Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2024**; 29(3): 113
https://doi.org/10.31083/j.fbl2903113

Review

Is Osteoarthritis a Vascular Disease?

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Academic Editor: Emerito Carlos Rodriguez-Merchan
Submitted: 16 December 2023 Revised: 8 February 2024 Accepted: 22 February 2024 Published: 19 March 2024

Abstract

Osteoarthritis (OA) is now considered as a multifaceted disease affecting various articular tissues, including cartilage, bone, synovium, and surrounding ligaments. The pathophysiology strongly implicates intricate chemical communication, primarily through cytokines, leading to the production of degradative enzymes in cartilage, inflammatory peptides in synovium, and structural changes in bone, resulting in characteristic clinical features such as joint deformities and loss of cartilage space seen on X-rays. Recent studies highlight the previously underestimated role of subchondral bone in OA, revealing its permeability to cytokines and raising questions about the influence of abnormal perfusion on OA pathophysiology, suggesting a vascular component in the disease's etiology. In essence, alterations in bone perfusion, including reduced venous outflow and intraosseous hypertension, play a crucial role in influencing the physicochemical environment of subchondral bone, impacting osteoblast cytokine expression and contributing to trabecular remodeling, changes in chondrocyte phenotype, and ultimately cartilage matrix degeneration in OA. Dynamic contrast (gadolinium) enhanced magnetic resonance imaging (DCE-MRI) was used to quantify perfusion kinetics in normal and osteoarthritic subchondral bone, demonstrating that decreased perfusion temporally precedes and spatially correlates with cartilage lesions in both young Dunkin-Hartley (D-H) guinea pigs and humans with osteoarthritis. Pharmacokinetic analysis of DCE-MRI generated data reveals decreased tracer clearance and outflow obstruction in the medial tibial plateau of osteoarthritic guinea pigs, coinciding with progressive cartilage degradation, loss of Safranin O staining, and increased expression of matrix metalloproteinases and interleukin-1. Positron emission tomographic (PET) scanning using ^{18}F-Fluoride reveals a relationship among bone blood flow, cartilage lesions, and ^{18}F-Fluoride influx rate in OA, highlighting the intricate relationships between decreased perfusion, altered bone metabolism, and the progression of osteoarthritis. These findings, supported by ^{18}F-Fluoride PET data, suggest the presence of venous stasis associated with outflow obstruction, emphasizing the role of decreased subchondral bone perfusion in the pathophysiology of OA and its association with reduced osteoblast activity and advanced cartilage degeneration.

Keywords: osteoarthritis; venous stasis; cytokines; cartilage degradation; subchondral bone; perfusion

1. Introduction

Osteoarthritis (OA) is considered to be a disease of all articular tissues, involving bone, cartilage, synovium and the fibrous capsule and surrounding ligaments. The pathophysiology of OA involves prominently, crosstalk or, chemical communication by cytokines among these tissues, stimulating the production of degradative enzymes particularly in cartilage, inflammatory peptides particularly in synovium, and structural extracellular matrix proteins particularly in bone. These chemical communications culminate in the pathophysiology of OA – subchondral bone plate hypertrophy, trabecular osteoporosis, cartilage matrix degradation, synovial inflammation, and ligamentous-capsular fibrosis and contracture which, in turn, produces the structural hallmarks of OA, cartilage degradation and subchondral bone sclerosis (Fig. 1). Clinical characteristics include angulatory deformities of joints with loss of articular cartilage space and bone sclerosis on X-ray (Fig. 2).

Chemical communication between synovium and cartilage has been known for some years notably, by the discovery of interleukin 1, named at the time, catabolin [1]. In a straightforward but elegant experiment, this study showed that a non-enzymatic cytokine elaborated from synovium could stimulate cartilage breakdown but only with live chondrocytes because of the stimulation of chondrocytic enzymes. Communication between bone and cartilage, on the other hand, was thought for many years not to occur because the subchondral bone plate was considered impermeable. More recently, it has been shown in several studies, that the subchondral plate is not impermeable but that bone in general, and the plate in particular, are quite conductive to a variety of cytokines permitting chemical communication between cartilage and bone [2,3]. These observations make imperative the understanding of the pathophysiology of subchondral bone in OA. This narrative review describes alterations in the perfusion of OA bone and the responses by osteoblasts to changing vascular conditions of their microenvironment, thus strongly suggesting that OA is influenced by abnormal perfusion and is a disease with a prominent vascular component in its etiopathology. Osteoblasts respond to changes in their physicochemical environment and, in particular, hypoxia induced by de-

