The Effects of Oxidized Low-Density Lipoproteins on the Pathogenesis of Osteoarthritis and Avascular Necrosis

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This summary is based on the following OREF presentation and related publications listed in the references:

Lowry, JK & Brannon, JK. Avascular Necrosis of the Femoral Head in Patients with Negative MRI: A Case Series of Core Decompression and Endoscopic Evaluation. Presented at the 2006 Mid-Central State Orthopaedic Society Annual Meeting, Catoosa, OK. OREF Scholarship Award.

ABSTRACT

Osteoarthritis (OA) and Avascular Necrosis (AVN) of the femoral head (FH) are associated with obesity, diabetes, ETOH abuse, and steroid use. However, the physiologic similarities between OA and AVN have not been recognized, nor have the physiologic similarities between OA/AVN and cardiovascular disease. Osteoarthritis and Avascular Necrosis are joint disorders, while atherosclerosis is a vascular disease resulting from the oxidation of low-density lipoproteins (ox-LDL) within the intima of the artery leading to inflammation and calcification of necrotic foam cells. The relationship between oxLDL, OA, and AVN has never been considered at the intraosseous level because of insufficient crosstalk between orthopaedic surgery and cardiology. This narrative review summarizes this relationship and how its understanding is key to the success of joint preservation and the avoidance of an arthroplasty.

Keywords: Low-Density Lipoproteins, OxLDL, Osteoarthritis, Avascular Necrosis, Atypical Avascular Necrosis, Cardiovascular Disease, OxLDL Storm, Aseptic Loosening

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INTRODUCTION

Orthopaedic surgery is a specialty fragmented among many subspecialties, e.g., Adult Reconstruction, Sports, Hand, and Upper Extremity, Tumor, Foot and Ankle, Trauma, Spine, and General Orthopaedics. While sub-specializations may facilitate a good outcome for specific orthopaedic conditions, joint preservation requires the combined skills of a Sports orthopaedist and an Adult Reconstruction orthopaedist. Indeed, a 55-year-old with osteoarthritis (OA), or avascular

necrosis (AVN) rarely visits a Sports orthopaedist for treatment. That said, the subspecialty of an orthopaedist may influence how a disease is understood, making the review of cardiovascular literature to broaden one's understanding of OA or AVN highly unlikely.[1,2] This so-called influenced understanding can be considered a confirmational bias, and it indirectly limits one's knowledge because a clinically relevant relationship between cardiovascular disease and osteoarthritis/AVN at the subcellular level is not broadly known.[1,2] That said, this summary will be meaningful to those who carefully read its content and follow their reading by a review of the citations provided.

OSTEOARTHRITIS & AVN

In 2002, Brannon endoscopically (intraosseous endoscopy) observed calcified marrow spaces within femoral heads having adjudicated AVN. This observation was noted before and after the debridement of the femoral head.[1] The purpose of intraosseous endoscopy (placing an arthroscope inside of the femoral head) was to document the presence of actively bleeding blood vessels that could supply a bone graft packed inside of the femoral head after core decompression and thorough debridement. This simple technique allowed for more precise debridement beyond core decompression because the arthroscope could direct the debridement process to areas of necrotic bone that did not appear on the MRI. Further, the visual observations of Brannon provided the rationale for avoiding an invasive revascularization procedure and revealed the presence of calcified marrow spaces in hips that were positive and negative for AVN on preoperative MRIs. Importantly, bone biopsies confirmed AVN in the hips that were negative for AVN on MRI.[1] The calcified marrow spaces, deep within an adjudicated AVN lesion, were identical to the calcified marrow spaces within the hips considered to be negative for AVN on MRI. Steinberg uses the size of the AVN lesion on MRI to predict outcome after core decompression and promotes the concept of *extent of involvement*. This staging system is based on the presence of a sclerotic margin surrounding *necrotic bone* (bone with calcified marrow spaces), and establishes a standard of care for AVN. However, the reasoning of Steinberg is irreconcilable in view of Brannon.[1] The surgical and histopathologic findings of Brannon support diffuse disease, while the staging system of Steinberg supports localized disease. Brannon implies there is a systemic basis for AVN in some cases in addition to the localized vascular event contemplated by Steinberg. Indeed, the findings of Steinberg are not insignificant, but they are systemically irrelevant to gaining an understanding of the similarities between OA and AVN. In 1936, Ernst Freund identified calcified marrow spaces in collected bone specimens from the first reported case of bilateral avascular necrosis.[2] Steinberg recognized Freund for being the first to describe bilateral disease but went no further. Thus, no efforts have ever been made to understand the etiology of the calcified marrow spaces of Freund in view of Brannon. In contradistinction to Steinberg, Brannon teaches endoscopic visualization of the avascular burden comprising the *extent of disease* within the femoral head. The avascular burden is the avascular bone (bone with calcified marrow spaces) throughout the femoral head. When a sclerotic margin is present on MRI, a diagnosis of AVN is easily made, and the disease is staged. However, when one evaluates a patient with a similarly situated hip with respect to chronic pain and the MRI is read as

