Corticosteroid and Avascular Necrosis (AVN): A Review Corticosteroid induced Osteonecrosis.

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Abstract:

Awareness of the need for the prevention of glucocorticoid-induced fractures is growing, but glucocorticoid administration is often overlooked as the most overlooked common cause of non-traumatic osteonecrosis. Glucocorticoid-induced osteonecrosis develops in 9-40% of patients receiving long-term therapy, although this can also happen with short-term exposure to high doses, after intra-articular Injection, and without glucocorticoid-induced osteoporosis. The name osteonecrosis is misleading since the primary histopathologic lesion is osteocyte apoptosis. Apoptotic osteocytes persist because they are anatomical and not available for phagocytosis and with glucocorticoid Excess, reduced bone turnover delays their replacement. Glucocorticoid-induced osteocyte apoptosis, a cumulative and unrecoverable defect, disrupts the mechanosensory function of the osteocyte's lacunar canal system and thus begins the unstoppable sequence of events leading to the collapse of the femoral head. Currently, Evidence suggests that bisphosphonates can act quickly relieves pain, increase walking ability, and delays joint collapse in patients with osteonecrosis.

Keywords: *Corticosteroid, Avascular Necrosis, Osteonecrosis, Bone fracture, Bisphosphonate, Preiser Disease, Keinbock's Disease.*

Introduction:

Avascular necrosis (AVN) is an uncommon but serious disorder in which interruption of blood supply results in bone tissue death and destruction of the articular surface of joints, most commonly the hip. [14]

The most widely used therapies for allergic rhinitis, asthma, and other inflammatory lung conditions continue to be inhaled and oral corticosteroids. Nevertheless, a number of studies have suggested that these medications may have long-term negative effects on bone metabolism and strength. Patients may be at risk for developing complications like hip and vertebral body fractures and osteonecrosis or AVN of the hip, shoulder, and knee depending on how frequently doctors administer oral or parenteral corticosteroids for urticaria, angioedema, and/or allergic inflammatory response flare-up [1]. Although AVN is strongly associated with several risk factors, including underlying rheumatologic conditions such as systemic lupus erythematosus, bisphosphonate use, radiation exposure, and heavy alcohol consumption [15, 16], systemic corticosteroid use has been implicated in almost one-third of all cases of AVN [17-19]. Several studies have investigated a proposed dose-dependent relationship between corticosteroid use and AVN with varied results. Cumulative total dose relationships have been reported to range from 440 to 9000 mg with relative risks (RRs) of AVN of 6 and 8.8 for the respective doses [20-22]. Controversy exists among studies examining the duration of corticosteroid treatment. Although some have shown that AVN can occur with therapy ranging from 28 to 700 days, [20] others found no risk associated with long-term treatment with corticosteroids. [23,24]

The purposes of this review are to define the currently known causes of osteonecrosis of bone and to define diagnostic options and potential treatments for **Avascular Necrosis (AVN)** or Osteonecrosis. [1]

Recognition of Corticosteroid-Induced Avascular Necrosis:

Less than 1 year after the introduction of cortisone for the treatment of rheumatoid arthritis in 1950, investigators became aware of injurious effects that were considered uncommon in Cushing's syndrome [2]. These effects included insomnia, gastrointestinal bleeding, post-cortisone-withdrawal syndrome, and hip fracture [3, 4]. As vertebral fractures and radiographic osteoporosis had not been observed, the investigators were uncertain whether the hip fractures were the result of falls due to steroid myopathy or merely coincidental with cortisone therapy. Nonetheless, efforts were made to reduce the glucocorticoid dosage [2]. Just a few years later, osteoporosis and fractures were recognized as skeletal complications of prolonged treatment with cortisone, prednisolone, and prednisone. The collapse of the femoral and humeral heads after high-dose therapy was described shortly thereafter [5, 6], sometimes for treatment that was hard to justify [7]. Femoral osteonecrosis has even been noted with occlusive topical glucocorticoid ointment [8,9]. Today, osteonecrosis develops in 9–40% of patients receiving long-term therapy and may occur without glucocorticoid-induced osteoporosis [10]. The first large series of patients with glucocorticoid-induced osteonecrosis was reported in 1971 [11]. Of 482 patients with osteonecrosis seen at the Mayo Clinic from 1961 to 1968, 77 had received glucocorticoids. The report caused some confusion because ''hematologic conditions,'' pancreatitis, pregnancy, rheumatoid arthritis, glomerulonephritis, colitis, and gout were all listed as causes of ''avascular necrosis,'' but these patients had been treated with glucocorticoids and there was no evidence that the conditions listed were independent causes of osteonecrosis, although that was assumed for more than 40 years [12].

