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Walking on water: subchondral vascular physiology explains how joints work and why they become osteoarthritic

Michael Beverly and David W Murray

Botnar Research Centre, Nuffield Orthopaedic Centre, University of Oxford, Oxford

Correspondence should be addressed to M Beverly
Email
michael.beverly@btinternet.com

- This review of bone perfusion introduces a new field of joint physiology, important in understanding osteoarthritis.
- Intraosseous pressure (IOP) reflects conditions at the needle tip rather than being a constant for the whole bone. Measurements of IOP *in vitro* and *in vivo*, with and without proximal vascular occlusion confirm that cancellous bone is perfused at normal physiological pressures.
- Alternate proximal vascular occlusion may be used to give a perfusion range or bandwidth at the needle tip more useful than a single IOP measure.
- Bone fat is essentially liquid at body temperature. Subchondral tissues are relatively delicate but are micro-flexible. They tolerate huge pressures with loading.
- Collectively, the subchondral tissues transmit load mainly by hydraulic pressure to the trabeculae and cortical shaft.
- Normal MRI scans demonstrate subchondral vascular marks which are lost in early osteoarthritis.
- Histological studies confirm the presence of those marks and possible subcortical choke valves which support hydraulic pressure load transmission.
- Osteoarthritis appears to be at least partly a vasculo-mechanical disease. Understanding subchondral vascular physiology will be key to better MRI classification and prevention, control, prognosis and treatment of osteoarthritis and other bone diseases.

Keywords

- intraosseous pressure
- subchondral
- hydraulic pressure
- MRI
- osteoarthritis
- vascular marks
- histology
- bone fat

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Introduction

Although the anatomy of the blood supply of bone has been well defined by dissection, injection and clearance studies, that work has of necessity been in static or dead material (1). William Hunter (1743) described a subchondral 'mesentery' (2) and the early anatomists such as Cooper (1840) dissected out the osseous blood supply (3). Murray Brookes (1963) defined the intraosseous blood supply (4). Intraosseous pressure (IOP) has been investigated by several authors including Azuma (1964) (5), Crock (1965) (6), Arnoldi *et al*. (1972) (7), Hungerford & Lennox (1985) (8) and Ficat (1985) (9). Few authors have measured bone blood flow during activity *in vivo* (10). However, if the primary purpose of the skeleton is to support activity, the way in which activity might affect perfusion under joints has been largely ignored (11). If activity does alter subchondral blood flow, it would have been invisible to previous examinations. For the past 40 years, there has been little further interest. While research into osteoarthritis has focused mainly on cartilage and synovium at the mechanical, macroscopic, microscopic, cellular, molecular and genetic levels, subchondral vascular aspects have escaped attention (12).

Traditionally, IOP has been studied *in vivo* but again only under static conditions (5, 13, 14, 15, 16, 17). It was thought to be raised in osteonecrosis, osteoarthritis and bone pain (9). However, there has been difficulty in defining normal IOP and in using it effectively for clinical purposes (18). IOP has been measured in patients undergoing decompression drilling or forage for painful osteonecrotic conditions. While pain relief is often dramatic and prolonged, IOP measurements bear no relationship to that relief (19).

Anatomy and physiology

This review sets out to introduce recent advances in the study of IOP and to show that osteoarthritis has a vasculo-mechanical basis.

It has long been assumed that IOP is essentially static or a constant for healthy bone but a standard model developed to study IOP found marked variability. However, there is a proportionate pulse pressure (PP) for any IOP recording. It is evident that in fact, there can be no such thing as a standard IOP. The variability is due to the random nature of the blood vessels encountered by the needle tip (20). In retrospect, it appears to have been an absurd notion that pressure inside a bone might be a measurable constant, uniform throughout the bone and present in all subjects.

Denham proposed that a force of several times body weight might transfer across joints during ordinary use (21). Others have demonstrated that with joint loading surface pressures were huge, possibly up to 18 MPa or 180 atmospheres equivalent to 135,000 mmHg or 2600 psi, nearly one hundred times car tyre pressure (22). Those forces are borne by relatively soft cartilage resting on a thin subchondral bone plate which is in turn supported by delicate bony trabeculae. Exactly how such tissues bear those loads has not been explained.

Bone fat at body temperature is essentially oily or liquid (23). Orthopaedic surgeons are aware that bone fat sprays from saws and drills during surgery or flows out of fractures and is seen, for example, as a fluid level on lateral x-rays. Bone fat is also unique in embolising with trauma and in being preserved during starvation (24).