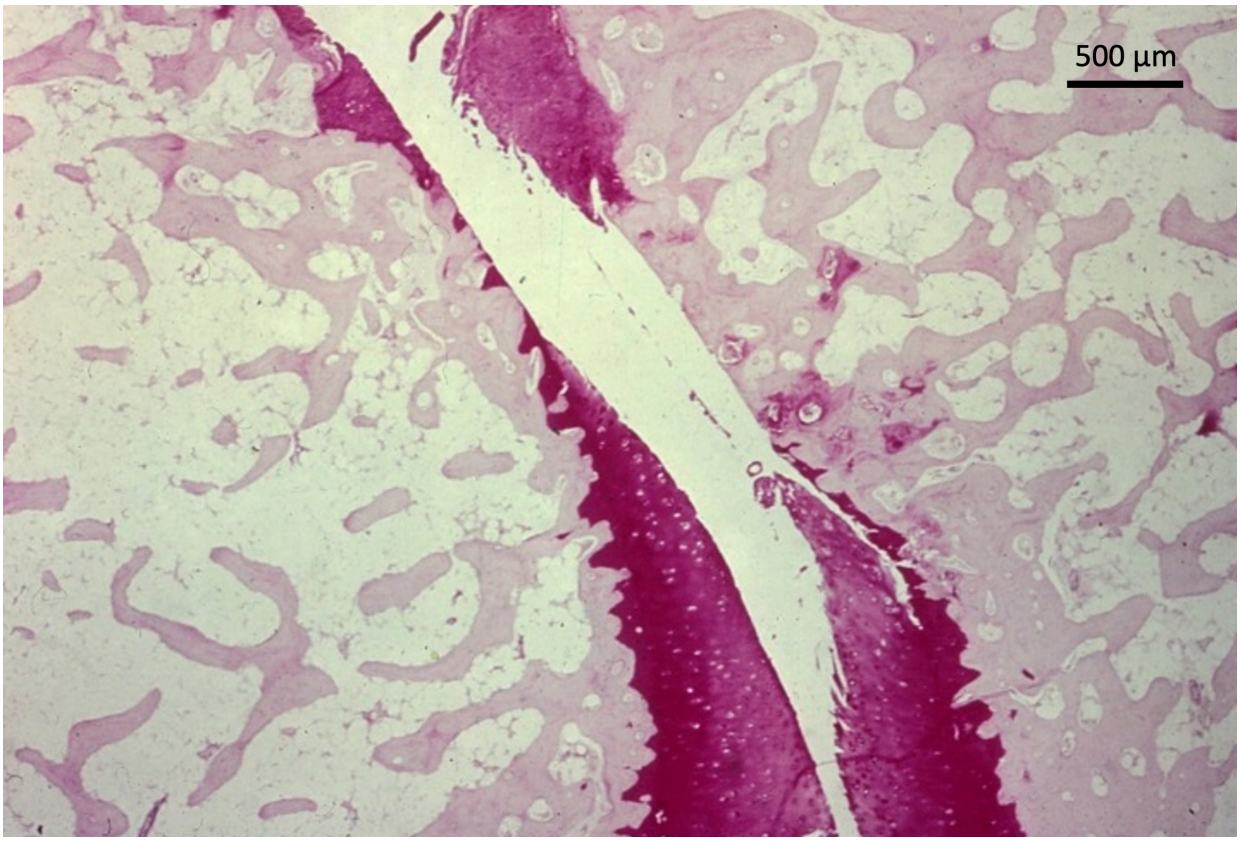

Fig. 1. Cartilage and Bone in Osteoarthritis. Subchondral plate hypertrophy, trabecular osteoporosis, and focal cartilage loss characteristic of osteoarthritis.

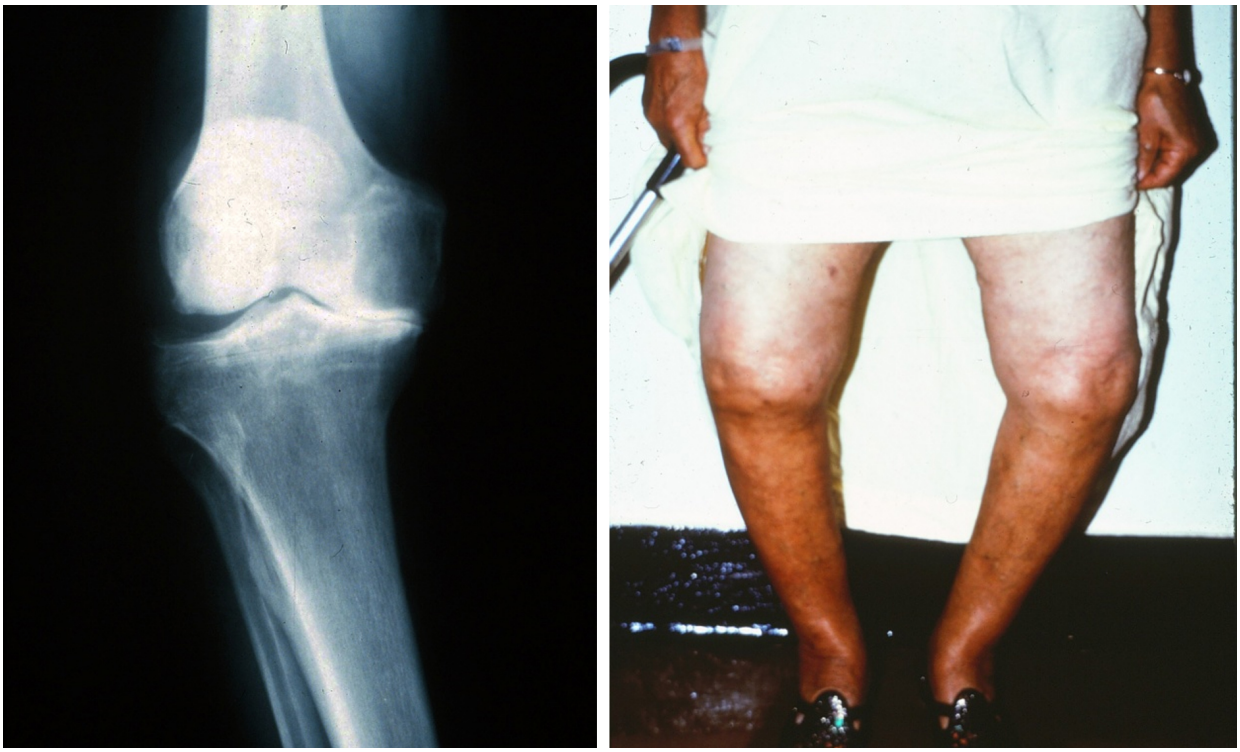

Fig. 2. Asymmetric Joint Loss in Osteoarthritis. (Left) loss of cartilage and bone from the medial tibiofemoral compartment and a varus tibio-femoral angle on radiography. (Right) a clinical example of varus knees.

creased perfusion, by producing a wide range of cytokines that contribute to inflammation and matrix remodeling in OA [4]. These cytokines can traverse through vascular and osseous pathways, through the subchondral bone plate, and into the joint [2]. Consequently, the physicochemical microenvironment of the subchondral bone, and in particular, environmental conditions induced by decreased perfusion, have become of great interest in OA. This review presents dynamic measurements of perfusion as a function of OA severity and indicates that venous outflow obstruction is associated with increasing OA severity. It further presents information that ^{18}F-Fluoride incorporation into bone matrix in OA is strongly associated with bone blood flow. These observations support the thesis that decreased bone perfusion and its physiologic sequelae are associated with OA and suggests mechanisms of these associations.

