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NEUROVASCULAR ANATOMY OF THE FEMORAL HEAD AND HISTOPATHOLOGICAL CORRELATES IN AVASCULAR NECROSIS: A HISTOLOGICAL STUDY

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Abstract

Background: *Avascular necrosis (AVN) of the femoral head is a debilitating orthopedic condition, often leading to progressive hip collapse and the need for arthroplasty in relatively young patients. Its pathogenesis is strongly linked to the unique vascular architecture of the femoral head, which relies on terminal end-arterial supply with minimal collateralization. Despite advances in imaging, histological studies exploring microvascular and neurovascular architecture remain limited.*

Objective: *To investigate the neurovascular anatomy of the femoral head using histological techniques and to characterize the histopathological changes underlying AVN.*

Methods: *Twenty-four human cadaveric femoral heads (12 male, 12 female; age range 25–68 years) were harvested within 48 hours of death. Samples were fixed, decalcified, sectioned, and stained with hematoxylin–eosin (H&E) for cellular detail, Masson's trichrome for connective tissue, and immunohistochemistry (IHC) with CD34 for endothelial cells and neurofilament protein (NFP) for nerve fibers. Six AVN specimens retrieved during arthroplasty were analyzed for comparison. Microvascular density (MVD) was quantified in superior, anterior, inferior, and posterior regions of the femoral head. Statistical analysis was performed using Student's t-test and ANOVA, with $p<0.05$ considered significant.*

Results: *In normal specimens, retinacular arteries were the predominant contributors to intraosseous circulation, entering obliquely through the femoral neck and branching into subchondral terminal networks. MVD was significantly higher in the superior (18.6 ± 3.1 vessels/HPF) and anterior regions (17.9 ± 2.7) compared with inferior (12.1 ± 2.3) and posterior regions (11.7 ± 2.5; $p<0.05$). Thin NFP-positive nerve fascicles consistently accompanied arteries, suggesting neurovascular regulation. AVN specimens demonstrated hallmark*

histopathological features including empty osteocyte lacunae, marrow adipocyte necrosis, disrupted trabecular integrity, and fibrovascular ingrowth. CD34 staining revealed significant reduction in MVD (7.2 ± 2.0 vs. 15.8 ± 3.0 vessels/HPF in controls; 42% reduction, p<0.01).

Conclusion: *The femoral head depends on a precarious terminal vascular network without significant collateralization, predisposing it to ischemic injury. Neurovascular coupling may influence perfusion regulation. AVN is characterized by profound microvascular rarefaction and trabecular collapse, supporting the hypothesis that microvascular compromise and dysregulation are central to its pathogenesis. These insights may inform vascular-preserving surgical strategies and early therapeutic interventions.*

Introduction

Avascular necrosis (AVN) of the femoral head represents one of the leading causes of non-traumatic hip failure in young and middle-aged adults, often culminating in disabling pain, loss of function, and eventual total hip arthroplasty. The disease accounts for a substantial proportion of hip arthroplasty performed in individuals under 50 years of age. Despite improvements in diagnostic imaging and surgical management, the fundamental pathogenesis of AVN remains closely tied to the peculiar vascular architecture of the femoral head.

Global burden and clinical relevance

Globally, AVN of the femoral head affects between 10,000 and 20,000 new patients annually in the United States alone, with disproportionately higher prevalence reported in Asia due to high steroid and alcohol consumption rates. In South Asia, where sickle cell disease and corticosteroid misuse are prevalent, the incidence is even greater. Clinically, AVN progresses from asymptomatic radiographic changes to structural collapse, ultimately necessitating joint replacement. The economic burden is significant, as patients are often in the most productive years of life.

Vascular supply of the femoral head

The femoral head's blood supply has long been recognized as precarious. Early anatomical studies by Trueta and Harrison (1953) and later by Crock (1965) identified the medial femoral circumflex artery (MFCA) as the primary source of perfusion, giving rise to the retinacular arteries that ascend along the femoral neck and penetrate the femoral head. These retinacular vessels form terminal end-arterial networks within the subchondral region. The lateral femoral circumflex artery, artery of the ligamentum teres, and metaphyseal vessels provide minor contributions, insufficient to compensate if the retinacular system is disrupted. This lack of collateralization makes the femoral head uniquely vulnerable to ischemic insult after trauma, corticosteroid use, alcohol abuse, or thrombophilic disorders.