Previous authors had discounted the possibility that bone might be hydraulically strengthened. But their experiments involved grease-saturated dried bones and isolated cubes of cancellous bone and were far from physiological (25, 26).

Most water-bright MRI images of normal subchondral bone show vascular marks which do not fit the standard model of bone circulation (27). Furthermore, the marks are diminished or lost in osteoarthritis (28).

Histological study confirms that the marks are vascular and suggests further evidence for a hydraulic pressure-based load-bearing physiology.

Collectively, these observations demonstrate that a review of the physiology of load bearing might be appropriate and that osteoarthritis research should focus more on vasculo-mechanical aspects.

IOP at rest

An *in vivo* model shows that needle flushing or clearance in normal bone, even in small volumes, 'the Ficat technique', forces saline, heparin, blood and bone fragments backwards into the delicate vascular tree and damages the local circulation, causing a prolonged drop in IOP as in Fig. 1, whereas after clearance by aspiration, recovery is rapid (9, 29).

Under stable conditions, IOP recordings exhibit wave patterns synchronous with the arterial pulse. Slower traces show there to be an underlying respiratory wave as in Fig. 2. With drug administration, recordings show a further wave pattern consistent with a circulation time of about 90 s.

There is IOP variability within and between subjects. IOP is not significantly influenced by gender, weight, site or size of needle, but there is a correlation between IOP and systemic blood pressure ($P < 0.0005$). More importantly, there is a correlation between IOP and the associated PP ($P < 0.001$). This indicates that IOP varies proportionately to the perfusion conditions at the needle tip rather than being a constant for the whole bone.

With proximal arterial occlusion, there is a significant loss in pressure (IOPa) and loss of PP ($P < 0.0001$). Proximal venous occlusion significantly raises pressure (IOPv) with preservation of the PP ($P < 0.012$). This shows that subchondral cancellous bone at rest behaves as a perfused tissue with IOP being mainly a reflection of arterial supply (20).

Furthermore, it is evident that with proximal arterial occlusion, the residual IOPa reveals the true back, venous drainage or tissue turgor pressure. Similarly, IOPv measured with proximal venous occlusion

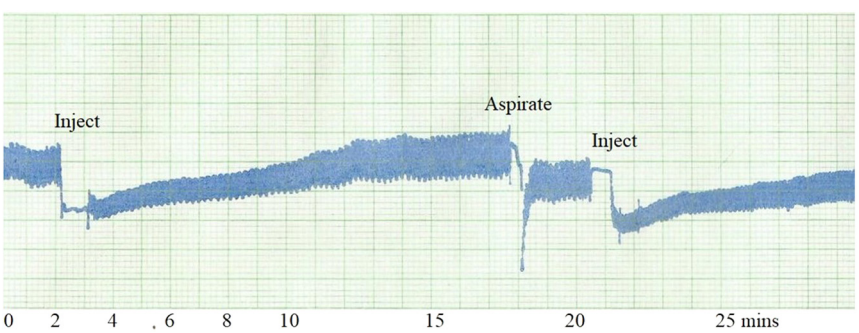

Figure 1
After injection, intraosseous pressure recovery is slow over 10 or more minutes. After aspiration recovery takes less than half a minute (Rabbit).

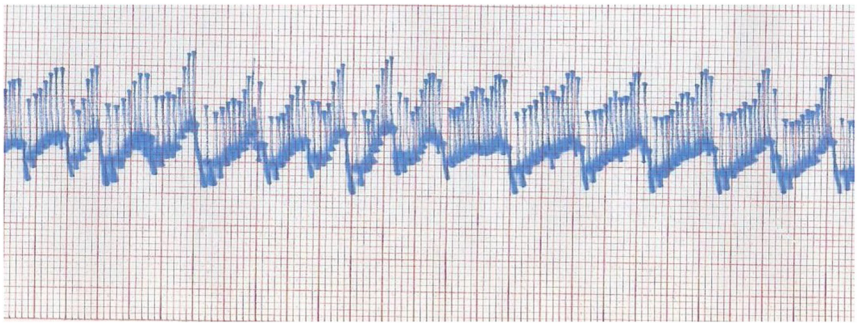

Figure 2
Intraosseous pressure trace showing cardiac and respiratory wave over about 2 min (Rabbit).

gives the best possible supply pressure obtainable at that needle tip. While a single measure of IOP is therefore variable and meaningless, reflecting only a random pressure encountered at the needle tip, alternate clamping of the proximal vessels offers a new subtraction technique (IOPv – IOPa) for exploring the physiology or 'bandwidth' of subchondral perfusion at the needle tip (30).