2. Osteoblast Cytokines and the Pathophysiology of OA

The contemporary paradigm of the pathophysiology of OA is that a large number of signaling cytokines, degradative enzymes, and biomechanical stresses interact to produce the stereotypical picture of OA. Regarding bone, an important recognition has been that bone is a conductive medium for cytokine transit and that the subchondral bone plate is porous, facilitating communication between the cartilage and osseous compartments such that pathologies in one space can affect tissues in another (Table 1). These observations have stimulated interest in the physiochemistry of subchondral bone and the response of osteoblasts to alterations in their subchondral environment. Osteoblasts are very sensitive to physicochemical cues in the subchondral bone microenvironment and, in response to changes in perfusion including pressure, fluid flow, oxygen concentration, and pH, alter their production of cytokines in ways that contribute to the pathology of OA [5]. Osteoblasts subjected to oxygen concentrations of 35–40 mmHg, levels of hypoxia seen in OA, alter their synthesis of cytokines, signaling peptides, and growth factors, including vascular endothelial growth factor (VEGF), insulin-like growth factor-2 (IGF-II), transforming growth factor beta (TGFß1), and tissue inhibitor of metalloprotease (TIMP-1) that are associated with bone remodeling, and cartilage degeneration, the histopathologic characteristics of OA. Activation of cell signaling pathways in osteoblasts including inflammatory peptides, (cyclooxygenase (Cox2), prostaglandin E2, and nitric oxide (NO), transcription factors (c-Fos and the early growth response protein (Egr1))), as well as enzymes, notably, matrix metalloproteinase-1, 3 (MMP-1, 3), and 13 occurs in response to reductions in subchondral perfusion and elevated intraosseous pressure [5,6]. OA osteoblasts also express elevated levels of cytokines and proteins that contribute to bone formation notably, type 1 collagen, osteocalcin, insulin-like growth factor-1 (IGF-1), and alkaline phosphatase, and that participate in remodeling of subchondral trabeculae and the subchondral bone plate. These are also responsible for the changes in bone structure observed in OA. OA osteoblasts also express elevated levels of cytokines that promote articular cartilage degeneration. OA osteoblasts produce a change in the chondrocyte phenotype that includes hypertrophy and matrix calcification [7]. Chondrocytes in co-culture with OA osteoblasts demonstrate reduced expression of cartilage type 2 collagen, parathyroid hormone related protein and receptor (PTHrP/PTH-R) and the *SOX9* gene, and increase the expression the matrix-degrading enzymes, MMP-3 and 13 while down regulating aggrecan synthesis [8]. Matrix metalloproteinases catalyze the degeneration of cartilage matrix. Although they can be active in cartilage homeostasis, MMP-3, among others, is primarily seen in pathologic cartilage [9]. MMP-3 levels have been shown to be associated with, and to be an independent predictor for, cartilage matrix damage and may serve as a potential prognostic biomarker for cartilage injury in osteoarthritis patients [10].

3. Consequences of Altered Perfusion in the Pathophysiology of OA

In summary, bone perfusion has profound effects on the subchondral bone physicochemical microenvironment. Decreased perfusion and hypoxia, venous occlusion, or intraosseous hypertension, have profound influences on the cytokine expression profile of osteoblasts which can result in alterations in the chondrocyte phenotype and trabecular remodeling that can contribute to articular degeneration in OA [11]. As a consequence, it is important to understand the kinetics of subchondral bone perfusion that could contribute to the pathology of osteoblasts in OA.

Interest in the relationship of perfusion, especially venous stasis, to OA was stimulated at St. Thomas' and Guy's Hospitals in the UK by Prof. Murray Brookes. Work by Dr. Brookes and his team demonstrated that venous occlusion, or stasis, had profound effects on bone and cartilage formation leading to OA. Brookes employed a preclinical venous ligation model to demonstrate that decreased venous outflow was associated with decreased subchondral pO_2 and pH and structural hallmarks of OA, trabecular remodeling and an increase in the thickness of calcifying cartilage [12]. Subsequent studies with static and dynamic imaging have demonstrated that venous outflow obstruction is a key component of the OA process [13]. Venous stasis leads to intraosseous hypertension which, in turn, reduces subchondral bone perfusion. Relationships have been described between perfusion alterations and intraosseous pressure [14]. A rise in intraosseous pressure of 26–45 mmHg results in a reduction of bone perfusion by 60% and intraosseous hypoxia. Venous outflow obstruction can reduce bone oxygen content by a factor of 1.5 within 30 minutes of occlusion [15]. Human OA bone has an oxygen concentration of 43 +/–4.6 mmHg compared to 63 +/–5.0 in normal human bone ($p < 0.05$) [16]. These observations and the known

Table 1. The Biology of Subchondral Bone in Osteoarthritis (OA).

Subchondral Plate	Absence of a barrier between intra-articular and subchondral compartments: - Allows chemical communication between cartilage and bone - Exposes articular cartilage to cytokines and enzymes from subchondral bone
Subchondral Bone	Osteoblasts change their cytokine expression in response to their physicochemical microenvironment notably, hypoxia and in OA: - Contribute to bone remodeling - Induce cartilage matrix breakdown

responses of osteoblasts to distortions in their microenvironment, especially hypoxia and pressure, have sparked interest in bone perfusion and its relationships to OA. A preclinical model of the Dunkin Hartley (D-H) guinea pig has been important in the assessment of bone perfusion in OA pathophysiology.

4. The Dunkin Hartley (D-H) Guinea Pig Model of OA

The D-H guinea pig exhibits the stereotypical cartilage lesions of human OA – loss of Safranin-O histochemical staining, articular fibrillation, and cartilage matrix clefts. Because OA develops spontaneously in the D-H guinea pigs and progresses according to a predictable time course, related to age of the animal, it is useful for the study of the pathogenesis of OA and potentially for the evaluation of disease-modifying agents [17,18]. In this model, OA occurs spontaneously without the need for surgical or traumatic intervention. Its temporal and structural features have been well-described providing a physiological platform for the exploration of pathology of OA (Fig. 3) [19]. Early cartilage lesions may be apparent by 9 months of age with obvious cartilage lesions and subchondral sclerosis apparent by 12 months of age; by 16 to 18 months of age, subchondral sclerosis and cartilage degeneration are observable primarily on the medial tibial plateau.

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) has been used to describe the relationship of subchondral bone perfusion to the development of OA in the D-H guinea pig model. The time course and spatial distribution of alterations in subchondral bone perfusion with developing OA have been characterized by comparing perfusion with the appearance cartilage lesions of developing OA [19]. In the D-H model, decreased perfusion temporally precedes the histopathologic characteristics of OA at 6–9 months of age (Fig. 4). Further, reduced perfusion is seen limited to the site of subsequent bone and cartilage lesions in the medial tibiofemoral compartment, leading to the conclusion that perfusion abnormalities both precede and anatomically localize at the location of eventual OA. By 9 months of age, when cartilage degeneration first appears but is, for the most part, superficial, delayed venous outflow is seen on DCE-MRI time-intensity curves, indicating that the primary circulatory event in OA pathophysiology is venous stasis [20]. These studies indicate that, in the D-H guinea pig OA model, venous stasis and associated compromised perfusion temporally precede and spatially localize with the eventual cartilage and bone extracellular matrix pathology. The observation of venous stasis has been supported by two other studies showing decreased elimination of contrast and venous stasis in both the rat femoral head and knee [21,22].

