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Introduction to osteonecrosis of the femoral head (OFH) and osteonecrosis of the jaw (ONJ)

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Osteonecrosis, meaning bone death or necrosis, can potentially affect any bone in the body. Some bones and a region of a bone are more prone to developing this condition due to their particular vascular anatomy, such as seen in the proximal femur. Those affecting the *subchondral* region are more clinically problematic than those affecting the *medullary* (metaphyseal or diaphyseal) or *intracortical* regions due to their proximity to the joint surface and predisposition to developing degenerative arthritis¹.

Historically, osteonecrosis was first observed clinically in the context of bone infection (osteomyelitis). In the pre-antibiotic era, osteomyelitis often produced bone necrosis, which led to separation and sequestration of the infected dead bone fragment (called *sequestrum*) from the living bone. Later, it became recognized that bone necrosis can also develop due to fracture and other causes in absence of infection. Phemister used the term "*aseptic* necrosis" to differentiate osteonecrosis that occurs in the absence of infection from those occurring from infection (*septic* necrosis)². The terminology further evolved to reflect the etiological nature of the condition (*avascular* necrosis). Currently the term "osteonecrosis" is preferred since not all bone death occur due to avascularity or ischemia.

In orthopaedics, osteonecrosis of the femoral head (OFH) has received greater clinical and research attention than those involving other regions due to its relatively common incidence, the serious nature of this condition, and the availability of osteonecrotic femoral heads for investigation following hip arthroplasty. OFH can severely limit the longevity of the hip joint by producing femoral head defor-

mity and premature degenerative arthritis, even in young adults. Legg-Calve-Perthes disease, an *idiopathic*, pediatric form of osteonecrosis, has the cumulative incidence of 1 in 740 boys and 1 in 3,700 girls³ and affects children between the ages of 2 and 14 years old. In adults, it is estimated that 21,000 new patients per year develop OFH in the US⁴. In the pediatric and adult population, several etiologic factors, such as trauma, corticosteroid use, and sickle cell disease, have been identified in addition to the idiopathic form. How some of these factors, such as corticosteroid and chronic alcohol abuse, produce osteonecrosis remains unclear.

In general, the pathophysiology, natural history, and treatment differ between the pediatric and adult forms of osteonecrosis. One major difference between the pediatric and adult OFH is the necrotic involvement (*chondronecrosis*) of the deep layer of the epiphyseal cartilage in the pediatric population along with osteonecrosis of the bony epiphysis^{5,6}. Since the deep layer of the epiphyseal cartilage is a hemi-spherical growth plate responsible for the growth of the secondary center of ossification, its involvement leads to growth arrest of the secondary center.

Other important differences between the pediatric and adult OFH are the healing time and the extent of repair, which vary considerably depending on the age of onset of OFH. Even within the pediatric population, the age of onset is one of the most important prognostic factors that determine the long term outcome⁷. In adults, most of the infarcted region of the femoral head remains necrotic with complete absence of revascularization and repair over time except at the junction of the living and necrotic bone^{1,8-12}. Eventually the necrotic portion of the femoral head collapses due to mechanical failure of the necrotic bone, producing a disruption in the smooth articular surface which leads to the development of premature osteoarthritis.

Following the induction of ischemic OFH, the earliest histological changes are seen in the marrow space with diffuse cell death, disorganization of the marrow stroma, and the

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loss of osteoblasts lining the trabeculae in the area of infarction. It may take several weeks before osteocytes demonstrate pyknotic nuclei, non-staining ghost cell outlines, or empty lacunae. Fibrovascular granulation tissue gradually invades the marrow spaces within the necrotic portion of the bone. This tissue consists of inflammatory, mesenchymal (fibroblast-like in appearance), and endothelial cells. Subsequent to initiation of the revascularization process, bone resorption and formation are seen, however, they may be uncoupled with some areas showing predominant bone resorption¹³⁻¹⁵.

In contrast to the traditional belief, the mechanical properties of the osteonecrotic femoral head has been shown to be compromised relatively early in an animal model of LCPD, the compromise occurring prior to the presence of bone resorption^{16,17}. The mechanism underlying this compromise is unclear. However, a study using quantitative backscatter electron imaging shows that the material properties (mineralization) of the necrotic bone are altered following ischemic osteonecrosis, at least in the femoral heads of immature pigs. In this study, a significant decrease in the amount of low mineralized matrix with a significantly higher degree and homogeneity of mineralization was observed in the calcified cartilage and trabecular bone following infarction¹⁸.