negative for AVN, a variety of diagnoses are entertained, none of which include Atypical AVN. Nonetheless, a scattered pattern of low signal intensity on T1, *mixed-signal heterogeneity,* should alert the physician to a possible diagnosis of Atypical AVN. When the marrow spaces are occluded, many secondary changes develop within the hip joint, such as congestion of the pulvinar and ligamentum teres causing lateral subluxation of the femoral head during mid-stance. This dynamic lateral subluxation leads to rim-loading, pincer lesions, and articular sided labral tears. When the blood flow from the superior retinacular and inferior vincula vessels are obstructed, alpha and beta CAM lesions may develop. The intraarticular sided joint changes result from obstruction of the transosseous blood flow due to calcified marrow spaces within the femoral head.[11] Similar to one's eyes watering when the nose is congested. Nonetheless, core samples taken from hips having Atypical AVN have been repeatedly diagnostic for disease on histopathology. Consistent herewith, Learmonth noted a success rate of only 14% following core decompression,[3] whereas Ficat noted a success rate of 89% following core decompression.[4] This significant variation in outcome implies that when treatment is decided based on the concept of a localized lesion (obvious MRI findings), substantial amounts of avascular bone, bone with calcified marrow spaces, may remain within the femoral head after core decompression. Brannon contemplated this shortcoming and developed a system to visually examine the core track to ensure that the native blood flow had been reestablished. Not surprisingly, the procedures of Urbaniak, Rosenwasser, and Mont remove the heretofore unrecognized necrotic bone of Brannon but are lauded for the success of their invasive approaches to a well-recognized lesion on MRI. However, these successes are rendered moot in view of Freund because these authors do not characterize the calcified marrow spaces. Lowry et al.[5] in 2006, and then Zaidi et al.[6] in 2010, attempted to characterize the observations of Brannon by noting significant levels of hypoxia-inducible factor 1-alpha (HIF-1α) associated with MRI negative and histology positive AVN. The presence of HIF-1α could explain micro hypoxia within the femoral head, but the calcified marrow spaces of Freund in view of Brannon remained unexplained. Nonetheless, near-identical hip pain to patients with MRI positive AVN is observed in patients with MRI negative AVN. These so-called MRI negative and histology positive hips reveal calcified marrow spaces on intraosseous endoscopy, **and *are likely the hips that go on to develop classic osteoarthritis.*** Worse yet, some patients may suffer from hip pain for many years until their x-rays begin to show degenerative disease. Therefore, how and why do marrow spaces calcify? What are the consequences of calcified marrow spaces relative to the longevity of the femoral head?

In 1948, Fremont Chandler described AVN as a coronary of the hip, and for a short time, AVN was known as Chandler's Disease. In his paper, Chandler described the femoral head as an end-organ similar to the heart. In his view, the foveal artery (the artery that supplies the epiphysis of the femoral head) made little to no contribution to the blood supply in the adult femoral head.[7] Then, in 1985, Brown and Goldstein, having received the Nobel Prize for characterizing cholesterol metabolism, identified low-density lipoprotein (LDL) receptors on liver cells. Low-density lipoproteins transport cholesterol and cholesterol esters through the bloodstream for use by various tissues. Subsequently, many investigators described the role of LDL (bad cholesterol) and high-density lipoproteins, HDL (good cholesterol), as biomarkers for atherosclerosis and ischemic cardiac events. Triglycerides are the major