5. Characterization of Bone Blood Flow and Comparison to OA by DCE-MRI

Quantification of perfusion kinetics by DCE-MRI in normal subchondral bone has been compared to perfusion, cartilage degeneration, and bone remodeling in established OA in the D-H guinea pig [23]. Venous outflow obstruction, secondary intraosseous hypertension, reduced perfusion, and hypoxia occur in OA [13,16]. It has been demonstrated, using DCE-MRI and pharmacokinetic modeling, that reduced perfusion spatially localizes with and temporally precedes eventual cartilage lesions in D-H guinea pigs [19]. Similar changes have also been shown to occur in human OA and avascular necrosis [24]. As described above, decreased perfusion of OA subchondral bone can alter the physicochemical environment of osteoblasts to which they respond by, (1) expressing altered cytokine patterns and remodeling the structural of both the subchondral trabeculae and bone plate and, (2) elaborating signaling cytokines which contribute to cartilage breakdown.

Several studies from our laboratory were conducted with a 3.0 Tesla GE HDx MRI Scanner. Animals were maintained in a custom device with a 7-loop, 3.2-cm-diameter inductively coupled solenoidal radiofrequency resonator. Data were analyzed using previously published in-house software based on a two-compartment model described by Brix [25]. The Brix model quantifies the kinetics of gadolinium exchange between the plasma and interstitial space [26]. Time intensity curves were created from contrast signal intensities within the region of interest (ROI). After DCE-MRI scanning, knees were excised, and tibias were decalcified. Coronal sections were cut at 5 µm thickness at the mid OA lesion or the central third of the tibia if no OA lesions were visible. Sections were stained with hematoxylin/Safranin O/fast green for histochemical analysis and graded by the criteria of Mankin [27]. OA lesions occurred primarily on the medial tibial plateau. The histological-histochemical scores described by Mankin

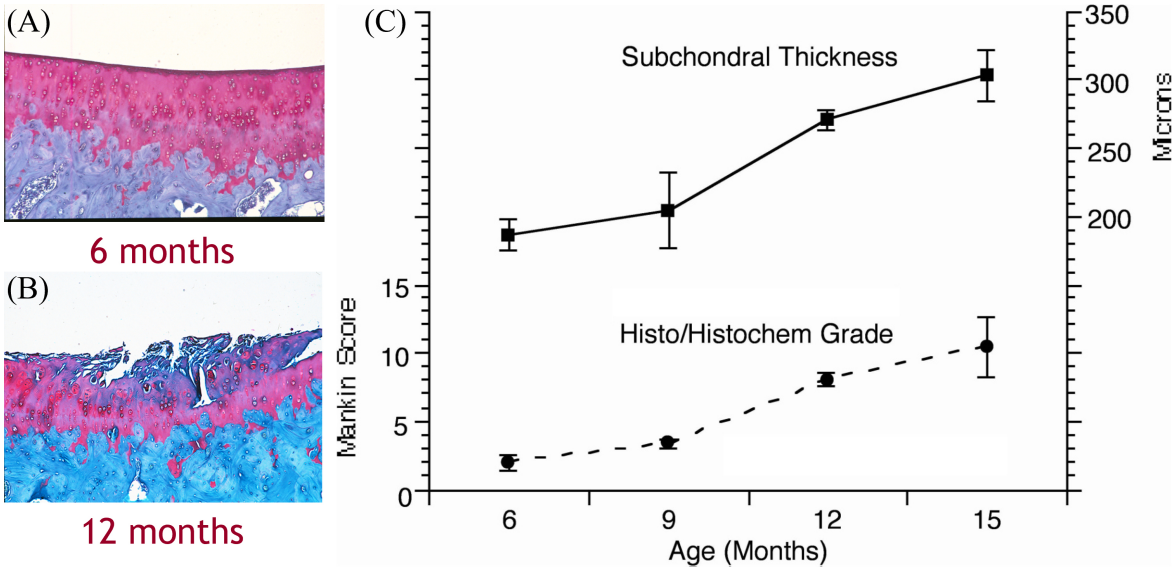

Fig. 3. Progression of Osteoarthritis in Dunkin-Hartley Guinea Pigs. (A) Normal cartilage with intact surface and Safranin O staining. (B) Surface fibrillation and loss of staining in osteoarthritis. (C) Characteristics of osteoarthritis beginning at 9 months of age and progressing substantially by 12 months of age.

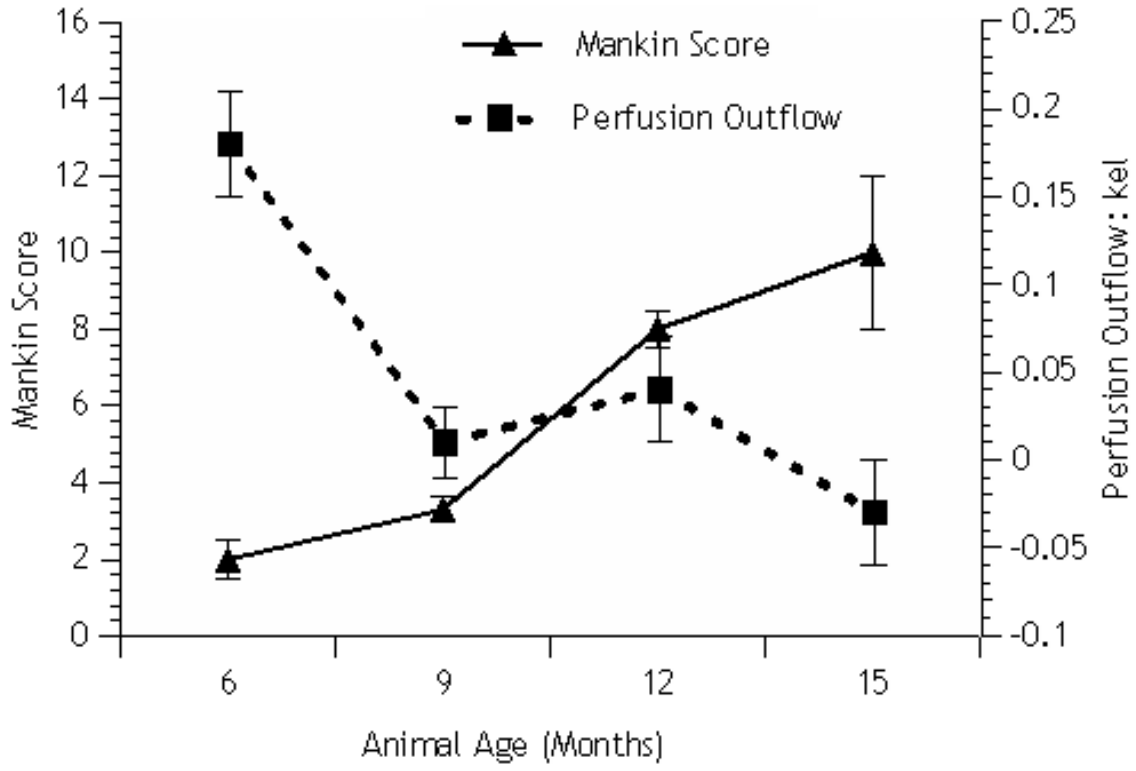

Fig. 4. Osteoarthritis developing between 9–12 months of age (Mankin score) [20]. Decreasing venous perfusion outflow (k_{el}) beginning at 6 months, and well established by 9 months of age, and preceding the structural changes of osteoarthritis.

were used to assess the severity of OA and ranged from 0–14 with higher scores indicating greater cartilage degradation. DCE-MRI time intensity curves characterized perfusion in the subchondral bone by decreased tracer clearance associated with increasing severity of OA (Fig. 5).