The average interval between initiation of treatment and the first symptoms of hip pain was 33 months, but several cases of osteonecrosis were noted after only 3 months. The earliest recognition was just 36 days after 16 mg/day of oral methylprednisolone (cumulative dose was 576 mg). A single ‘‘dose-pack’’ of methylprednisolone may begin with more than 32 mg/day and contain a total dose of as much as 800 mg, so just one dose pack is arguably already a risk for glucocorticoid-induced osteonecrosis. Sadly, patients are seldom warned about this complication or the need to see their doctor if they experience persistent joint pain and radiological surveillance for osteonecrosis in patients receiving high-dose glucocorticoids is restricted to research studies [12]. As a result, osteonecrosis is the most common glucocorticoid-related complication associated with successful litigation [13].

Diagnosis:

Persistent hip, knee, or shoulder pain, especially with joint movement, tenderness, or reduced range of motion, warrants magnetic resonance imaging (MRI) [10, 13, 16]. The subchondral crescent sign on radiographic examination is pathogenomic for osteonecrosis but this sign is not early and MRI can clearly show extensive osteonecrosis before any change in the shape of the femoral head or appearance of a fracture crescent (**Fig. 1**). A wide variety of radiographs showing glucocorticoid-induced osteonecrosis can be found at images on www.google.com.

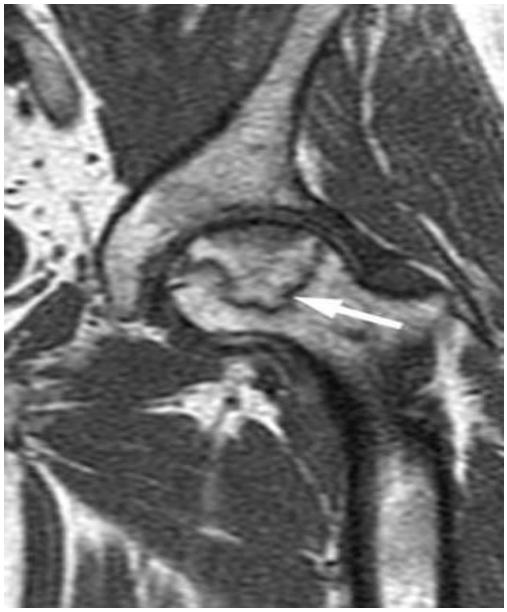

Figure 1: MRI of osteonecrosis. The loss of marrow fat (indicated by arrow) gives a dark signal typical of edema with T1 MRI imaging.

AVN Staging System:

A data compared *prospective screening* with MRI of patients considered to be at high risk of AVN with a *reactive strategy* of MRI and X-ray investigation of patients complaining of hip pain. Eighty patients newly started on corticosteroids were studied for two years with MRI every six months or sooner if hip pain occurred. The MRI and X-ray findings were compared to those in a population of 100 patients who presented with hip pain and who were subsequently diagnosed as having AVN. MRIs were graded with the University of Pennsylvania staging system in which stages 0–II are pre-fracture hips, stages III and IV have fractures of varying severity, and stages V and VI indicate joint space narrowing and arthritis. [25] Overall, nine (11%) of prospectively screened hips developed AVN. All were diagnosed in stage 0 or I, and all were able to be treated with hip sparing procedures, either bisphosphonates or core

decompression. No patient underwent a hip replacement. By contrast, of 100 patients with hip pain diagnosed reactively as AVN, 12 were stage I, 34 were stage II, 10 stage III, 29 stage IV, and 15 stage V (***Table 1***). Forty-five percent of these patients underwent hip replacement within two years after diagnosis. These data confirm a study done on AVN after solid organ transplantation.70 In that study, 103 hips of patients undergoing solid organ transplantation were studied prospectively with MRI. AVN was diagnosed in 8 of 103 hips (8%). All hips were diagnosed in Stage I. All cases of AVN of the femoral head developed within 10 months after the transplant. Seven of the eight hips with AVN were asymptomatic at the time of diagnosis. These data collectively suggest that identifying high-risk patients by understanding etiological relationships and subjecting at-risk populations to prospective screening can diagnose AVN at a pre-fracture stage where joint-preserving treatments can be used.