source of fat in the foods we eat, and this fat crosses the small intestine to enter the vascular system via the lymphatics as a chylomicron consisting of triglycerides (TG), cholesterol, and cholesterol esters. As the TGs are delivered to the tissues and a series of metabolic reactions occur, the density of the lipoprotein increases from that of a chylomicron and a very low-density lipoprotein (VLDL) having the lowest, to the HDL having the highest. When LDL levels in the bloodstream are high, the liver downregulates its receptors for LDL. This excess LDL continues to circulate in the bloodstream which may then enter the intima, the tissue surrounding the inside lining cells of the arteries of the heart. The LDL passes through small gaps between the cells that comprise the internal lining of the artery and into the extracellular matrix, (ECM). The LDL then binds to biglycan, encoded on the X chromosome, a small leucine rich repeat proteoglycan (SLRP) within the etracellular matrix, where it can be oxidized to oxidized LDL, oxLDL. The oxidation of LDL occurs when LDL in the bloodstream or the ECM reacts with free radicals. The internal lining of the artery is called the endothelium and this endothelial lining, comprised of endothelial cells, is found throughout the entire venous and arterial vascular systems. While there are no receptors for LDL on endothelial cells, there are receptors on endothelial cells for oxLDL. One can expect more oxLDL in the bloodstream when free radical and LDL levels are high. That said, the recently identified receptor for oxLDL is a 52k Da transmembrane protein called the lectin-like oxidized low-density lipoprotein receptor (LOX-1) encoded on chromosome 12p. LOX-1 has properties of single nucleotide polymorphisms (SNPs) that give rise to the splicing variant LOXIN. LOXIN has been shown to dimerize with native LOX-1 and protect endothelial cells from damage by oxLDL by reducing the number of LOX-1 receptors on endothelial cell membranes for binding of oxLDL.[8,9]

In Figure 1, note the difference in color between the calcified marrow spaces and the spongy (cancellous) bone. The calcium deposited is a pathologic process. These calcium deposits obstruct the blood flow through the marrow spaces. This pattern of calcification is identical to the calcified marrow spaces within the avascular bone described by Steinberg. Additionally, this type of calcification is observed after debridement when residual necrotic bone remains inside of the femoral head. This observation has not been recognized because most treatment for AVN is anchored on the wisdom of Steinberg, and treating surgeons have not looked inside of the femoral head in contradiction to the observations of Learmonth[3] and Ficat.[4] When a core decompression is performed based on the MRI of Steinberg, the avascular burden of Brannon is missed, and an arthroplasty remains the forthcoming salvage procedure in failed cases. This undermines a search for how the nature of the subchondral bone contributes to arthritic disease. That said, when the marrow spaces are occluded, the osteocytes within the cancellous bone are unable to receive oxygen and nutrients from the blood supply, and as a result, the osteocytes die, i.e., avascular necrosis. Not recognizing the fundamental concept of occluded marrow spaces as *mixed-signal heterogeneity* on MRI early in the course of treatment for chronic hip pain, when the MRI is unrevealing for adjudicated AVN, may result in the hip progressing to osteoarthritis. The MRI of Steinberg and its sclerotic margin imply circumscription of a localized area of necrotic bone when the necrotic bone may be more diffuse within the femoral head. The diffuse presence of necrotic bone is evidenced by *mixed-signal heterogeneity* on MRI and the uncircumscribed bone having near identical MR signals as the bone circumscribed according to Steinberg. This must be reconciled. In some cases, the AVN lesion *may* be highly localized, but, here again, the marrow spaces within the

lesion are occluded. Thus, the shared observation between OA and AVN is the occluded marrow spaces, while their shared pathologic event is the calcification of avascular bone. The term subchondral sclerosis is used ubiquitously to describe an x-ray finding, thereby shrouding deeper thought beyond mechanical explanations on how and why sclerosis developed in the first cause. It is important to note that treatment for AVN should include restoration of the bone's porosity and its transosseous blood flow. Therefore, grafting the femoral head with non-porous bone graft substitutes of any kind should be avoided. Further, grafts substitutes that promote increased bone density are silent on bone porosity and should be avoided as well. Synthetic bone grafts require a diseased FH to act on the synthetic bone graft, when the bone graft used should act (providing needed cells and proteins) on the FH. Blind debridement through an 8 mm to 9 mm core track, while less invasive than the Trapdoor, the Lightbulb, or the FVFG procedures, still makes the assumption that disease is confined to the obvious findings on the MRI. Notwithstanding any of the above, the methods of synthetic bone grafting in the treatment of AVN is considered by Brannon to be the removal of dead bone and its replacement with something that was never really alive. These kinds of considerations have guided development at OSI over many years, leading to safer and more efficient ways to thoroughly debride the FH and harvest large volumes of autologous cancellous bone and bone marrow through a stab incision at the iliac crest. A synthetic bone graft is the least favorable of several grafting options.