Three quantitative parameters were extracted from the compartmental fit of the time intensity curve [23]. The amplitude, A, is related to the size of the extracellular extravascular space; k_{ep} reflects the permeability surface area product. The elimination constant, k_{el}, quantifies clearance or

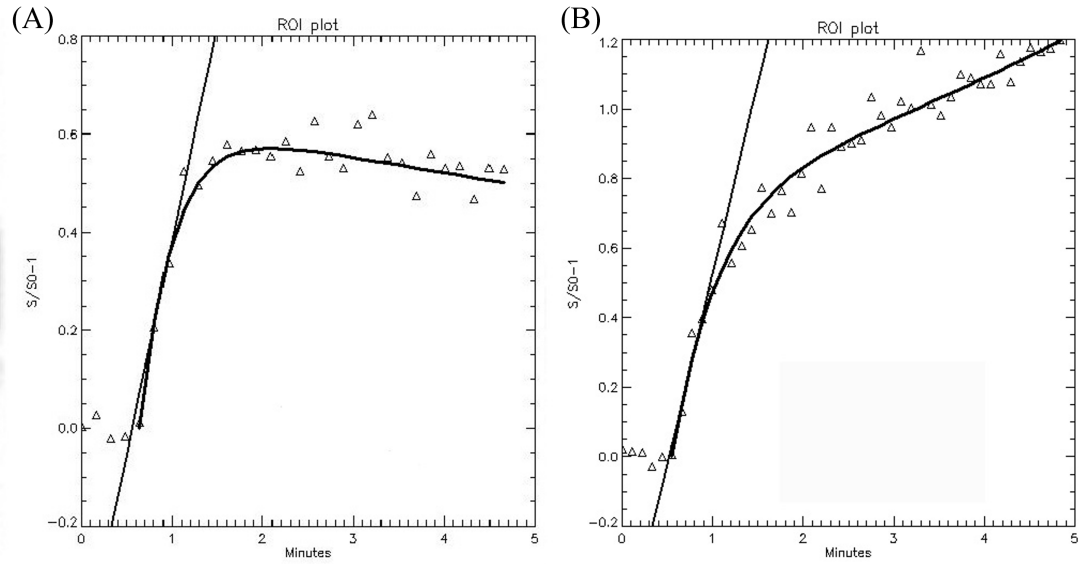

Fig. 5. Time-intensity curves of contrast clearance in Dunkin Hartley guinea pig osteoarthritis based on age [19]. (A) At 6 months of age, before osteoarthritis, normal venous flow was indicated by an elimination constant of 0.06. (B) By 12 months of age, with established osteoarthritis, the elimination constant averaged –0.11, reflecting obstruction of venous outflow.

washout of the contrast agent from the bone. Pharmacokinetic analysis has demonstrated that the clearance of the contrast agent (k_{el}) from the medial tibia decreased with the Mankin score indicating increased severity of OA indicating venous stasis and outflow obstruction (R^2 = 0.54, p = 0.015) (Fig. 6). Other pharmacokinetic parameters exhibited no changes with either age or OA severity in either the medial or lateral tibia.

Coincident with decreasing tracer clearance and decreased perfusion, histochemistry revealed progressive loss of Safranin O staining, cartilage fibrillation, and eburnation in progressively severe OA [28]. Mean Mankin scores at 18 months of age were 11.7 +/–0.3. Immunohistochemistry revealed decreased aggrecan epitopes, and increased MMP-3 (stromelysin), MMP-13 (collagenase), and IL-1, consistent with cartilage breakdown. Another study, using 12-month-old Dunkin Hartley guinea pigs, described structural features of the developing OA and confirmed these observations [29]. Reduction in cartilage Safranin O staining, reduced cartilage thickness, and cartilage fibrillation, with relatively high mean Mankin scores of 10.9 +/–0.9 were observed in the medial tibial plateau cartilage.

6. Positron Emission Tomography (PET) Comparing Perfusion and Bone Isotope Uptake

PET with ^{18}F-Fluoride has been used to determine the relationship of bone perfusion and incorporation of the isotope in bone to demonstrate the effects of osseous circulation on bone matrix formation. ^{18}F-Fluoride reflects perfusion when sampled for the first 2 minutes after injection. For the succeeding 45 minutes, the isotope becomes progressively incorporated into bone matrix and can be used to assess bone metabolism.

In one study,^{18}F-Fluoride PET data of D-H guinea pig knees were acquired on a Siemens/CTI Concorde Focus 220 µPET scanner. ^{18}F-Fluoride was produced on a 19.2 MeV Ebco Cyclotron and was administered with an activity level of 1.4 mCi/kg [23]. Data were summed in post-processing with two second frames to accurately quantify the blood pool within two minutes after injection of the radionuclide. Images were then summed at two-minute intervals up to one hour after isotope injection to assess bone uptake of the isotope and mineralization. Regions of interest were defined using the mid coronal plane image which included both the medial and lateral tibial plateaus.

^{18}F-Fluoride PET data analysis was derived from a three-compartment model devised by Hawkins [30]. The model consists of three compartments: plasma, extravascular, and bone. Date analysis was performed with the PMOD 3.1 package [31]. ^{18}F-Fluoride PET describes a perfusion phase occurring within 2 minutes after injection of the isotope, permitting assessment of blood volume and flow in subchondral bone. ^{18}F-Fluoride description of bone blood flow has been confirmed with ^{15}O-H_2O PET [32]. 45–60 minutes after isotope injection, ^{18}F-Fluoride is incorporated into the hydroxyapatite crystal of the bone [33]. The net incorporation of fluoride into the bone crystal is the net fluoride influx rate and reflects the extent of osteoblastic activity and mineralization.

