

## Long-term Steroid complications – prepared by Malcolm R Hooper HyperMED

Osteonecrosis is the term used to describe the loss of the structural integrity of bone leading degenerative changes and ultimate osteoclastic death.

Boss et al (2003), *Osteonecrosis of the Femoral Head of Laboratory Animals: Comparative Study of Osteonecrosis in Man and Experimental Animals*. Boss et al, describes the chain of events leading to cellular destruction of the bone; citing numerous experimental models, which duplicate the *circulatory deprivation* to bone cells – *avascular necrosis*.

Boss et al, when the primary and supportive collateral circulation is compromised their an especially high risk of ischemic injury. Catterall (1981) identifies the *head at risk* involved in the etiopathogenesis of Legg-Calvé-Perthes disease (involving the femoral head). Winet (1998), states that in the final analysis, the reduced uptake of bone-seeking isotopes implicates disruption of the blood supply in triggering all cases of osteonecrosis. Boss (2003) states that experimental disruption of the blood circulation in animals with life-long persisting degenerative changes duplicates Perthes disease in children (congenital anomaly and degenerative changes of the hip).

Boss (2003) reports crucial differences are evident in the *replacement of dead tissue by viable tissue between fractured and avascular bones*. The fracture site with adequate blood supply releases immune related factors that activate macrophage (involved in the clean up of the damaged area) and osteoclast (positive bone cell responses) resorption of necrotic (dead and damaged) material and stimulate fibrogenesis (new cellular structures), angiogenesis (new capillary support), chondrogenesis (new cartilage), and osteogenesis (new bone cell development).

In avascular bone, dead tissue is replaced by viable bone by a process called creeping substitution. However, if the damaged region has considerable compromise of the essential blood supply then the creeping substitution is usually a protracted and ineffective process (the region is essential weakened).

Catterall (1981) identified that creeping substitution is very poor where chronic ischemia exist in bone structures. Glowacki (1998) cited that in humans, when compared to animal controls; when inadequate blood supply to the damaged bone structure resulting in poor and inadequate angiogenesis (poor new capillary development) resulting in extremely ineffective bone cellular replacement which was structurally inadequate and architecturally deformed (arthritic deformity). Stiffness, strength, and toughness of any newly formed, immature bone are inferior to those of mature bones.

### Corticosteroid induced osteonecrosis

A drug that continues to be over prescribed is *corticosteroid* based medications; Boss (2003) states *corticosteroids are a pivotal risk factor in the development of avascular osteonecrosis*. Boss further states that *corticosteroid medication may cause avascular disease resulting in osteonecrosis!*

The pathogenetic mechanisms involved in steroid-induced osteonecrosis are poorly understood. Bouteiller (1983) reported the effects after *short-term, high-dosed steroid therapy in occasional patients, most cases are diagnosed after long-term treatment*. *By the fifth month of methylprednisolone therapy for lupus erythematosus*, the incidence of *osteonecrosis is close to 50%* of patients screened by sensitive techniques.

Fisher (1978) identified that in *steroid-treated patients* who have never manifested clinical signs of osteonecrosis but whose bones, at autopsy, contain scant viable osteocytes. *Lipid (fat) emboli plug the capillary dynamics within*

*bone; primarily subchondral capillaries and arterioles which are the essential structures found at the articulating surfaces of joints.*

Fisher (1978) demonstrated after intra-arterial fat infusions, *lipid-containing emboli block the vessels and result in necrosis of rabbits' femoral heads.* High-dose steroid regimens in animal studies resulted in the arteries, mainly those of the subchondral zone, *occluded by fat emboli and lipid-loaded fibrin-platelet thrombi, which are partly derived from the steroid-induced fatty liver.*

Corticosteroids disturbs lipid metabolism in the animal model reflected in hypertrophy of bone marrow adipocytes and an elevated ratio of low-density to high-density lipoprotein cholesterol. This lipid-induced hypertrophy of the fat cells cannot expand the marrow cavity within the inflexible osseous cage. Consequently, the intraosseous pressure rises, leading to *sinusoidal compression, venous stasis, and, eventually, arterial obstruction, accounting for the ischemic osteonecrosis.*

Wang (2000) reported the *steroid-induced cholesterol deposition reduces the fluidity and permeability of the cell membranes, contributing to the death of the osteocytes. Microfractures, accumulating in the fragile remodeled bone, further compress the subchondral vessels, further compromising the already unstable circulation.*

The blood flow may be reduced up to *one third after continuous steroid treatment for 10 weeks.* A failing blood supply of this magnitude would by itself be insignificant but would exacerbate cell death incidental to other conditions. Lastly, *intraosseous hypertension inhibits regeneration of the blood vessels.* Steroid medication increases the intraosseous pressure in spite of regional poor and decreased blood flow. Treating the animals with the platelet aggregation-reducing and fibrinolytic aprotonin decreases the levels of the serum lipids, preventing osteonecrosis ie aspirin which maybe more effective than corticosteroids!