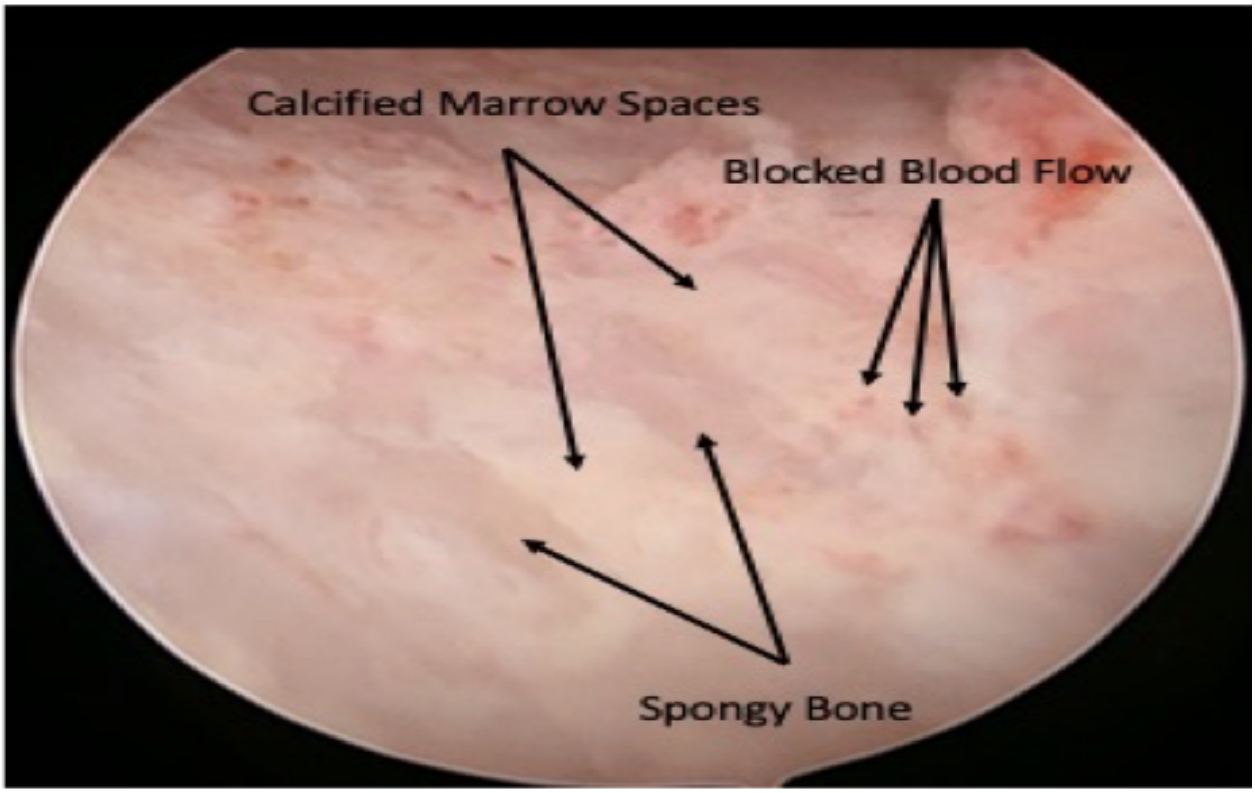

Figure 1: Intraosseous Endoscopy. Core decompression of the femoral head (FH) has been completed and an arthroscope has been placed inside of the FH core track. Intraosseous endoscopy reveals the occluded marrow spaces of Freund. Occlusion of the marrow spaces with calcium is induced by oxLDL. Note the histologic confluence between the trabeculae and the calcium deposits, signaling a metabolic process that leads to calcification of the marrow spaces. This must be differentiated from mineralization, a normal physiologic process, characteristic of bone formation.