PET images displayed asymmetric isotope uptake as a function of the severity of OA (Fig. 7). Time activity curves quantified uptake of ^{18}F-Fluoride in several anatomic locations within the knee. The pharmacokinetic fit of the ^{18}F-

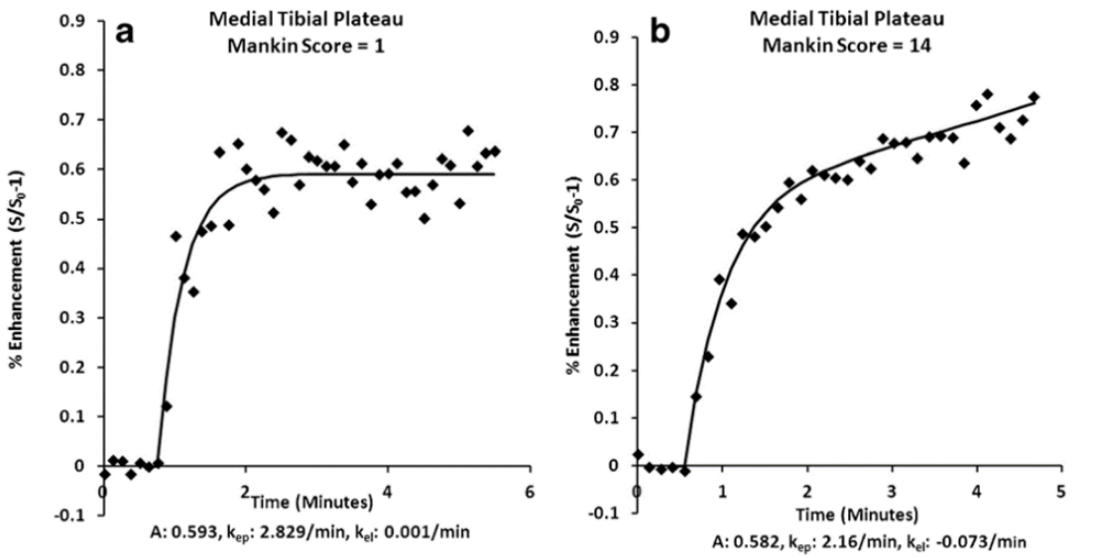

Fig. 6. Time-intensity curves based on severity of osteoarthritis [23]. (a) Normal perfusion demonstrated by a normal time-intensity curve in an animal with a Mankin score of 1 (minimal osteoarthritis). (b) Venous stasis shown by delayed clearance of contrast after 2 mins. of contrast infusion in an age-matched guinea pig with a Mankin score of 14 (severe osteoarthritis).

Fluoride time activity curve was used to describe blood volume (V_b), bone blood flow (K_1), and influx rate of the ^{18}F-Fluoride isotope (K_i) [30]. At 2 minutes after isotope injection, blood flow into the OA medial tibia approximated two-thirds that of the lateral tibia without OA. With increasing severity of cartilage degeneration in the medial tibia, the blood volume (V_b) progressively ($R^2 = 0.64$, $p = 0.005$) (Fig. 8a). Assuming complete extraction of the isotope after injection, the transfer constant, K_1, represents bone blood flow. With increasing OA in the medial tibia, a progressive decrease in bone blood flow was observed ($R^2 = 0.52$, $p = 0.019$) (Fig. 8b). The net fluoride influx rate (K_i) corresponds to the incorporation of the isotope into the bone matrix and the rate of bone formation. With increasing severity of OA in the medial tibia, isotope influx rates of isotope in the bone decreased ($R^2 = 0.40$, $p = 0.05$) (Fig. 8c). A significant association was found between the net isotope influx rate (K_i) and the blood flow (K_1) in the medial tibia ($R^2 = 0.95$; $p < 0.001$) (Fig. 8d).

The date derived from PET scanning confirm the observation that reduced blood flow is associated with the severity of OA and extends that observation to describe a relationship between decreased bone perfusion and abnormal bone metabolism as shown by decreased ^{18}F-Fluoride influx. The observations with PET demonstrate relationships among bone blood flow (K_1), OA cartilage lesions, and altered bone metabolism, the latter shown by ^{18}F-Fluoride influx rate (K_i). Several other studies support the finding that decreased blood flow is associated with decreased influx rate in OA. In one study, ^{18}F-Fluoride was incorporated in proportion to bone blood flow supporting observations of an association between bone blood flow and bone formation ($R^2 = 0.74$; $p < 0.001$) [32]. Another study demonstrated a significant correlation between fluoride influx rate and the mineral formation [34]. Increased ^{18}F-Fluoride uptake and bone formation have been shown to occur coincident with enhanced blood flow [31]. A study in human bone confirmed an association of K_i with biochemical and histological markers of bone formation [35]. These studies together suggest the intimate relationships of bone formation and blood flow with dependence of bone matrix formation upon perfusion.

7. Discussion

The relationships observed from DCE-MRI time intensity curves suggests an enhanced and prolonged signal intensity and a reduction in the elimination constant, k_{el}, during the contrast clearance phase, both occurring with increasing severity of OA. Other perfusion parameters derived from time intensity curves are not changed indicating the specificity of venous stasis. Delayed contrast clearance was seen only at the location of OA at the medial tibia, and coincident with the OA severity. Bone not involved in OA, at the lateral tibia, displayed normal contrast clearance. These results are supported by other studies reporting venous outflow obstruction in guinea pigs before the appearance of cartilage lesions, and with subsequent studies with DCE-MRI [19,36]. The prolonged and elevated signal enhancement seen in the contrast clearance phase suggests the presence of venous stasis and venous outflow obstruction. In static imaging and physiologic studies of established human hip OA, similar findings of impaired venous drainage, obstruction to venous outflow, and venous stasis have been described in association with reduced per-