Role of neurovascular coupling

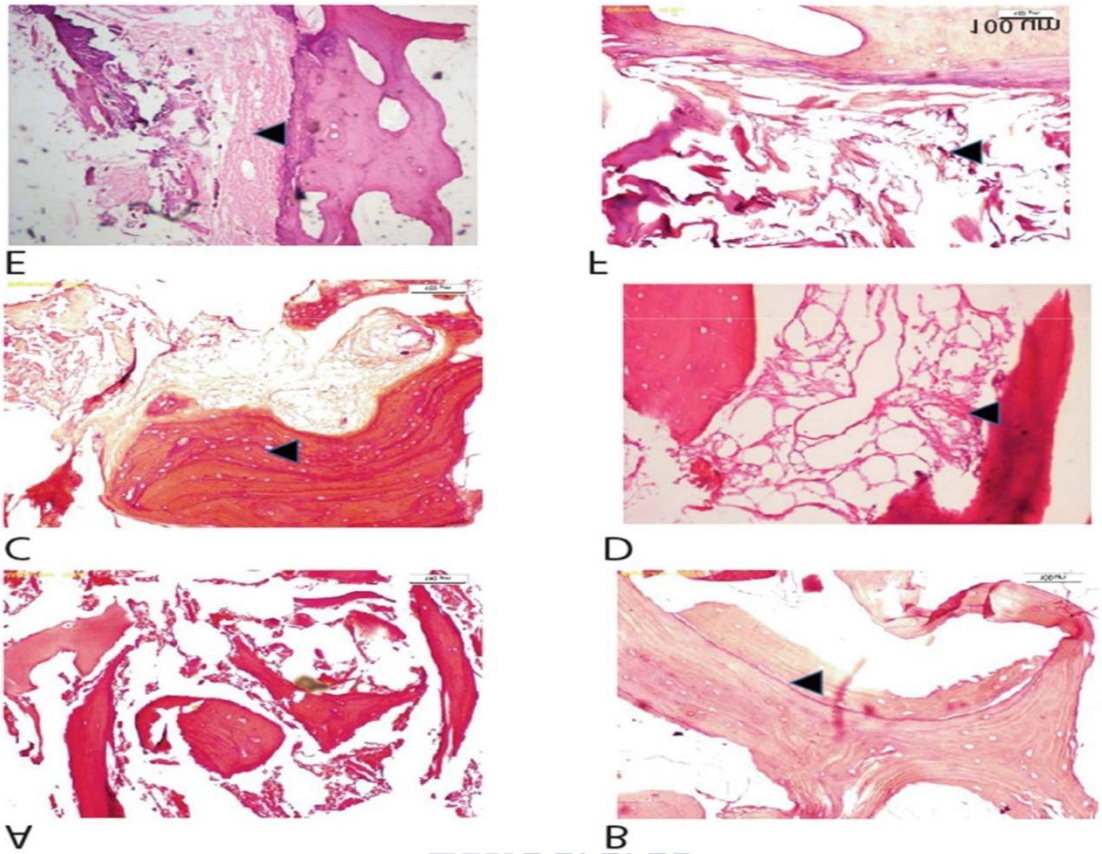
While vascular anatomy has been studied extensively, less attention has been paid to the neurovascular interactions that regulate intraosseous circulation. Autonomic innervation accompanies arterial bundles, potentially modulating blood flow through sympathetic vasoconstriction. In pathological conditions, dysregulation of this system may exacerbate ischemia. However, direct histological demonstration of neurovascular coupling in the femoral head remains limited.