Current treatment options for pediatric OFH include *non-operative* means, such as restriction of weight-bearing and activities, bracing, and casting, and *operative* means, such as femoral and pelvic osteotomies. In adults, core decompression, free vascularized fibular graft, femoral osteotomies, and joint arthroplasty are some of the treatment options¹⁹⁻²¹. The operative procedures that are aimed at removing the necrotic bone while stimulating revascularization and repair, such as core decompression with autologous bone grafting and free vascularized fibular graft, have shown variable clinical results depending on the stage of the disease. Since total hip replacement is an operation not suitable for a young active patient, there is a great need to develop simple, effective treatment strategies to stimulate revascularization and repair following OFH.

Bisphosphonate (BP) therapy has gained a considerable attention as a treatment to prevent femoral head deformity following osteonecrosis²²⁻²⁸. The biological basis for BP therapy is derived from clinical and experimental studies that reveal osteoclastic bone resorption as a predominant aspect of repair following osteonecrosis¹⁵. Various experimental studies^{22-25,29} and three clinical studies including a randomized clinical trial on adult osteonecrosis²⁶⁻²⁸ support the hypothesis that inhibition of osteoclastic resorption can have a protective effect on the femoral head structure following osteonecrosis. This hypothesis is further supported by the findings of the protective effects of RANKL inhibition on the osteonecrotic femoral heads in immature pigs³⁰. In previously mentioned pre-clinical and clinical studies, BPs were administered orally or systemically (subcutaneous) using a repeated dosing regimen. A study on distribution of systemically administered BP shows that the delivery of the drug to

the necrotic bone is limited when the femoral head is avascular and repeated dosing is necessary³¹. Recently, a local intra-osseous administration of BP that allows direct delivery of the drug to the necrotic bone has been shown to decrease the femoral head deformity in an experimental model of LCPD³². It remains to be shown whether new bone formation occurs on the necrotic bone protected by BP or RANKL inhibition, and whether the protective effect is maintained over long-term. It also remains to be shown whether normal bone remodeling is restored over time following BP treatment.

It is paradoxical that BP therapy is emerging as a new treatment for OFH while it is also seen as a causal factor in the development of osteonecrosis of the jaw (ONJ). Far less is known about BP-related ONJ than OFH and the true nature of this disease still needs to be defined³³⁻³⁵. Clinically, ONJ is noted by the appearance of exposed yellow-white, hard bone in the mandible or maxilla. The patient may or may not be symptomatic. It is strongly associated with high dose intravenous aminobisphosphonate use (zoledronic acid > pamidronate but not exclusive to these) in the patients with multiple myeloma and metastatic breast cancer, but it is not solely limited to these patients. Patients being treated with oral BPs (alendronate and risedronate) for osteoporosis and Paget disease of bone have also developed this condition, but to far less extent than those with malignancy. Another strong risk factor for this condition is preceding dentoalveolar surgery.

Although many case reports and institutional reviews have been published since 2003, only a few studies have reported on the histopathological changes observed in the areas of ONJ. In one study, similarities and differences between this condition and osteoradionecrosis have been reported. It is also interesting to note that in this study, bone necrosis (empty osteocyte lacunae) was found to be patchy rather than confluent³⁶. Similarly, imaging studies (panoramic radiograph, CT, MRI, bone scan) on the condition have been limited. Reported histological changes include necrotic bone with inflammatory infiltrate, fibrosis of the medullary spaces, osteoclastic resorption, pseudoepitheliomatous hyperplasia, and staining positive for Actinomyces (gram positive anaerobe which normally colonize oral cavity, upper respiratory tract, GI tract, and female genital tract)^{36,37}. The findings from the imaging studies include osteosclerosis, poorly healing or nonhealing extraction sockets, sequestrum, periapical lucencies, osteolysis, widened periodontal ligament space, encroachment of the mandibular canal, periosteal new bone formation, oroantral fistula, and soft tissue thickening³⁸⁻⁴¹. Based on these studies it is difficult to make any conclusive statements about the pathogenesis of this condition. However, the findings of sequestration, osteosclerosis and lysis, periosteal new bone formation, oroantral fistula, presence of bacterial agent (Actinomyces), and some clinical response to antimicrobial therapy in the early stage are consistent with the clinical picture of osteomyelitis. It remains to be seen whether BP-related ONJ is "aseptic necrosis" of bone that presents after

dental procedure or local oral mucosal injury in the form of osteomyelitis, or whether it is a type of "septic necrosis" occurring in an "at risk" environment and patient produced by the effects of high levels of BP on bone or soft tissues that promote osteomyelitis, or whether it is something completely different⁴²⁻⁴⁵.

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