Table 1. *Prospective and Reactive Screening with MRI.*

	Uni. of Pennsylvania Staging					
	0	I	II	III	IV	V
Prospective (AVN= 9/80)	3	6	0	0	0	0
Reactive (AVN= 100/100)	0	12	34	10	29	15

Etiology:

The widely accepted view in the literature is that a reduction in subchondral blood supply is responsible for osteonecrosis. However, there are numerous risk factors and theories on the development of this vascular impairment [26]. Shah et al. [27] succinctly categorize these into six groups:

1. **Direct cellular toxicity**
   - Chemotherapy
   - Radiotherapy
   - Thermal injury
   - Smoking

2. **Extraosseous arterial fracture**
   - Hip dislocation
   - Femoral neck fracture
   - Iatrogenic post-surgery
   - Congenital-arterial abnormalities

3. **Extraosseous venous**
   - Venous abnormalities
   - Venous stasis

4. **Intraosseous-extravascular compression**
   - Hemorrhage
   - Elevated bone marrow pressure
   - Fatty infiltration of bone marrow due to prolonged high-dose corticosteroid use

- Cellular hypertrophy and marrow infiltration (Gaucher's disease)
- Bone marrow edema
- Displaced fractures

5. **Intraosseous-intravascular occlusion**
- Coagulation disorders such as thrombophilia and hypo fibrinolysis
- Sickle cell crises

6. **Multifactorial**

In a small percentage of cases mutations in the COL2A1 gene which codes for type 2 collagen production have demonstrated autosomal dominant inheritance patterns. [28] However, in many cases, a cause cannot be identified, and these patients receive the designation of idiopathic osteonecrosis.

Repetitive trauma, like assembly line work, can lead to AVN over time. Nontraumatic risks for AVN include anything that can impact vascular flow to the bone. Radiation can induce bone marrow changes leading to AVN. [29] Hyperlipidemia causes significant blockage of small blood vessels reducing the blood flow that provides bone with nutrients. Medical conditions like sickle cell anemia can also diminish the vascular supply to the bone. [30]

Anatomy with low collateral capabilities or retrograde vasculature, such as the carpus, are at increased risk for necrosis. [31] Unique anatomy also plays a role in the talus, where a considerable portion of its surface area consists of articular cartilage, which also restricts opportunities for blood flow. [32]

Glucocorticoids used at high doses and for prolonged periods can induce osteonecrosis via osteocyte apoptosis. Apoptosis disrupts the lacunar-canicular system. [33] Other risk factors for AVN: alcohol misuse, blood dyscrasias, and autoimmune diseases such as Lupus, etc. The cause of interrupted blood flow is unknown for twenty-five percent of people with AVN. For example, in Kienbock's and Preiser's disease, the exact cause of AVN is usually inexplicable. [34,35]

Table 2: **Etiologic Factors Associated with Osteonecrosis**
Trauma
Glucocorticoids
Alcohol
Idiopathic
Sickle cell disease
Radiation Gaucher’s disease
Caisson disease (decompression sickness)

Table 3: **Risk factors for glucocorticoid-induced osteonecrosis**
Dose and duration of therapy
Intra-articular administration
Polymorphisms in VEGF, GR, 11b-HSD2, COL2A1, PAI1, P-glycoprotein
Underlying disorders: renal insufficiency, transplantation, graft vs. host disease, inflammatory bowel disease, HIV, acute lymphoblastic leukemia
Dexamethasone causes greater skeletal complications than prednisone

VEGF vascular endothelial growth factor, GR glucocorticoid receptor, 11b-HSD2 11b-hydroxysteroid dehydrogenase type2, COL2A1 collagen type II, PAI1 plasminogen activator inhibitor 1, HIV human immunodeficiency virus

Epidemiology:

Osteonecrosis is most frequently found in the hip, although it can also occur in the humerus, knee, and talus, and it is less frequently seen in the smaller wrist bones such the lunate. Although the jaw can be impacted, this study will concentrate on the more typical types that are reported to an orthopedic surgeon.

Ten percent of total hip arthroplasties in the United States are due to AVN, and typically affect ages 30-65 years old. Males tend to be more affected by ON overall, but autoimmune conditions affecting women like Lupus are also significant. [36] Less common variants, such as Preiser disease (osteonecrosis of the scaphoid), tend to affect the dominant hand of middle-aged women most.[37] In contrast, Keinbock's disease (osteonecrosis of the lunate) is more common in middle-aged males involved in manual labor, and there have even been case reports involving children.