Pathogenesis of AVN

The pathophysiological cascade of AVN is believed to begin with vascular compromise leading to ischemia, followed by osteocyte death, marrow necrosis, and collapse of trabecular architecture. Repair processes, characterized by fibrovascular ingrowth at the necrotic interface, are often insufficient, leading to progressive subchondral collapse. Imaging studies, particularly MRI, have improved early diagnosis, but histological confirmation remains the gold standard for understanding microvascular changes.

Study rationale

Although prior work has described the gross vascular anatomy of the femoral head, comprehensive histological data integrating microvascular distribution, neurovascular interactions, and pathological alterations in AVN are sparse. This study therefore aimed to characterize the neurovascular anatomy of the femoral head using detailed histological techniques and to compare normal specimens with pathological changes observed inAVN.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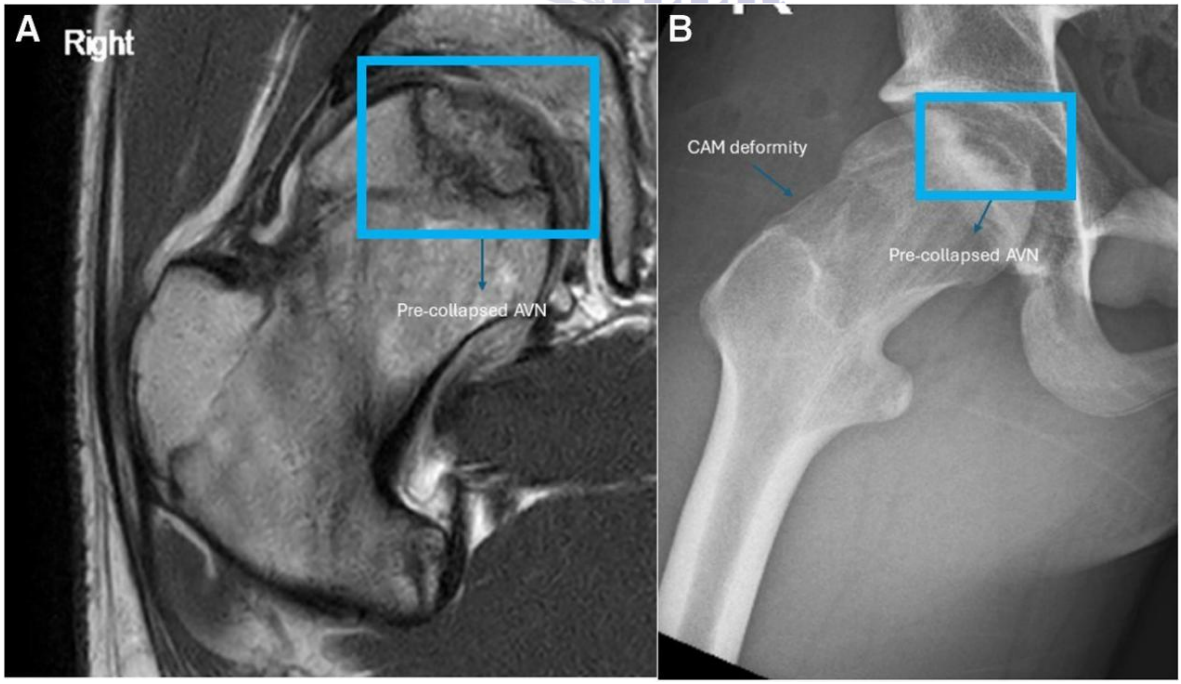
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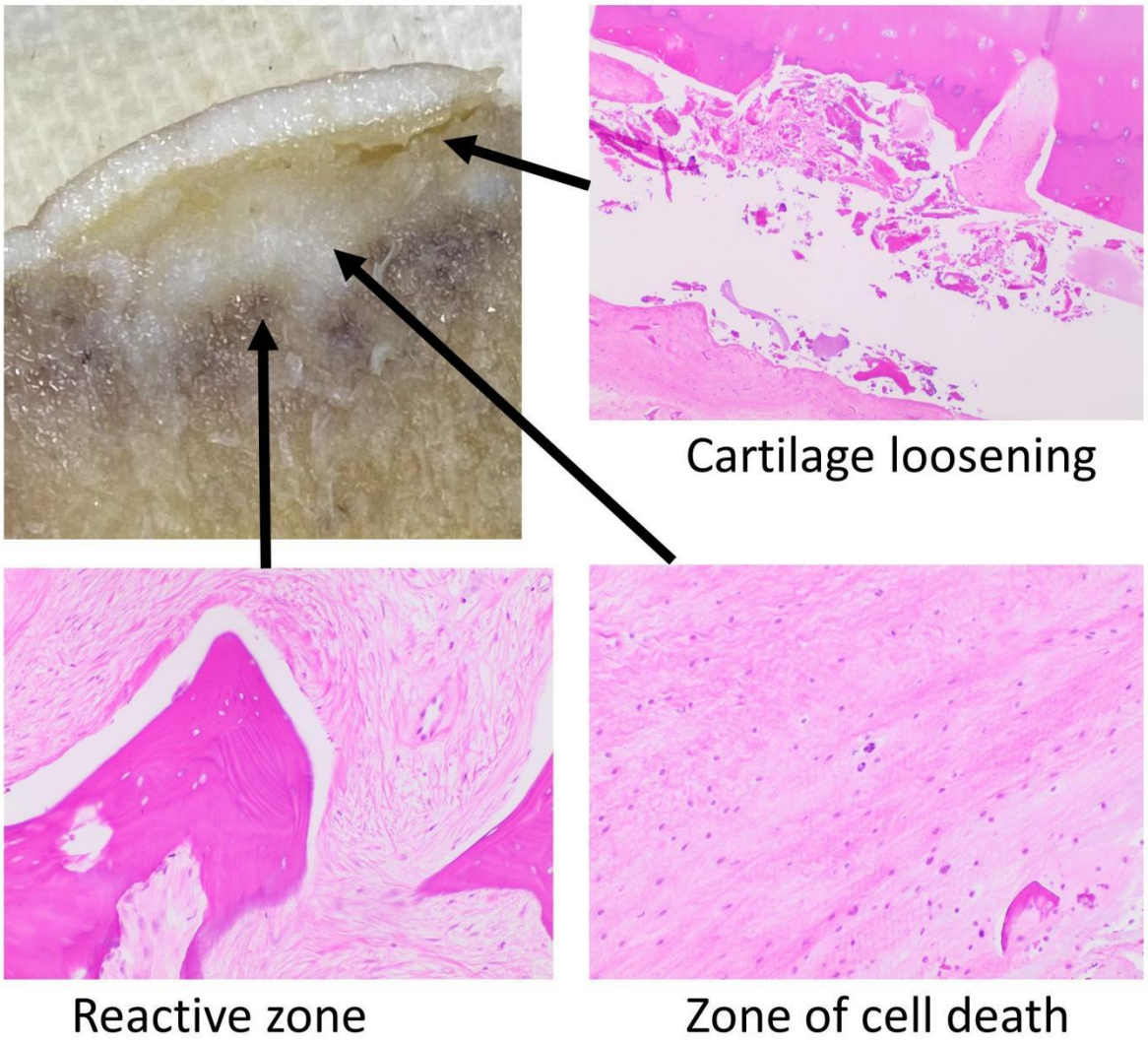