OXIDIZED LDL, CARDIOVASCULAR DISEASE, AVN & CALCIFIED MARROW SPACES

Free radicals are generated under normal metabolic conditions or conditions wherein tissue cells experience decreased oxygen, e.g., hypoxia, and an acidic environment. This scenario is common within the bone where excess fat imparts pressure on the small blood vessels (capillaries) that travel throughout the marrow spaces resulting in decreased blood flow. These areas of decreased blood flow experience micro hypoxia resulting in increased levels of HIF-1α, as noted by Zaidi et al.[5] The level of free radicals may increase as cells experience increasingly hypoxic conditions. Once the oxLDL is formed, it binds to the endothelial cell via LOX-1, which stimulates the endothelial cell to release cytokines IL-1α, IL-1β, IL-6, and TNFα, and the chemokine, such as CCL2. The released cytokines are proinflammatory, and the released chemokine recruits monocytes to the area as scavenger cells. Once monocytes enter the area, they differentiate into macrophages that engulf the oxLDL, becoming foam cells in cardiovascular disease, CVD. Foam cells increase in size as larger amounts of oxLDL are engulfed. These foam cells die through a process of apoptosis, thus providing a necrotic nidus for their extracellular matrix calcification by trans-differentiated smooth muscle cells (osteoblast-like cells). This process leads to plaque formation, e.g., calcification of the blood vessels around the heart, and comprises CVD. Regarding bone, bone lining cells (osteoblast) residing along the trabeculae of cancellous bone may initiate calcification (a pathologic process–note the difference in the color of the deposited calcium within the marrow spaces in Figure 1 above, also see Reference 1, Figure 4), not ossification (a physiologic process–the process of mineralization of type I collagen), of the marrow spaces through extracellular matrix vesicle deposition onto the necrotic cancellous bone. As the calcification process within the marrow spaces continues, the blood supply to the cancellous bone is further compromised and additional osteocytes die. The calcified cancellous bone may now appear dense and be considered subchondral sclerosis on x-ray or *mixed-signal heterogeneity* on MRI. This pattern of mixed-signal heterogeneity may present as a starburst within the center of the femoral head (densely sclerotic bone surrounded by osteopenic bone) on axial CT images.[1] This process of calcification may augment the mechanically induced thickening of the cancellous bone postulated by Pugh, Radin, and Rose.[10] Further, the calcified marrow spaces obstruct the *transosseous blood flow* within the femoral head causing the blood flow to become stagnant where the superior retinacular, inferior vincular, and foveal arteries enter the bone.[11] Within the joint, at the foveal artery, the ligamentum teres becomes congested along with the pulvinar leading to a space occupying effect within the cotyloid fossa. This intraarticular congestion decreases the space available for the ligamentum teres, SALT, within the cotyloid fossa and leads to lateral subluxation of the femoral head during midstance, rim loading, and articular sided labral tears as the femoral head progresses toward OA.[12,13] Once the cotyloid fossa pulvinar calcifies, it is called a central acetabular osteophyte. A pincer lesion at the rim of the acetabulum is a common finding as well. Relative to the superior retinacular and inferior vincular arteries, the stagnant blood flow in these areas of the femoral head along with intraosseous fat lead to the development of alpha and beta CAM lesions, and bone spurs (osteophytes) in some cases. In view of the information that can be obtained by visually examining the core decompression track, OSI developed and patented a unique intraosseous endoscopy system to eliminate the assumptions often made about AVN. The intraosseous visual observations made

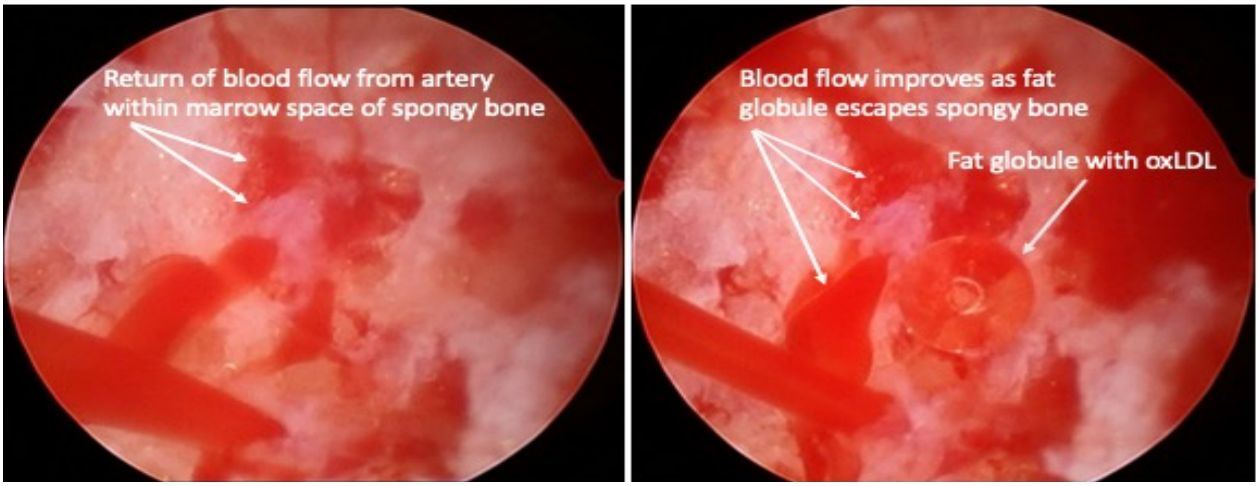

Figure 2: Endoscopic image after debridement of the femoral head in Figure 1. The arthroscope reveals bleeding cancellous bone from an artery within a marrow space. If the above core decompression alone does NOT restore the transosseous blood flow, additional debridement is required. Blind debridement is characteristic of the Lightbulb, the Trapdoor, and the FVFG procedures, and the MRI of Steinberg is silent on the presence of occluded marrow spaces.