In ischaemic bone, the difference is small, while in healthy bone, the perfusion bandwidth is large. It is possible that the raised IOP found by previous authors merely reflects the intraosseous injection itself into poorly drained tissue (9). The subtraction technique has not previously been reported but appears to be applicable elsewhere.

For example, a more logical method of investigation of perfusion in calf compartment syndromes might be to record the compartment pressure initially with a proximal venous pressure cuff in position (Pv) followed by elevating the limb to empty the veins, then measuring the compartment pressure with a proximal arterial cuff in position (Pa). Subtracting the difference (Pv – Pa) gives a measure of the perfusion range obtainable at the needle tip. If the difference is large, there is good perfusion at the needle tip and decompression might be delayed. If there is a narrow bandwidth, perfusion is poor and decompression is more urgent.

IOP during loading

Subchondral IOP during loading, with and without vascular occlusion shows similar changes throughout the limb. *In vivo* simultaneous triple recordings at the femoral head, femoral condyle and proximal tibia show the changes present at all sites as in Fig. 3. A one-body weight load causes a rise in IOP ($P < 0.0002$). During arterial occlusion, IOP falls, and with the same load, there is only a small gain in IOP ($P < 0.002$). During venous occlusion, IOP rises, and with loading, there is a proportionately greater rise in IOP ($P < 0.003$).

Alternate saline injections at all three sites show that pressure is transmitted throughout the length of a bone but not across the knee joint. IOP is therefore not a constant but is reduced by proximal arterial occlusion and increased by proximal venous occlusion. Whatever the perfusion state, loading increases IOP. Subchondral bone is micro-flexible and physiological loading causes subchondral pressure rises often well above perfusion pressures (31, 32, 33). Load is evidently transferred partly by hydraulic pressure onto the trabeculae and so to the cortical shaft.

Steroid-treated model

Corticosteroids have long been associated with osteonecrosis and it is generally accepted that steroids

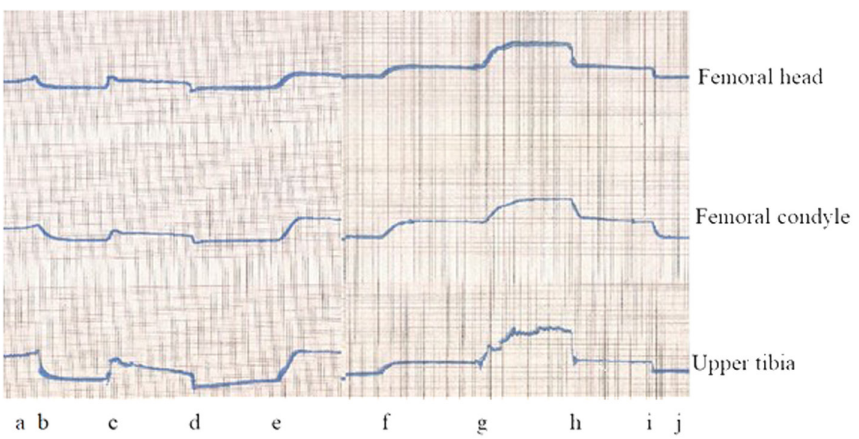

Figure 3
Triple recording from femoral head, femoral condyle and upper tibia with (A) basal state, (B) proximal arterial clamp applied, (C) load one-body weight applied, (D) load removed, (E) arterial clamp removed, (F) proximal venous clamp applied, (G) load one-body weight applied, (H) load removed, (I) venous clamp removed, and (J) return to basal state. Each trace 0–100 mmHg pressure range, total duration 10 min (Rabbit).

cause fat cell swelling leading to ischaemia (34, 35, 36, 37, 38). IOP measured in control and steroid-treated rabbits followed by angiography shows that the femora retain more barium in the steroid-treated group. In this particular model, steroids cause cachexic weight loss ($P < 0.003$) and there appears to be less fat in the bone with a raised resting IOP ($P < 0.002$). In this example, the raised IOP appears to be secondary to better perfusion through increased intraosseous vascular space, confirmed by photographs and x-ray micro-angiography as in Fig. 4. In this model, the IOP increases because of better perfusion at the needle tip. More importantly, this indicates that it is possible to manipulate intraosseous volume to change intraosseous perfusion (39).

Perfused bovine foot loading model

Freshly culled calf forefeet may be perfused with calf serum with IOP measured with and without a proximal tourniquet. Skeletal external fixator loading and more physiological loading by direct hoof pressure with both static and dynamic loading regimes to resemble walking may be explored (40).