Drugs used in the treatment of AVN:

The drugs most often used in the treatment of osteoporosis are in the class of **bisphosphonates** (*formerly called diphosphonates*). These are analogs of naturally occurring inorganic pyrophosphate, an endogenous inhibitor of bone mineralization that has been found in body fluids that include plasma, urine, and synovial fluid.[46] Pyrophosphate is the simplest form of polyphosphates, substances that inhibit the crystallization of calcium salts. Polyphosphates have been used as water softeners and have industrial applications as anti-scaling additives in washing powders and oil brines.[47] Bisphosphonates were first synthesized by German chemists in 1865, with etidronate, a nonnitrogen-containing bisphosphonate, synthesized as early as 1897.[47] This class of drugs is characterized by a strong affinity for hydroxyapatite in bone, a long skeletal half-life, and inhibition of bone resorption. Bisphosphonates have been used in clinical practice for the treatment of metabolic bone diseases that include heterotopic ossification, osteogenesis imperfecta, hypercalcemia of malignancy, Paget's disease of bone, metastatic bone disease, and multiple myeloma.[48] Table 4, shows the comparative features of commonly used bisphosphonate used in AVN. [49-56]

Table 4:	**Alendronate**	**Risedronate**	**Ibandronate**	**Zoledronate**
Brand name	Fosamax	Actonel	Boniva	Reclast
Approval date	1995	2000	2003	2007
Affinity ranking for Hydroxyapatite	2	4	3	1
Ranking of antiresorptive Potency	4	2	3	1
Administration	oral	oral	Oral, I.V	I.V
Dose	10 mg/day	5 mg/day, 75 mg/day for 2 consecutive days once monthly	Oral 150 mg/month, IV 3 mg every 3 months over 15-30 seconds	5 mg every 12 months over at least 15 minutes
Reduction of vertebral fracture risk	Yes	Yes	Yes	Yes

Reduction of non-vertebral fracture risk	Yes	Yes	Not demonstrated	Yes
Reduction of hip fracture Risk	Yes	Yes	Not demonstrated	Yes

Treatment / Management:

Osteonecrosis of the Hip

Many patients will ultimately need a total hip arthroplasty however joint salvaging procedures such as core decompression report with varying results. Core decompression is most effective in the early stages of osteonecrosis and when the lesions only involve a small amount of the weight-bearing surface of the femoral head.[38] The procedure may use vascularized bone grafts or biologic agents that promote bone repair. Interestingly Zhao et al. [39] used perfusion studies to show core decompression is more effective in femoral heads with venous congestion than those with arterial compromise.

SONK

The majority of cases resolve following a trial of protected weight-bearing and physiotherapy. As SONK is more common in the older person a uni-compartmental knee replacement provides a good functional outcome with a relatively short rehabilitation time.[40] However, a total knee replacement may be more appropriate in larger lesions. Smaller lesions following intraosseous decompression have achieved good operative results.

Osteonecrosis of the Shoulder

Operative management is classified according to staging. For early disease, core decompression is the preferred treatment option. Humeral head resurfacing or hemiarthroplasty is recommended for moderate disease, reserving a total shoulder replacement in advanced disease.[10]

Osteonecrosis of the Talus

The incidence of osteonecrosis of the talus in talar neck fractures is reduced by utilizing a procedure to achieve operative anatomic reduction and stable fixation.[27]

Keinbock's Disease

Treatment in early-stage disease aims to revascularize the lunate either directly using bone grafts or indirectly utilizing procedures to offload the lunate. Immobilization, including external fixation, is often attempted in stage 1 and 2 disease. [41] Surgical options address the carpal collapse in stage 3, whereas advanced disease may warrant joint sacrificing procedures such as wrist arthrodesis.[41]

Preiser Disease

Early-stage treatment options involve immobilization, cortisone injections, radial wedge osteotomy, and bone graft. Later stages may warrant arthroscopic debridement, scaphoid excision, proximal row corpectomy, or even arthrodesis. Typically, surgical intervention is unavoidable in most cases.[37]

Conclusion:

AVN is a progressive and disabling condition and, if untreated, leads to subchondral fracture and joint incongruity, usually requiring arthroplasty. Because joint preserving therapies are most effective before subchondral fracture, the key to successful treatment lies in identifying at-risk patients and diagnosing AVN before joint compromise. Surgical core decompression has salvaged approximately two-thirds of pre-fracture hips but is not useful in post-fracture hips. [42,43] At the moment, joint preserving therapies are focused on the structural consequences of AVN and the prevention of trabecular resorption and subchondral fracture. Several studies have demonstrated that bisphosphonates can suppress osteoclastic resorption of subchondral trabeculae and prevent joint incongruity. [44] A better understanding of the pathogenesis of AVN might focus treatment on earlier stages of the disease to reverse or prevent mechanisms leading to ischemia. Corticosteroids have several deleterious effects on both the ischemic/necrotic and repair/resorption phases of AVN. Lovastatin has been shown to prevent corticosteroid-associated AVN by multifactorial mechanisms including counteracting the effects of corticosteroids on the differentiation of precursor cells in bone marrow from adipocytes to osteoblasts. [45] Because AVN can be detected by MRI before the structural compromise, it would seem prudent to periodically screen patients newly exposed to corticosteroids and treat early lesions pharmacologically. This would be especially useful in patients undergoing renal transplantation or with SLE who are at particularly high risk of AVN. The drugs most commonly used to treat osteoporosis are bisphosphonates: stable analogs of naturally occurring inorganic pyrophosphate. The bisphosphonates share a common chemical structure with side chain variations that convey differences in their pharmacological properties, such as affinity for bone mineral and inhibitory effect on osteoclastic bone resorption.[48]

REFERENCE;

1. David Weldon, MD, The effects of corticosteroids on bone: osteonecrosis (avascular necrosis of the bone), Ann Allergy Asthma Immunol. 2009; 103:91–98.
2. E.W. Boland, N.E. Headley, Management of rheumatoid arthritis with smaller (maintenance) doses of cortisone acetate. JAMA 144, 365–372 (1950).
3. R.H. Freyberg, C.H. Traeger, M. Patterson, W. Squires, C.H. Adams, C. Stevenson, Problems of prolonged cortisone treatment for rheumatoid arthritis. JAMA 147, 1538–1543 (1951)
4. A.J. Bollet, R. Black, J.J. Bumin, Major undesirable side-effects resulting from prednisolone and prednisone. JAMA 157, 459–463 (1955).
5. W.G. Heiman, R.H. Freiberger, Avascular necrosis of the femoral and humeral heads after high-dosage corticosteroid therapy. N. Engl. J. Med. 263, 672–675 (1960).
6. V. Pietrogrande, R. Mastromarino, Osteopathia da prolungato trattmento cortisonico. Ortop. Tramatol. 25, 791–810 (1957).
7. S.M.S. Nasser, P.W. Ewan, Depot corticosteroid treatment for hay fever causing avascular necrosis of both hips. Br. Med. J. 322, 1589–1591 (2010)
8. C.J. McClean, R.F.J. Lobo, D.J. Brazier, Cataracts, glaucoma, and femoral avascular necrosis caused by topical corticosteroid ointment. Lancet 345, 330 (1995).
9. T. Kubo, A. Kojima, S. Yamazoe, K. Ueshima, T. Yamamoto, Y. Hirasawa, Osteonecrosis of the femoral head that developed after long-term topical steroid application. J. Orthop. Sci. 6, 92–94 (2001).
10. R.S. Weinstein, Clinical practice: glucocorticoid-induced bone disease. N. Engl. J. Med. 365, 62–70 (2011).