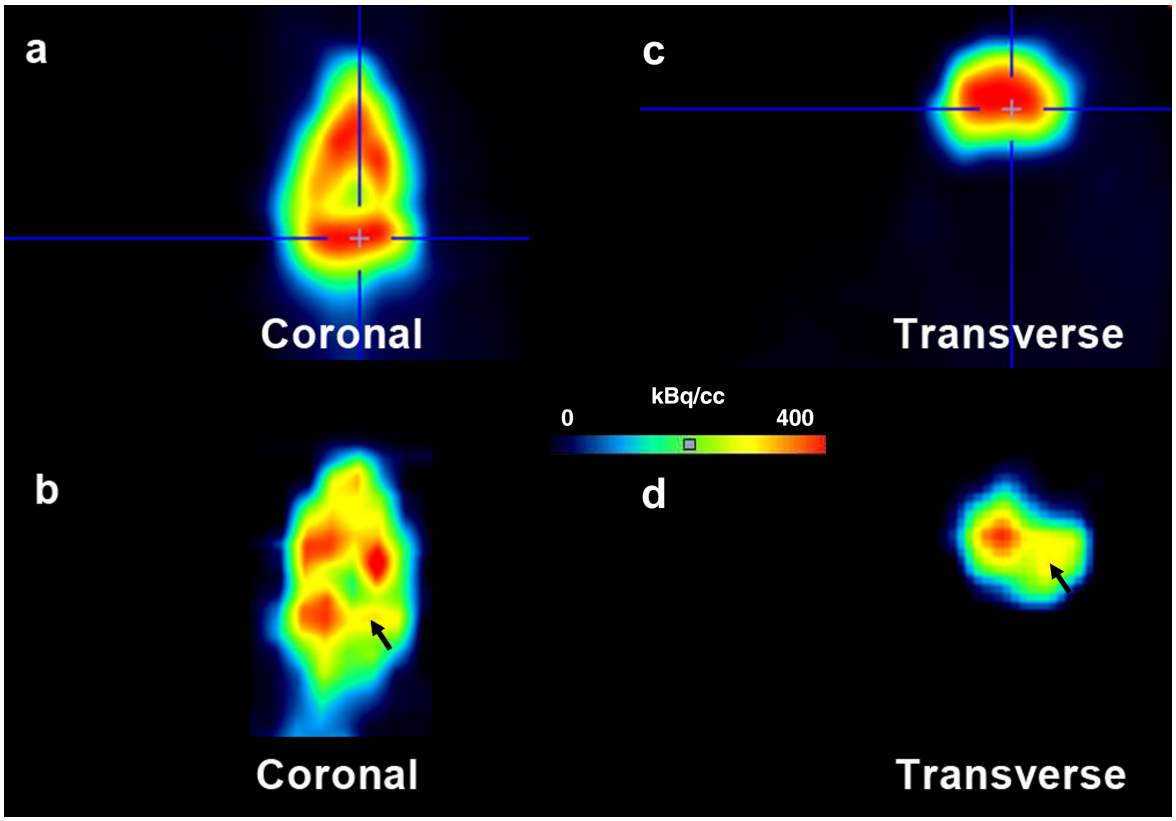

Fig. 7. Positron emission tomographic (PET) scan using false colors to delineate ^{18}F Fluoride in perfusion and matrix uptake. Red color indicates normal perfusion and matrix incorporation; yellow color indicates deficient isotope concentration. (a) Coronal image of knee showing symmetrical ^{18}F Fluoride medially and laterally in both the femur and tibia. (b) Coronal image showing deficient isotope at the medial tibial plateau with osteoarthritis (arrow). (c) Transverse image of normal proximal tibia showing medial-lateral symmetry. (d) Osteoarthritic tibial plateau with deficient isotope (arrow).

fusion, and hypoxia [13–16]. As a group, the earlier physiologic vascular studies together with the preclinical functional perfusion studies are strongly suggestive of venous stasis and a "venous outlet syndrome" resulting in hypoxia, contributing to a compromised physicochemical environment of osteoblasts and resulting in metabolic and structural changes in subchondral bone as pathologic features of OA [13–16,37].

The data obtained from PET scans support the findings that decreased subchondral bone perfusion is associated with the severity of OA and demonstrates a relationship between decreased perfusion and reduced osteoblast activity (decreased ^{18}F-Fluoride influx) associated with OA severity. ^{18}F-Fluoride, time activity curves of the tibias exhibit a decrease in perfusion and isotope incorporation, limited to the medial tibia, coincident with severe cartilage degeneration. Specifically, these observations were, (1) A decrease in blood volume and flow associated with more severe cartilage degeneration; (2) A decrease in Fluoride incorporation with more severe OA; and (3) A highly significant association between blood flow and ^{18}F-Fluoride incorporation into bone matrix. These findings indicate that reduced perfusion was associated with both decreased ^{18}F-Fluoride incorporation into bone and advanced cartilage degeneration confirming associations among blood flow, bone remodeling, and cartilage degeneration in OA. Several previous studies also demonstrated significant associations between bone blood flow and ^{18}F-Fluoride influx rate, and, in porcine bone, ^{18}F-Fluoride was incorporated into bone in proportion to bone perfusion demonstrating that perfusion is related to bone matrix synthesis ($R^2 = 0.74$; $p < 0.001$) [32,34,35]. Together, these data are consistent with findings that decreased bone blood flow is associated with decreased ^{18}F-Fluoride influx rate (K_i) and decreased bone matrix formation.

There are some limitations to this study. The research was conducted in a guinea pig preclinical model, although one with documented similarity to human OA. Models need to be chosen to display outcomes of interest and the D-H guinea pig model was temporally suitable to spontaneous OA and to be a source of OA tissue resembling that of humans. Blood flow was not measured directly but was inferred from well-established functional imaging models. The study focused on the relationship of perfusion in subchondral bone to OA. This is not to imply that other pathophysiologic events do not contribute to OA but to indicate