### **Immune Reaction-induced Osteonecrosis**

Matsui (1995) reported that the extent of necrosis in femoral epiphyses, metaphyses, and diaphyses increases from the first to the third week after the second of two injections of horse serum in sensitized rabbits.

Early on there are significantly more necrotic marrow cells than osteocytes. Nakata (1996) *reported that: Antigen-antibody complexes are deposited in the vascular walls close to the osteonecrotic lesions, substantiating the role of an immune reaction in the pathogenesis of this model of osteonecrosis. Thrombi clog arterioles and small arteries near foci of extravasated red blood cells.*

### **Role of Apoptosis in Experimental Osteonecrosis**

Boss (2003); *Apoptosis refers to programmed cell death;* has also been identified in the destructive changes associated with bone degeneration and ultimate bone death - osteonecrosis.

*Oxygen deprivation modifies the expression of the stress protein genes. Apoptotic bodies and DNA fragmentations are observed in the avascular ischemic osteocytes and marrow cells of necrotic femoral heads of rats.*

*Programmed death; Apoptotic osteocytes and osteoblasts amass in the bone of prednisolone-treated mice as a result of the cumulative and irreparable disruption of the mechanosensory function of the osteocytic network, starting a chain of events leading to collapse of the femoral head.*

The bone loss in the methylprednisolone-treated rabbits, histologically obvious before the time at which femoral capital necrosis is first discernible, is more than just a consequence of decreasing synthesis. It is also due to an increased breakdown of the osseous matrix, which correlates with apoptosis of the osteocytes and osteoblasts.

This is important; *raising the levels of Oxygen saturation into hypoxic and ischemic tissue will change the Apoptosis of the region.*

### **Hyperbaric Oxygenation treats Osteonecrosis**

Boss (2003); Healing of vascular-deprived necrotic femoral heads is expedited by an exposure of the rats to hyperbaric Oxygen.

Levin (1999): *HyperOxygenation-mediated relief of the ischemia apparently boosts fibroblastic, angioblastic, osteoblastic, and osteoclastic activities.* Peskin (2001) *Non-weight bearing further encourages repair processes affected by the Hyperbaric Oxygenation.*

Cruess (1986) described the complex nature of osteonecrosis as *microembolic events, vascular impediment, adipocytic hypertrophy, and lipid-incurred osteocytic death, alone or in combination,* playing etiopathogenic roles of unequal magnitudes under different circumstances.

### **Summary**

*Apoptosis*; programmed cell death, has been identified in the destructive changes associated with bone degeneration and ultimate bone death – osteonecrosis and the effects of degenerative arthritis.

Osteonecrosis is described as *microembolic events, vascular impediment, adipocytic hypertrophy, and lipid-incurred osteocytic death, alone or in combination and often accelerated through steroid medication.*

*Ischemia (inadequate blood supply and capillary dynamics) leads to Oxygen deprivation, which modifies the expression of the stress protein genes. Apoptotic bodies and DNA fragmentations are observed in the avascular ischemic osteocytes and marrow cells of necrotic femoral heads resulting in weakened replacing bone and supporting ligamentous architecture.*

This is an extremely important component of bone destruction – *prolonged steroid use, inadequate underlying neurovascular support and capillary dynamics, additional vascular compromise due to steroids, fatty emboli due to elevated lipids and negative effects of steroid medication; presence of opportunistic antigen-antibody deposited in the vascular walls adjacent to the osteonecrotic lesion.*

*Hyperbaric Oxygenation (HBOT): raises the levels of Oxygen saturation into hypoxic and ischemic tissue directly impacting the cellular apoptosis of the region; HBOT corrects the ischemia state and boosts fibroblastic, angioblastic, osteoblastic, and osteoclastic activities inhibiting osteonecrosis.*