11. D.E. Fisher, W.H. Bickel, Corticosteroid-induced avascular necrosis. J. Bone Jt. Surg. Am. 53, 859–873 (1971).
12. H.F. Mankin, Nontraumatic necrosis of bone (osteonecrosis). N. Engl. J. Med. 326, 1473–1479 (1992).
13. J.J. Nash, A.G. Nash, M.E. Leach, D.M. Poetker, Medical malpractice and corticosteroid use. Otolaryngol. Head Neck Surg. 144, 10–15 (2011).
14. Avascular necrosis after oral corticosteroids in otolaryngology: Case report and review of the literature Patrick Kennedy, Jr., B.A., Ahmed Bassiouni, M.B.B.S., Alkis Psaltis, M.B.B.S., Jastin Antisdel, M.D.,4 and Joseph Brunworth, M.D (Allergy Rhinol 7:e50 –e54, 2016; DOI: 10.2500/ar.2016.7.0142).
15. Seamon J, Keller T, Saleh J, and Cui Q. The pathogenesis of nontraumatic osteonecrosis. Arthritis 2012:601763, 2012.
16. Goh SK, Yang KY, Koh JS, et al. Subtrochanteric insufficiency fractures in patients on alendronate therapy: A caution. J Bone Joint Surg Br 89:349 –353, 2007.
17. Powell C, Chang C, Naguwa SM, et al. Steroid-induced osteonecrosis: An analysis of steroid dosing risk. Autoimmun Rev 9:721–743, 2010.
18. Ninomiya S. An epidemiological survey of idiopathic avascular necrosis of the femoral head in Japan. Annual Report of Japanese Investigation Committee for Intractable Disease, 1989.
19. Shigemura T, Nakamura J, Kishida S, et al. Incidence of osteonecrosis associated with corticosteroid therapy among different underlying diseases: Prospective MRI study. Rheumatology (Oxford) 50:2023–2028, 2011.
20. Aaron RK, Voisinet A, Racine J, et al. Corticosteroid-associated avascular necrosis: Dose relationships and early diagnosis. Ann NY Acad Sci 1240:38 – 46, 2011.
21. Santori FS, Santori N, and Piccinato A. Avascular Necrosis of the Femoral Head: Current Trends. New York, NY: Springer Science & Business Media, 2004.
22. Bauer M, Thabault P, Estok D, et al. Low-dose corticosteroids and avascular necrosis of hip and knee. Pharmacoepidemiol Drug Saf 9:187–191, 2000.
23. Shigemura T, Nakamura J, Kishida S, et al. Incidence of osteonecrosis associated with corticosteroid therapy among different underlying diseases: Prospective MRI study. Rheumatology 50: 2023–2028, 2011.
24. Nakamura J, Ohtori S, Sakamoto M, et al. Development of new osteonecrosis in systemic lupus erythematosus patients in association with long-term corticosteroid therapy after disease recurrence. Clin Exp Rheumatol 28:13–18, 2010.
25. Steinberg, M.E., G.D. Hayken & D.R. Steinberg. 1995. A quantitative system for staging avascular necrosis. J. Bone Joint Surg. Br. 77: 34–41.
26. Alexander H. Matthews; Donald D. Davis; Michael J. Fish; David Stitson, Avascular Necrosis, 2022. https://www.ncbi.nlm.nih.gov/books/NBK537007/
27. Shah KN, Racine J, Jones LC, Aaron RK. Pathophysiology and risk factors for osteonecrosis. Curr Rev Musculoskelet Med. 2015 Sep;8(3):201-9.
28. Liu YF, Chen WM, Lin YF, Yang RC, Lin MW, Li LH, Chang YH, Jou YS, Lin PY, Su JS, Huang SF, Hsiao KJ, Fann CS, Hwang HW, Chen YT, Tsai SF. Type II collagen gene variants and inherited osteonecrosis of the femoral head. N Engl J Med. 2005 Jun 02;352(22):2294-301.
29. Meixel AJ, Hauswald H, Delorme S, Jobke B. From radiation osteitis to osteoradionecrosis: incidence and MR morphology of radiation-induced sacral pathologies following pelvic radiotherapy. Eur Radiol. 2018 Aug;28(8):3550-3559.