with OSI's system answered many questions and helped reconcile the work of Freund with that of Steinberg in view of Urbaniak by providing a framework to pursue how and why the marrow spaces calcify and become occluded in AVN, Atypical AVN, and Osteoarthritis. Being the first to document the intraosseous presence of oxLDL in patients with chronic knee pain, bone marrow edema lesions, and osteoarthritis, Brannon strongly believes that oxLDL plays a major role in the pathologic calcification of the marrow spaces. This rationale is based on the fact that vascular smooth muscle cells (VSMC) have been shown to trans-differentiate into calcifying vascular smooth muscles cells (C-VSMCs) after stimulation by cytokines released from macrophages having engulfed oxLDL. Thus, trans-differentiated C-VSMCs keep their own identity while using mechanisms that osteoblasts use to mineralize bone.[23] Extracellular matrix genes and genes involved in tissue mineralization constitute important common mimicries between pathologic vascular calcification by C-VSMCs and physiologic bone mineralization by bone lining cells (osteoblast), making the role of osteoblast, native to cancellous bone, crucial to understanding pathologic calcification of marrow spaces. The left panel in Figure 2 reveals active bleeding from the intraosseous blood vessels described by Boraiah et al. after core decompression.[11] The blood flow is initially sluggish. The right panel shows how the intraosseous blood flow improves as the intraosseous fat escapes. These kinds of findings by Brannon over the past 20 years have contributed to the success of the Hip Tool Bone Graft Stabilization procedure, allowing many patients with AVN and Atypical AVN to avoid a "revascularization" procedure. OSI's approach debrides necrotic bone to a bleeding host bed, as shown above, restores the bone's porosity, and then stabilizes the autologous bone graft placed inside of the femoral head cavity with the Hip Tool. As described in the above reading, the blood vessels that supply the femoral head are obstructed intraosseously, and secondarily create changes within the joint space. That said, OSI provides its patented specialized hip arthroscopy system, The Q™, to address the articular-sided changes of AVN during a single procedure. The articular sided

changes are congestion of the cotyloid fossa, CAM and pincer lesions, and articular-sided labral tears.[1,12,13,17] The single procedure of hip arthroscopy combined with core decompression and thorough debridement with bone graft stabilization has preserved many hips over several years.

In the case of the knee, the marrow spaces within the cancellous bone in the patellofemoral sulcus become increasingly occluded, and the space available for the excess intraosseous fat is continuously decreased. As a result, the excess fat is forced to exit at the osteochondral junction, the bone's weakest point, wherein a bone spur will develop and oxLDL is released into the joint space. OxLDL is destructive to articular cartilage and simultaneously causes inflammation within the joint.[14] The menisci become increasingly trapped as the bone spurs enlarge. The knee is often staged as having mild, moderate, or severe osteoarthritis according to the Kellgren-Lawrence system.