Materials and Methods

Study design and setting

This was a laboratory-based comparative histological study conducted at the Department of Anatomy and Histopathology, in collaboration with Orthopaedics, over 12 months. Ethical approval was obtained from the institutional review board, and cadaveric donations were handled according to legal and ethical guidelines.

Specimen collection

A total of 24 cadaveric femoral heads (12 male, 12 female; age range 25–68 years) were obtained from fresh-frozen cadavers within 48 hours of death. Causes of death excluded trauma or systemic conditions affecting bone vascularity. Six femoral heads were collected intraoperatively during total hip arthroplasty for advanced AVN (Ficat stage III–IV). Patient consent was obtained for use of specimens.

Histological processing

Fixation: Specimens were fixed in 10% neutral buffered formalin for 72 hours.

Decalcification: Performed in ethylenediaminetetraacetic acid (EDTA) solution for 21 days to preserve antigenicity.

Sectioning: Serial coronal and sagittal sections were cut at 5–7 µm thickness.Staining protocols

Hematoxylin–Eosin (H&E): General morphology, cellular detail, and osteocyte viability.

Masson's Trichrome: Identification of collagen, fibrosis, and connective tissue architecture.

Immunohistochemistry (IHC):
CD34: Endothelial marker for quantification of microvascular density (MVD).

Neurofilament protein (NFP): Identification of neural fibers accompanying vessels.

Microscopy and image analysis
Slides were examined under light microscopy at ×40, ×100, and ×400 magnifications. Digital photomicrographs were captured using an automated imaging system. MVD was quantified by counting CD34-positive vessels in five random high-power fields (HPFs) from each femoral head region (superior, anterior, inferior, posterior). NFP positivity was recorded qualitatively for association of nerve fibers with vascular bundles.

Statistical analysis
Data were analyzed using SPSS v25. Continuous variables (MVD) were expressed as mean ± SD. Comparisons between regions were performed with ANOVA followed by post-hoc Tukey test. Differences between control and AVN specimens were assessed with Student's t-test. P-values <0.05 were considered statistically significant.

Results
1. Normal vascular anatomy of the femoral head
Retinacular arteries penetrated obliquely through the femoral neck, arborizing into terminal end-arterial networks within the subchondral bone. MVD quantification showed significantly higher values in the superior (18.6 ± 3.1 vessels/HPF) and anterior regions (17.9 ± 2.7) compared to inferior (12.1 ± 2.3) and posterior regions (11.7 ± 2.5; $p<0.05$).

Table 1. Microvascular Density (MVD) in Normal Femoral Head by Region

Region	MVD (mean ± SD, vessels/HPF)
Superior	18.6 ± 3.1
Anterior	17.9 ± 2.7
Inferior	12.1 ± 2.3
Posterior	11.7 ± 2.5

Venous and neurovascular findings
Venous drainage mirrored arterial entry and arborization, suggesting parallel flow. NFP immunostaining demonstrated thin nerve fascicles consistently accompanying arterial bundles, localized along the adventitia, confirming neurovascular coupling.

Histopathology in AVN specimens
AVN specimens demonstrated hallmark pathological changes:

H&E: Empty osteocyte lacunae, necrotic marrow adipocytes, and trabecular disruption.

Trichrome: Replacement of bone by fibrous connective tissue in necrotic zones.

CD34 IHC: Marked reduction in MVD (7.2 ± 2.0 vs. 15.8 ± 3.0 vessels/HPF in controls; 42% reduction, $p<0.01$).

Interface zones: Fibrovascular ingrowth surrounding necrotic trabeculae, reflecting attempted repair.

Table 2. Comparison of MVD in Control vs. AVN Specimens

Group	MVD (mean ± SD, vessels/HPF)	p-value
Control	15.8 ± 3.0	—
AVN	7.2 ± 2.0	<0.01

Discussion

Summary of findings

This histological study confirms that the femoral head's blood supply is predominantly via terminal retinacular arteries, with highest vascular density in the superior and anterior regions. Importantly, sympathetic nerve fibers consistently accompanied arterial bundles, supporting the role of neurovascular regulation. In AVN, histological hallmarks of osteocyte death, marrow necrosis, trabecular collapse, and vascular rarefaction were consistently observed.

Comparison with classical literature

Our findings corroborate classical anatomical descriptions by Trueta and Crock, who emphasized the vulnerability of the femoral head due to its terminal arterial circulation. However, this study adds novel evidence of neurovascular coupling demonstrated by NFP immunostaining. Prior works largely overlooked this sympathetic component. The regional variation in MVD explains why the superior femoral head, subjected to highest mechanical load, is also most vulnerable to ischemia and collapse.