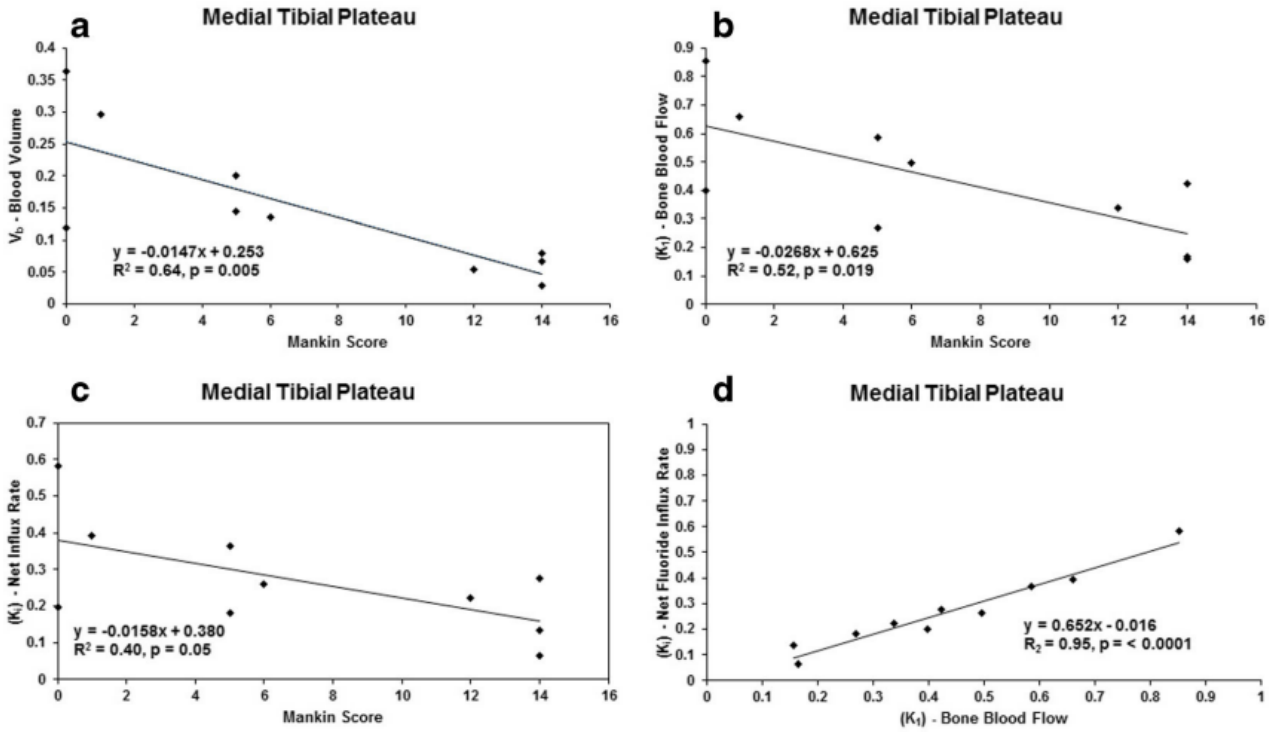

Fig. 8. ^{18}F PET scan data in the subchondral bone of the medial tibia [23]. (a) Bone blood volume decreases with osteoarthritis severity. (b) Bone blood flow decreases with osteoarthritis severity. (c) Net ^{18}F Fluoride influx rate decreases with osteoarthritis severity. (d) ^{18}F Fluoride influx rate into bone is tightly associated with bone blood flow.

that recent observations of the relationship of bone and cartilage is relatively underappreciated. Other articles in the special issue deal with complementary issues in OA pathology.

Imaging with DCE-MRI and ^{18}F-Fluoride PET can be used to demonstrate abnormalities in OA bone and correlate them with metabolic and structural abnormalities. Pharmacokinetic modeling can be used to demonstrate kinetic parameters including arterial perfusion and venous outflow, and to associate that information with subchondral bone metabolism and structural changes relevant to the pathophysiology of OA. The primary findings are venous stasis and hypoxia, and their significance most likely lies in changes induced in osteoblast cytokine expression that contribute to pathological skeletal remodeling and cartilage degeneration. The observations with dynamic imaging add to previous static vascular studies a functional pathophysiological context and suggest that further studies would be advantageous on perfusion as a contributor to the pathophysiology of OA [38].

The emphasis of this review has been on the perfusion changes in subchondral bone and the likely role they play in the pathogenesis of OA. Newer information has delineated, by functional imaging altered perfusion of subchondral bone in OA, the effects of perfusion alterations on the physicochemical microenvironment of osteoblasts, the responses of osteoblasts to environmental changes, and the porosity of bone creating a “cartilage-bone functional unit”. This report delineates cartilage-bone interactions, stimulated by perfusion alterations—important, but not exclusive, pathophysiologic contributions to OA. It is important to note that crosstalk takes place between synovium and cartilage has been observed for many years. In fact, as pointed out in the Introduction, the chemical communication between synovium and cartilage was the first to be identified in the context of OA pathology. In ensuing years, many other inter-relationships between synovial and cartilage pathology have been identified. Synoviocyte hyperplasia, hypertrophy, and fibrosis have been accompanied by secretion of pro-inflammatory cytokines notably, IL-1and 6, TNF-α, and VEGF which function as signaling molecules to chondrocyte matrix degradation and the ligamentous capsule fibrosis and contribute to the whole joint concept of OA pathology. Synovitis and its induced tissue damage contribute to pain, loss of joint function, and contractures that characterize OA [39]. Synovial angiogenesis has been observed to contribute to synovitis in OA, possibly stimulated by VEGF, a known stimulus to blood vessel development [40]. In fact, synovial pathology in OA has been shown by DCE-MRI [41]. Endothelial cells are present in joint structures and angiogenesis is implicated in OA pathogenesis possibly through endothelial produced VEGF [42]. Increased VEGF expression has been associated with matrix breakdown by in chondrocytes [43,44].

8. Conclusions

This review has concentrated on the demonstration of perfusion alterations and osteoblastic metabolic consequences in a preclinical model of OA. It is to be noted that systemic vascular comorbidities coexist with knee OA in humans. Patients with osteoarthritis (OA) exhibit higher than expected prevalences of cardiovascular comorbidities including ischemic coronary disease, cerebrovascular and peripheral arterial disease, and venous thromboembolism [45–47]. Patients with OA are generally considered to be at higher risk of death from cardiovascular disease than individuals in the general population. The coincidence of obesity, hypercoagulation, type 2 diabetes, and inflammation in both OA and cardiovascular diseases has suggested shared similarities in their pathophysiology and phenotypes, possibly associated with the metabolic syndrome [48]. Structural and physiologic abnormalities have been demonstrated in retinal arterioles, and carotid and popliteal arteries in patients with generalized and hand OA [49,50]. However, convincing evidence of arterial pathology is still elusive for both sexes and in hip and knee OA [50,51]. A systematic review has delineated some of the similarities and uncertainties between Atherosclerotic Peripheral Vascular Disease (ASPVD) and OA [45]. However, the association between vascular pathology and knee OA has remained inconclusive because some studies reported a positive association between structural arterial pathology and OA while other studies have found no association between arterial pathology and knee OA [45]. The association between ASPVD and OA may be stronger in systemic hypertension. Knee OA is more prevalent among hypertensive individuals compared with normotensive individuals. A number of systematic reviews have indicated a closer relationship between hypertension and structural damage in knee OA than with OA pain [52]. Mechanistically, hypertension is thought to increase intraosseous pressure and contribute to hypoxia in the subchondral bone, altering osteoblast expression of both signaling and structural cytokines. This, in turn, contributes to bone remodeling and cartilage matrix breakdown [52]. Other studies have supported the observation that systemic hypertension is associated with OA, and one has suggested that antihypertensive medications could reduce the incidence of OA in hypertensive individuals [53]. The pathophysiological coincidences between ASPVD and OA are explored in more detail in another paper in this special issue.

Abbreviations

IGF-1, insulin-like growth factor-1; VEGF, vascular endothelial growth factor; PTHrP, parathyroid hormone related protein; PTH-R, parathyroid hormone receptor; MMP, matrix metalloproteinase.

Author Contributions

Conceptualization, RKA. Investigation, JO and RKA. Writing—original draft, JO and RKA. Writing—review and editing, JO, JPD, and RKA. Original reference work, JPD and RKA. Project administration, JO. Funding acquisition, RKA. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research was funded by a grant from the Miriam Hospital.

Conflict of Interest

The authors declare no conflict of interest. Given the role as Guest Editor, Roy K. Aaron had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Emerito Carlos Rodriguez-Merchan.

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