30. Naseer ZA, Bachabi M, Jones LC, Sterling RS, Khanuja HS. Osteonecrosis in Sickle Cell Disease. South Med J. 2016 Sep;109(9):525-30.
31. Schmitt R, Kalb KH, Christopoulos G, Grunz JP. Osteonecrosis of the Upper Extremity: MRI-Based Zonal Patterns and Differential Diagnosis. Semin Musculoskelet Radiol. 2019 Oct;23(5):523-533.
32. Gross CE, Sershon RA, Frank JM, Easley ME, Holmes GB. Treatment of Osteonecrosis of the Talus. JBJS Rev. 2016 Jul 12;4(7)
33. Weinstein RS. Glucocorticoid-induced osteonecrosis. Endocrine. 2012 Apr;41(2):183-90.
34. Afshar A, Tabrizi A. Avascular Necrosis of the Carpal Bones Other Than Kienböck Disease. J Hand Surg Am. 2020 Feb;45(2):148-152.
35. Lluch A, Garcia-Elias M. Etiology of Kienböck disease. Tech Hand Up Extrem Surg. 2011 Mar;15(1):33-7.
36. Lespasio MJ, Sodhi N, Mont MA. Osteonecrosis of the Hip: A Primer. Perm J. 2019;23.
37. Lin JD, Strauch RJ. Preiser disease. J Hand Surg Am. 2013 Sep;38(9):1833-4.
38. Stubbs AJ, Atilla HA. The Hip Restoration Algorithm. Muscles Ligaments Tendons J. 2016 Jul-Sep;6(3):300-308. [PMC free article] [PubMed]
39. Zhao DW, Yu XB. Core decompression treatment of early-stage osteonecrosis of the femoral head resulted from venous stasis or artery blood supply insufficiency. J Surg Res. 2015 Apr;194(2):614-621.
40. Karim AR, Cherian JJ, Jauregui JJ, Pierce T, Mont MA. Osteonecrosis of the knee: a review. Ann Transl Med. 2015 Jan;3(1):6.
41. Allan CH, Joshi A, Lichtman DM. Kienbock's disease: diagnosis and treatment. J Am Acad Orthop Surg. 2001 Mar-Apr;9(2):128-36.
42. Aaron, R.K. et al. 1989. The conservative treatment of osteonecrosis of the femoral head. A comparison of core decompression and pulsing electromagnetic fields. Clin. Orthop. Relat. Res. 249: 209–218.
43. Mont, M.A. & D.S. Hungerford. 1995. Non-traumatic avascular necrosis of the femoral head. J. Bone Joint Surg. Am. 77: 459–474.
44. Agarwala, S. et al. 2005. Efficacy of alendronate, a bisphosphonate, in the treatment of AVN of the hip. A prospective open-label study. Rheumatology (Oxford) 44: 352–359.
45. Cui, Q., G.J. Wang & G. Balian. 1997. Steroid-induced adipogenesis in a pluripotential cell line from bone marrow. J. Bone Joint Surg. Am. 79: 1054–1063.
46. Russell R.G., Bisaz S., Fleisch H., Currey H.L., Rubinstein H.M., Dietz A.A., et al. (1970) Inorganic pyrophosphate in plasma, urine, and synovial fluid of patients with pyrophosphate arthropathy (chondro-calcinosis or pseudogout). *Lancet* 2: 899–902 [PubMed]
47. Fleisch H.(2000) *Bisphosphonates in Bone Disease: From the Laboratory to the Patient*, 4th edition, Academic Press: San Diego, CA [Google Scholar]
48. E. Michael Lewiecki Bisphosphonates for the treatment of osteoporosis: insights for clinicians, Ther Adv Chronic Dis. 2010 May; 1(3): 115–128. doi: 10.1177/2040622310374783
49. Dunford J.E., Thompson K., Coxon F.P., Luckman S.P., Hahn F.M., Poulter C.D., et al. (2001) Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. *J Pharmacol Exp Therapeutics* 296: 235–242 [PubMed]
50. Cummings S.R., Black D.M., Thompson D.E., Applegate W.B., Barrett-Connor E., Musliner T.A., et al. (1998) Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures — Results from the fracture intervention trial. *JAMA* 280: 2077–2082 [PubMed]

51. Reginster J.-Y., Minne H.W., Sorensen O.H., Hooper M., Roux C., Brandi M.L., et al. (2000) Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int* 11: 83–91 [PubMed]
52. Chesnut C.H., III, Skag A., Christiansen C., Recker R., Stakkestad J.A., Hoiseth A., et al. (2004) Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 19: 1241–1249 [PubMed]
53. Black D.M., Delmas P.D., Eastell R., Reid I.R., Boonen S., Cauley J.A., et al. (2007) Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 356: 1809–1822 [PubMed]
54. Black D.M., Thompson D.E., Bauer D.C., Ensrud K., Musliner T., Hochberg M.C., et al. (2000) Fracture risk reduction with alendronate in women with osteoporosis: The Fracture Intervention Trial. *J Clin Endocrinol Metab* 85: 4118–4124 [PubMed]
55. Harris S.T., Watts N.B., Genant H.K., McKeever C.D., Hangartner T., Keller M., et al. (1999b) Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis—a randomized controlled trial. *JAMA* 282: 1344–1352 [PubMed]
56. Black D.M., Cummings S.R., Karpf D.B., Cauley J.A., Thompson D.E., Nevitt M.C., et al. (1996) Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 348: 1535–1541 [PubMed]