Perfusion changes cause a gradual alteration in IOP over the course of 30–60 s as the limb fills or empties. Static loading causes an instantaneous increase in subchondral IOP whether the bone is non-perfused, perfused or perfused and with a proximal venous tourniquet ($P < 0.0001$). Under all perfusion states, IOP is proportional to the load ($R^2 = 0.984$).

On removal of load, IOP falls below the pre-load value. Repetitive hoof pressure loading leads to a falling IOP whether the foot is perfused or not. A falling IOP with repeat loading suggests that there is a one-way valve within the system, possibly to aid subchondral circulation with exercise (33). Subchondral pressures are frequently well above arterial supply pressure confirming that load is transmitted through subchondral bone partly by hydraulic pressure as in Fig. 5.

X-ray and MRI

Previously undescribed water-bright radiating vascular marks are present in all normal joints on T2 MRI scans as in Fig. 6. They are less obvious in smaller bones, on curved surfaces or in osteoarthritis. They are best seen on the flat subchondral upper tibial slices.

Plain x-rays scored for osteoarthritis on the Kellgren–Lawrence (K–L) scale show more arthritis medially. Contemporary MRI scans of the same knees with standard axial PD_SPAIR slices from the upper tibia show fewer vascular marks medially. Laterally, there are more vascular marks and less K–L osteoarthritis.

The vascular marks are present in the first subchondral upper tibial slice, peak at 6–10 mm depth below the joint surface and are absent by 16 mm depth. There is no correlation between the MRI marks and left or right side, gender, weight, BMI or age, but there is an inverse correlation between the number of marks and K–L grade of osteoarthritis both medially ($P < 0.001$) and laterally ($P < 0.002$) as in Fig. 7. The previously undescribed subchondral vessels seen on PD_SPAIR or T2 water-bright axial plane images are reduced or lost in early osteoarthritis. This offers new insight into the possible vascular aetiology of osteoarthritis (28). It also offers a potential means of diagnosing, classifying and following treatments in osteoarthritis.

Histology

If the subchondral region is slightly flexible and transmits force partly by hydraulic pressure, it might be expected that there would be anatomical modifications to support

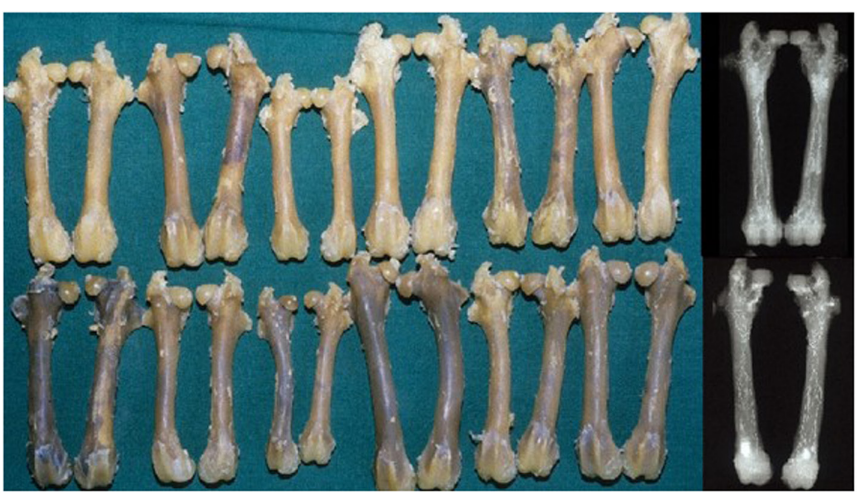

Figure 4
Top row steroid-treated, then angiogram and decalcification. Bones are whiter due to retaining more barium than lower row controls. Typical angiograms from each group on the right side (rabbit).