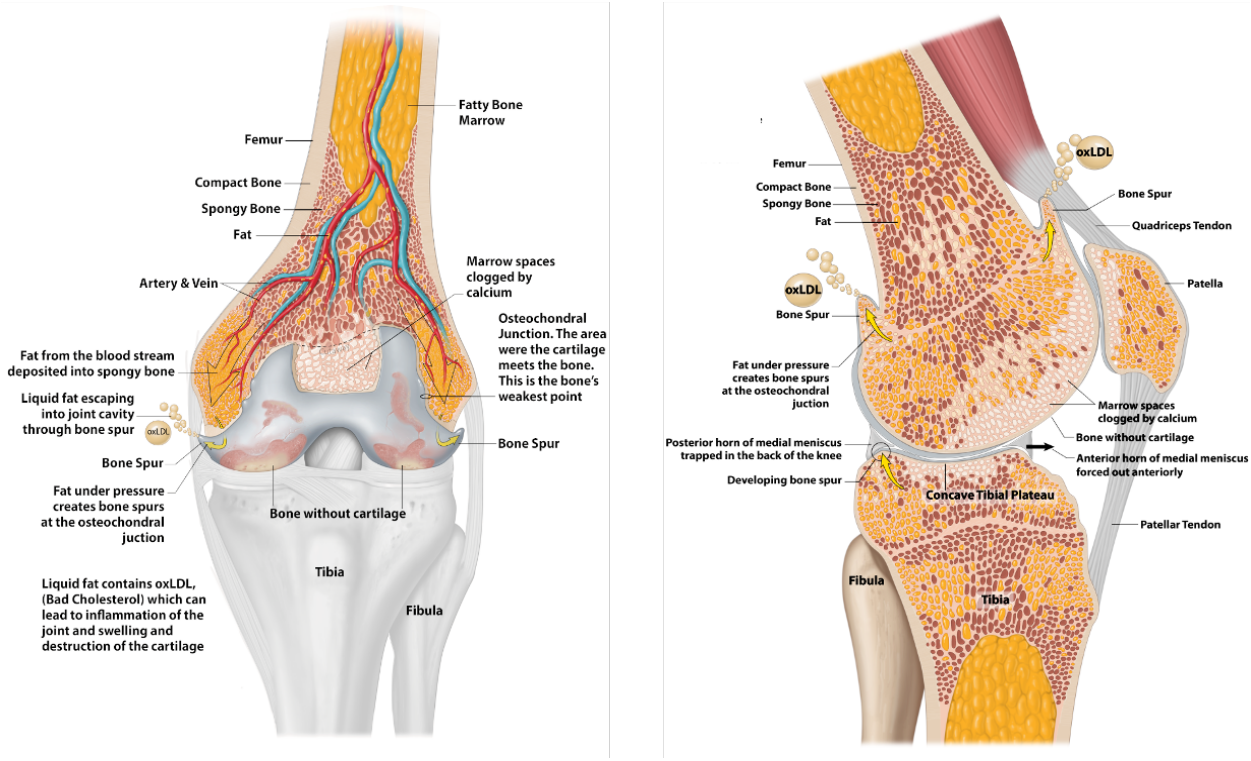

Figure 3: Artist rendition of OA of the knee. Calcified marrow spaces resulting from cytokine-mediated matrix vesicle deposition of calcium by bone lining cells (osteoblast). Increased intraosseous pressure forces the fat within the marrow spaces to exit the bone at the bone's weakest point, the osteochondral junction. As the fat exits, bone spurs develop at the osteochondral junction. The exiting fat comprises LDL, oxLDL, cholesterol, and cholesterol esters. Importantly, intraosseous oxLDL is engulfed via the LOX-1 scavenger receptors on macrophages. Once engulfed, the macrophages are polarized to the M1 phenotype resulting in a profound increase in proinflammatory cytokines, IL-1α, IL-1β, TNF-α, and M1-surface marker CD86 expression. These proinflammatory cytokines may give rise to the bone marrow edema lesions seen on MRI, resulting in osteopenia and intraosseous insufficiency fractures. OxLDL is destructive to articular cartilage as well. Increased intake of saturated fats and trans fats contribute to the intraosseous fat load within the bone.

The relationship between CVD, OA, AVN, Atypical AVN, and, potentially, aseptic loosening is apparent through the shared unfavorable metabolic product, oxLDL.

While cardiology has extensively studied oxLDL and the use of statins to lower the incidence of ischemic cardiac events, orthopaedics appears to have missed this correlation relative oxLDL induced calcification of marrow spaces. This missed correlation within orthopaedics is likely due to subspecialization and the recognized success of arthroplasty. However, the increasing volumes of joint replacements and revisions are not sustainable, aside from an analysis of the lifetime costs of OA in the United States.[15] While the success of total knee arthroplasties is not insignificant, they are systemically irrelevant, because how and why the joint becomes arthritic has not been fully elucidated, aside from concepts that hinge on the articular cartilage failing first, its senescence, and recently, high levels of N-*myc* downstream-regulated gene 3, NDRG3, in arthritic knees. More specifically, NDRG3 has been shown to function as a hypoxia-inducible lactate sensor, playing key roles in the promotion of hypoxia responses in a HIF-independent manner.[24,25] However, a cause-and-effect relationship is not apparent, because intraosseous hypoxia emanates from vascular occlusion, making NDRG3 a downstream finding versus an upstream cause of OA. That said, a broader view of OA (focusing on the underlying bone in addition to the overlying cartilage) allows one to reconsider OA and AVN in view of perceived putative physiologic differences amongst them. Thus, multiple questions are raised. When performing a total knee replacement, is there a large amount of oxLDL released into the circulation upon deflation of the tourniquet, comprising an **oxLDL storm**? Do these oxLDL bind to the endothelial lining of the deep veins and cause inflammation leading to clot formation and a DVT after a total knee arthroplasty? Could an oxLDL storm explain fat embolism syndrome in patients with a long bone fracture? The binding of oxLDL to endothelial cells leads to platelet aggregation. Additionally, platelets express CD36 class B scavenger receptors, providing endothelial independent activation and release of inflammatory cytokines.[27] Cardiac data has shown that plaque formation, which requires binding of oxLDL to endothelial cells and macrophages, is more likely in areas where laminar flow is absent.[16] This summary postulates that the binding of oxLDL to endothelial cells is more likely in areas where blood flow is sluggish, as is the case in the deep veins of the legs. **Is there a cause-and-effect relationship between increased levels of circulating oxLDL after a total knee arthroplasty and DVT?** Regarding aseptic loosening, does oxLDL contribute to the chronic inflammation observed through the release of proinflammatory cytokines and M1 polarization of macrophages? **The accumulation of excess fat within the bone and oxidation of LDL does NOT cease after the knee is replaced.** While autophagy is considered the primary mechanism of aseptic loosening, the role oxLDL may play in aseptic loosening has not been considered.[16,26] Basic physiology teaches beta fatty acid oxidation and that the intestinal absorption of triglycerides into the vascular system is via the lymphatics. This knowledge allows one to consider triglycerides, cholesterol, and cholesterol ester molecules, unaffected by the first-pass effect of the liver, as biomarkers of one's diet, save for the inborn error of metabolism in familial hypercholesterolemia described by Brown and Goldstein. Further, the SNPs on chromosome 12p for LOX-1 oxLDL receptors may help explain why OA is NOT solely a disease of obese patients with diabetes and hypertension. To what degree is the LOX-1 gene expressed? The orthopaedist should counsel his or her patients about fat intake after an arthroplasty, irrespective of the benefits of a normal BMI, recognizing that oxLDL is still produced in the replaced knee and that such unfavorable metabolic byproduct may accumulate at the bone prosthesis interface and contribute to loosening of the

