receptor. Neurotransmitter: a chemical signal that transmits a message from one neuron to a target cell across a synapse (for example glutamate). Nociceptor: a sensory nerve receptor that responds to damaging or potentially damaging stimulation (chemical, thermal or mechanical). Activation threshold: the minimum difference in electrical charge between the cell and its surroundings that will lead to the generation of an action potential. Cartilage: a flexible tissue composed of a network of collagen, trapping large proteins within it. Cartilage is produced by cartilage cells called chondrocytes. Articular (or hyaline) cartilage covers articulating bone surfaces.


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Central sensitisation

When the pain signals reaching the dorsal horn are intense or prolonged, they set up a process called central sensitisation. This process is called central sensitisation, which improves the protection afforded to the joint by the experience of pain. Because the process increases the sensation of peripheral pain, patients will be more inclined to rest to avoid further pain and protect the area.

One of the chemical mediators of this process is prostaglandin. This is produced by the projection neuron, and is diffused back to the primary afferent nerve, where it causes an increased release of glutamate and substance P.

Prostaglandin also acts on the projection neuron itself, turning off the glycine receptor, one of the inhibitory neurotransmitters. Glycine is needed to stop mechanoceptor A-beta fibres causing the nociceptive-specific projection neurons to fire.

Usually, A-beta fibres do not cause the nociceptive-specific projection neuron to fire because of this glycine block. However, once the block is removed by prostaglandin, the A-beta fibre signals lead to firing of the nociceptive-specific projection neuron.

Unlike the WDR cell, this neuron cannot distinguish between pain and touch, so any input of sufficient intensity leads to a pain signal being fired off to the brain. This is why touch can sometimes cause pain. Pain caused by innocuous (non-harmful) touch is called allodynia.

Once the pain stimulus is removed or its intensity diminishes, central sensitisation stops and the dorsal horn stops amplifying pain signals.

Central sensitisation can become pathological – it stops having a purpose and becomes disproportionate to the nociceptive input. Very little or no painful stimulus is required to evoke pain in some cases.

This sort of central sensitisation was first described in connection with pain related to neuropathic pain. It is now known to be important in OA pain.

Central sensitisation can help to explain why the amount of joint damage and inflammation does not always correlate with the amount of pain experienced. It also explains why people with OA feel pain in response to touch.

Discussion

OA is a painful disease of the synovial joints. It usually starts in people aged 40 and over, and increases in prevalence with age.

Factors that increase the risk of OA include being overweight and having metabolic syndrome. Participating in a lot of heavy lifting, twisting and kneeling, and...
high-level impact sports can also increase the likelihood of OA developing. There also appear to be genetic influences, which help to explain why certain ethnic groups have a higher prevalence of OA than others.

Research has helped understanding of the pathophysiology of OA, and the pain it causes. OA affects all the joint tissues, and the changes in those tissues cause inflammation that can vary in intensity.

OA pain is caused by inflammatory mediators, which can lead to central sensitisation of the pain processing cells in the dorsal horn of the spinal cord. Central sensitisation means pain signals are amplified in the dorsal horn, and projection neurons become far more sensitive to pain and touch signals. People with OA may therefore have pain that is disproportionate to the damage of the joint seen on X-ray.

References