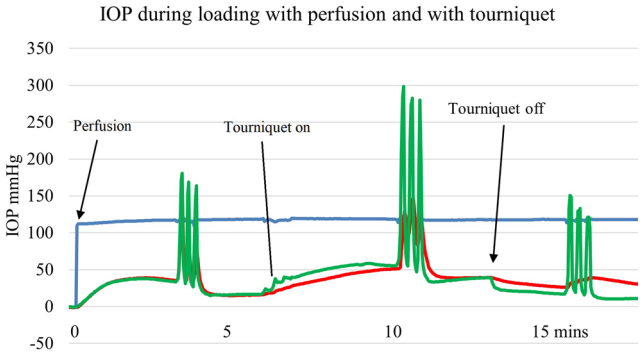

Figure 5
An example of intraosseous pressure (IOP) with loading during perfusion (left group), with perfusion and tourniquet (central group) and perfusion alone (right group). Blue – serum perfusion pressure, Red – metacarpal epiphysis IOP, Green – metacarpal subchondral IOP. Each group shows the effect of a static load of 10 kg applied for 10 s with 10-s intervals, × 3. The tourniquet was applied at 6 min and removed at 12 min (arrows) (bovine).

that function. Hunter described vessels just below the cartilage (Hunter's mesentery), but these have largely been forgotten. There are usually multiple fine subchondral capillaries immediately below healthy cartilage which appeared to be proportional in number to the thickness of the cartilage (23). Burkhardt described, but did not give reasons for, capillary choke-valve-like cells and muscular cuffs around periosteal veins (41). The water-bright vascular marks seen on MRI scans are plainly visible histologically in normal bone as in Fig. 8. Where those vessels penetrate the cortex near the articular margin there are complex distortions as in Fig. 9. Those distortions would act as choke valves when the surrounding IOP is raised during load bearing.

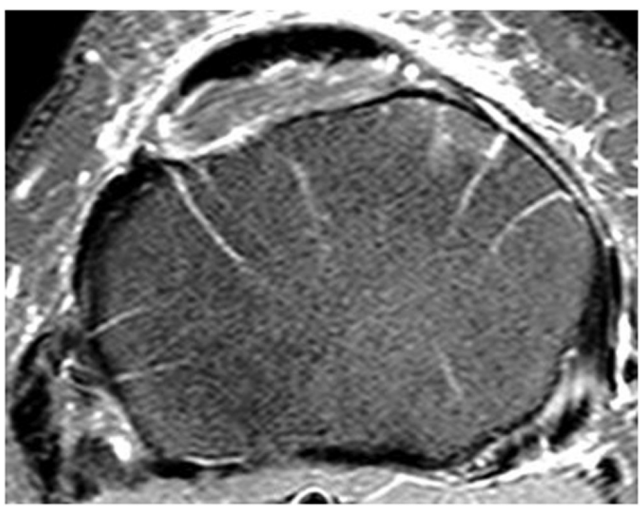

Figure 6
A normal proximal tibial slice from a PD_SPAIR MRI scan showing the radiating water-bright vascular marks (human).

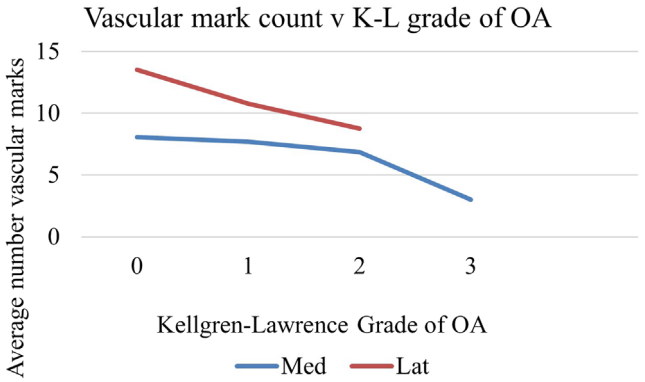

Figure 7
The number of vascular marks in upper tibial slices with Kellgren–Lawrence grade of osteoarthritis medially and laterally (human).

Although fat does not actually flow under load, adipocytes are large thin-walled cells containing fat which at body temperature is oily or fluid. In an enclosed environment, such tissue is capable of transmitting high pressure. The capillaries and red cells are also subject to great pressure, but as there is no flow, these delicate structures suffer no damage from turbulence. The subchondral tissues collectively act as a medium of force transfer at least partly by hydraulic pressure, transferring load onto the trabeculae. Those, in turn, coalesce and transfer the load onto the cortical shaft and so along to the next joint. At the next joint, the reverse occurs with the load being transferred from the cortex to the trabeculae and in turn to the slightly flexible subchondral tissues, hydraulically supporting the next joint surface.