prosthesis. Could oxLDL levels serve as a biomarker of potential aseptic loosening in early continued chronic knee pain after an arthroplasty? Would comparing preoperative levels with downstream postoperative levels in relation to continued pain and aseptic loosening be beneficial? Arthroscopy for osteoarthritis with a meniscus tear or mechanical symptoms can potentially be beneficial when the basic science of the disease being treated is thoroughly understood.[18,21]

Clearly, the above can be viewed from countless perspectives, with a plethora of commentary about its source and the intent thereof; none of which is relevant because an understanding of the role oxLDL plays in arthritic disease is needed. A summary has been provided of the peer-reviewed literature on OA, AVN, Atypical AVN, and CVD, as it relates to oxLDL, with a view of aseptic loosening, and at a minimum, one should be motivated to read through these references and ask the questions the author asked.[22] What causes calcification and occlusion of the marrow spaces?

CONCLUSION

This summary does not purport to provide the answer to the etiology of OA. However this summary does elucidate the similarities between OA, AVN, and Atypical AVN. It can be reasoned that unrecognized AVN (Atypical AVN, bone with occluded marrow spaces due to ectopic calcification) may comprise the hips, knees, and shoulders that go on to develop OA. Not surprisingly, OA is more common in females in view of the biglycan gene being encoded on the X-chromosome. Again, the author notes that biglycan retains LDL in the ECM, wherein it is ultimately oxidized. More importantly, oxLDL is hypothesized to be the shared metabolic byproduct amongst these diseases. The literature is replete with the role of oxLDL in calcific CVD. Yet, the orthopaedic literature has not considered the role oxLDL may play in OA nor its presence in the bone or the joint fluid of an arthritic hip, knee, or shoulder. It has be shown that oxLDL induces platelet aggregation and is proinflammatory at the endothelial level. Its release from the bone during a total knee, in particular, may help explain postoperative DVTs. The author reasons that the release of oxLDL during arthroplasty leads to an **oxLDL storm**. Understanding this unmitigated release of oxLDL may be critical to the postoperative management of patients that do undergo a major arthroplasty. The author believes that thinking more broadly about oxLDL ensures more predictable outcomes following joint preservation and continues to be crucial to its clinical success described by the author over the past 20 years. The author is confident that the reasoning and data provided herein, comprising a broader view of OA and AVN, to include the mimicries between C-VSMCs and osteoblast cannot be ignored.

The use of the joint preservation products developed at OSI in one's practice is independent of any duty of care owed to a patient. The orthopedist must act as a responsible steward of data and resources, counseling the patient so that they are aware of the options they might have for joint pain based on the orthopaedist's best recommendations.

Limitations of the Study

This study was based on available scientific literature, and no clinical trials were conducted to execute the conclusion.

Conflict of Interest

The author is the sole contributor of the opinions described herein and the sole inventor of OSI's medical products.

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Publication Consent

Not required.

Data and materials availability

All relevant data of this study are presented in the paper.

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