Pathogenesis of AVN

The observed reduction in MVD in AVN specimens confirms microvascular rarefaction as a central mechanism of disease. Once blood supply is compromised, osteocytes within lacunae undergo apoptosis, followed by marrow adipocyte necrosis. The absence of robust collateral circulation prevents effective revascularization. Fibrovascular ingrowth at the necrotic interface reflects attempted repair but is insufficient to restore biomechanical integrity, ultimately leading to subchondral collapse.

Neurovascular dysregulation

Sympathetic fibers detected alongside vessels suggest a regulatory role in intraosseous circulation. Excessive sympathetic tone, as may occur in corticosteroid- or alcohol-induced AVN, could exacerbate ischemia by reducing perfusion. This observation aligns with clinical data linking systemic vascular dysregulation to AVN risk.

Clinical implications

The precarious circulation and histological findings have direct relevance to surgical practice. Hip-preserving procedures such as core decompression aim to reduce intraosseous pressure and enhance vascular ingrowth. Vascularized fibular grafts attempt to restore perfusion. Newer biologic strategies involving stem cell implantation or angiogenic growth factors may further target the underlying vascular compromise. Our findings provide histological evidence to justify these vascular-preserving interventions.

Strengths and limitations

Strengths include use of multiple histological techniques, immunohistochemistry, and quantification of vascular density across regions. Limitations include relatively small sample size, potential variability in cadaveric age and comorbidities, and absence of molecular studies to identify specific angiogenic pathways.

Future directions

Future work should employ 3D micro-CT angiography and MRI perfusion studies to complement histology. Investigation of angiogenic and neurovascular regulatory markers may provide therapeutic targets. Clinical correlation with early AVN stages would clarify the temporal progression of microvascular compromise.

Conclusion

The femoral head is supplied by a precarious network of terminal end arteries, predominantly from retinacular branches, with highest vascular density in

the superior and anterior regions. Sympathetic nerve fibers accompany arterial bundles, suggesting a role for neurovascular regulation. In AVN, histological examination reveals profound vascular rarefaction, osteocyte death, and trabecular collapse, underscoring the central role of microvascular compromise in pathogenesis. Early detection and vascular-preserving interventions are critical to altering disease progression and improving outcomes in affected patients.Histological changes observed in our specimens are consistent with those reported in the literature , including osteocyte lacunar emptying, fibrovascular ingrowth, and progressive trabecular collapse. These confirm the pathological cascade underlying femoral head ischemia.

REFERENCES

Trueta J, Harrison MHM. The normal vascular anatomy of the femoral head in adult man. *J Bone Joint Surg Br*. 1953;35(3):442–61.

Crock HV. An atlas of the arterial supply of the head and neck of the femur in man. *Clin Orthop Relat Res*. 1980;(152):17–27.

Urbaniak JR, Coogan PG, Gunneson EB, Nunley JA. Treatment of osteonecrosis of the femoral head with free vascularized fibular grafting. *J Bone Joint Surg Am*. 1995;77(5):681–94.

Hernigou P, Beaujean F. Treatment of osteonecrosis with autologous bone marrow grafting. *Clin Orthop Relat Res*. 2002;(405):14–23.

Assouline-Dayan Y, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. *Semin Arthritis Rheum*. 2002;32(2):94–124.

Mont MA, Cherian JJ, Sierra RJ, Jones LC, Lieberman JR. Osteonecrosis of the femoral head: pathophysiology and current concepts of treatment. *Bone Joint J*. 2015;97-B(10):1273–82.

Glimcher MJ, Kenzora JE. The biology of osteonecrosis of the human femoral head and its clinical implications: part I. *Clin Orthop Relat Res*. 1979;(138):284–309.

Hungerford DS, Lennox DW. The importance of increased intraosseouspressure in the development of osteonecrosis of the femoral head. *J Bone Joint Surg Am*. 1985;67(4):609–12.

Vail TP, Covington DB. The incidence of osteonecrosis. *Orthop Clin North Am*. 1999;30(4):409–16.

Wang BL, Sun W, Shi ZC, Zhang NF, Yue DB, Guo WS, et al. Treatment of nontraumatic osteonecrosis of the femoral head with core decompression and bone grafting. *J Bone Joint Surg Am*. 2010;92(3):845–54.