Discussion

In summary, cartilage itself is soft and slightly flexible but transmits huge forces. Much of the subchondral tissue is composed of large thin-walled adipocytes. Bone fat is essentially fluid at body temperatures. The subchondral capillaries and trabeculae are relatively fine or delicate compared to cortical bone. Loading raises

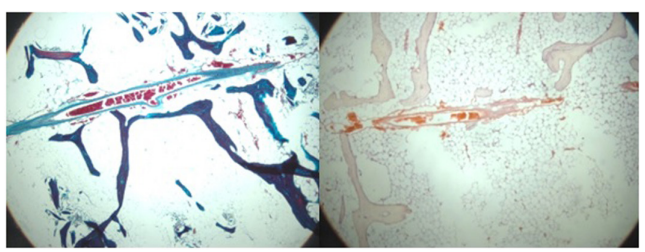

Figure 8
Example of vessels seen in the subchondral plane about 1 cm below the tibial joint surface. Goldner's trichrome and Masson's trichrome × 20 (human).

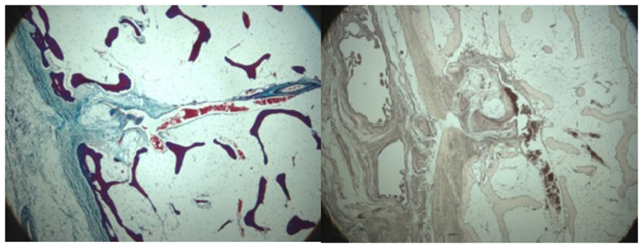

Figure 9
Vascular distortion or choke valves where vessels approach cortex (on left side) Goldner's trichrome and Masson's trichrome x 20 (Human).

subchondral bone pressure. At the cortical margin, complex vascular distortions exist which may be choke valves to prevent high-pressure flow from the cancellous interior. Collectively, these beautifully designed structures tolerate high pressures and pass those forces onto the larger trabeculae and cortical shaft (40). Arthritic bone has fewer vessels suggesting a possible vasculo-mechanical association with osteoarthritis as in Fig. 10.

Osteoarthritis and osteoporosis have long been recognised to be almost mutually exclusive conditions. The stiffer subchondral bone of the early arthritic flexes less and is, therefore, less well perfused than the thinner and more flexible subchondral bone of the osteoporotic subject who thereby retains healthy cartilage.

The vasculo-mechanical approach might also explain weather-related bone pain. The onset of a falling barometric pressure results in relative congestion in poorly perfused bone. It would explain osteoarthritic bone pain being aggravated by prolonged rest and relieved by movement and gentle exercise. Other bone diseases such as sickle cell disease, caisson disease, Perthes disease, juvenile osteomyelitis, osteonecrosis and osteochondritis dissecans patterns are also explained by an embolic or vasculo-mechanical approach.

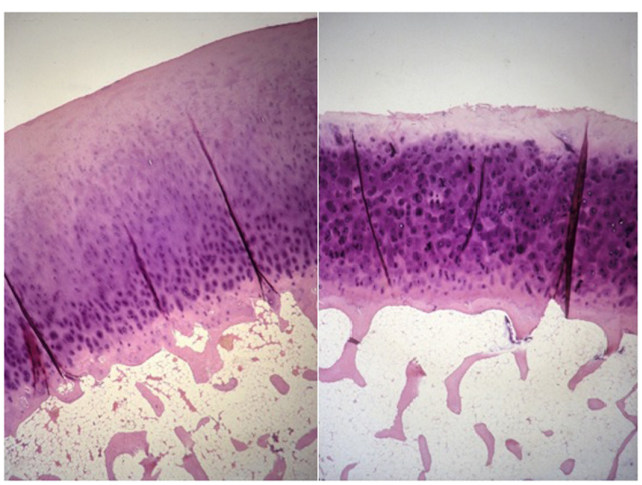

Figure 10
Left: normal femoral head with plentiful subchondral vessels; Right: early osteoarthritic femoral head with none. H+E × 20 (human).

Conclusion

This fresh approach to the understanding of joint function introduces a new field of subchondral physiology. IOP measurement may be useful for the study of bone circulation and other compartments at the needle tip level if logically combined with selective proximal vascular occlusion. Subchondral tissues appear to be beautifully designed to support the enormous forces of load transmission, mainly by hydraulic pressure. A 'vasculo-mechanical' interpretation of subchondral circulation and the observed loss of vessels in the subchondral region may be key in understanding the development of osteoarthritis and could explain other bone joint pathology. The loss of vessels on MRI scans may offer a means of diagnosis, classification and disease monitoring in osteoarthritis. In due course, this new appreciation of subchondral physiology should lead to further research and better treatments for osteoarthritis and other bone diseases.

ICMJE conflict of interest statement
The authors confirm that there is no conflict of interest.

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Author contribution statement
M Beverly caried out a review of previous experimental work and wrote the paper. D Murray advised and read the manuscript.

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