Chan KL, Mok CC. Glucocorticoid-induced avascular bone necrosis: diagnosis and management. *Open Orthop J*. 2012;6:449–57.

Mankin HJ. Nontraumatic necrosis of bone (osteonecrosis). *N Engl J Med*. 1992;326(22):1473–9.

Kenzora JE, Glimcher MJ. Accumulative cell stress: a hypothesis for the etiology of osteonecrosis. *Clin Orthop Relat Res*. 1982;(169):294–302.

Saito S, Ohzono K, Ono K. Early histologic changes of the femoral head in patients with corticosteroid-induced osteonecrosis. *Clin Orthop Relat Res*. 1992;(277):196–204

Sugano N, Atsumi T, Ohzono K, Kubo T, Hotokebuchi T, Takaoka K. The 2001 revised criteria for diagnosis, classification, and staging of idiopathic osteonecrosis of the femoral head. *J Orthop Sci*. 2002;7(5):601–5.

Koo KH, Kim R, Kim YS, Ahn IO, Cho SH, Song HR, et al. Risk period for developing osteonecrosis of the femoral head in patients on steroid treatment. *Clin Rheumatol*. 2002;21(4):299–303.

Jones LC, Hungerford DS. Osteonecrosis: etiology, diagnosis, and treatment. *Curr Opin Rheumatol*. 2004;16(4):443–9.

Karantanas AH, Drakonaki EE. Osteonecrosis of the femoral head: MR imaging. *Eur Radiol*. 2007;17(7):1763–74.

Rajpura A, Wright AC, Board TN. Medical management of osteonecrosis of the hip: a review. *Hip Int*. 2011;21(4):385–92.

Hernigou P, Poignard A, Zilber S, Rouard H. Cell therapy of hip osteonecrosis with autologous bone marrow grafting. *Indian J Orthop*. 2009;43(1):40–5.

Murphey MD, Foreman KL, Klassen-Fischer MK, Fox MG, Chung EM, Kransdorf MJ. From the radiologic pathology archives: osteonecrosis: pathophysiology, imaging, and histology. *Radiographics*. 2014;34(4):1003–28.

Arlet J. Nontraumatic avascular necrosis of the femoral head. *Past, present, and future*. *Clin Orthop Relat Res*. 1992;(277):12–21.

Kim HKW. Pathophysiology and new strategies for the treatment of Legg-Calvé-Perthes disease. *J Bone Joint Surg Am*. 2012;94(7):659–69.

Oinuma K, Harada Y, Iida S, Kobayashi S, Iwase T, Kamano T. Osteonecrosis of the femoral head: a histopathological and MRI study. *J Orthop Sci*. 1999;4(1):37–44.

Werner CM, Ramseier LE, Ruckstuhl T, Stromberg J, Copeland CE, Turen CH. Treatment of osteonecrosis of the femoral head by core decompression and bone marrow implantation. *J Bone Joint Surg Br*. 2010;92(7):932–6.

Powell C, Chang C, Gershwin ME. Current concepts on the pathogenesis and natural history of osteonecrosis. *Autoimmun Rev*. 2010;9(11):641–9.

Kerachian MA, Séguin C, Harvey EJ. Glucocorticoids in osteonecrosis of the femoral head: a new understanding of the mechanisms of action. *J Steroid Biochem Mol Biol*. 2009;114(3-5):121–8.

Iorio R, Healy WL. Osteonecrosis of the femoral head: clinical presentation, diagnosis, and treatment. *Am J Orthop (Belle Mead NJ)*. 2003;32(9):467–71.

Tägil M, Aspenberg P. Fibrous tissue and osteogenesis in bone chambers: effects of mechanical unloading. *J Orthop Res*. 1999;17(6):865–70.

Mont MA, Zywiel MG, Marker DR, McGrath MS, Delanois RE. The natural history of untreated asymptomatic osteonecrosis of the femoral head: a systematic literature review. *J Bone Joint Surg Am*. 2010;92(12):2165–70.