Mouth and Body Connection

Osteoporosis and Osteonecrosis of the Jaws:

an underestimated problem with multiple ramifications

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Abstract

In the past 12 months a growing number of cases osteonecrosis of the jaws (ONj) in patients taking bisphosphonates have been reported worldwide in both the media and the scientific literature. ONj and its relationship with bisphosphonates, a class of pharmaceutical drugs used in the treatment of osteoporosis and hypercalcemia in cancer patients, are still debated in legal and medical circles.

In this article we will review both disease processes and the possible impact of bisphosphonates. A better understanding of the pathophysiological mechanisms involved could improve diagnosis and treatment of chronic ischaemic bone diseases (CIBD) such as oral osteoporosis and ONj. Bisphosphonates are not the only etiological factor involved in ONj, so a greater emphasis on other etiological factors such as heavy metals, gut toxicants, GI tract and hepatic fucntion, as discussed in this article, is recommended as part of a more comprehensive approach in the management of CIBD such as oral osteoporosis and ONj.

KEY WORDS: Acetaldehyde, anoxia, bisphosphonates, bone infarcts, cadmium, chronic ischaemic bone diseases (CIBD), exogenous estrogens, metallo-estrogens, gut dybiosis, hepatotoxicity, hyperemia, hypoxia, ischaemia, metalloestrogens, osteonecrosis of the jaws (ONj), osteocavitations, osteoporosis, periodontitis, veinous insufficiency.

Introduction

Chronic ischaemic bone diseases (CIBD) are characterized by gradual degenerative cancellous bone tissue damage related to altered blood flow. The degree of damage and the ability of bone tissue to repair itself is directly related to the severity and duration of the impaired perfusion with effects ranging from hyperemia, transient ischaemia, persistent ischaemia with hypoxia to complete infarction and anoxia. Numerous factors can be involved and will be discussed as we review the pathophysiological mechanisms involved in osteoporosis and osteonecrosis.

In dental medicine , oral osteoporosis and osteonecrosis of the jaws (ONj) are CIBD that can significantly impact on oral and systemic health and the U.S. National Institute of Health (NIH) considers osteoporosis as a devastating disorder with significant physiological, psychological and financial consequences. While the impact in craniofacial bones is acknowledged, there is a lack of reliable prevalence rate so the NIH recommends that more attention should be paid to skeletal health, especially in persons with conditions known to be associated with secondary osteoporosis. Of significance is the uniqueness of the maxilla and mandible. They are the only bones with teeth in them and numerous pathological processes related to the teeth and multiple therapeutic dental interventions may occur over a lifetime, including but not limited to, implantation of various foreign materials and repetitive injections of local anaesthetics with vasoconstrictors. Teeth are entirely dependant on healthy jaws both for their function and support. Finally the association between oral osteoporosis, systemic osteoporosis, periodontal diseases and cardiovascular diseases has been proven and recent complications with bisphosphonates treatment of systemic osteoporosis leading to complex cases of ONj have highlighted the pertinence of the NIH recommendation.

Osteoporosis Defined

Osteoporosis is a bone disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fracture, especially of the hip, spine and wrist. It is generally characterized as primary (idiopathic) or secondary, depending on the presence or absence of associated medical conditions, surgical procedures or medications known to be associated with accelerated bone loss[1]. Secondary osteoporosis is sometimes a purely local phenomenon, confined to particular bones or parts of them[2].

Osteoporosis results from abnormal organic matrix formation rather than abnormal bone calcification, as ▸

in osteomalacia. In general, in osteoporosis, the osteoblastic activity is less than normal, and consequently the rate of new bone formation is depressed. Living bone becomes osteoporotic as a result of osteoclastic bone resorption secondary to reactive hyperemia [3] such as can occur in venous outflow problems initiated by a venous thrombotic process or venous insufficiency.

WHAT ARE THE CAUSES OF OSTEOPOROSIS ?

Multiple factors can be involved including, but not limited to, poor nutrient absorption to the extent that sufficient protein matrix cannot be formed, deficiency in vitamin C (which is apparently necessary for the secretion of intercellular substances by all cells, including osteoblasts)[4] , hormonal imbalances and exogenous oestrogens[5,6]. The role of heavy metals as exogenous oestrogens has been raised by recent reports of the ability of certain metal ions to also bind to oestrogen receptors and to give rise to oestrogen agonist responses in vitro and in vivo. This has resulted in the realisation that environmental oestrogens can also be inorganic and such xeno-oestrogens have been termed metallo-oestrogens. These metallo-oestrogens include aluminium, antimony, arsenite, barium, cadmium, chromium (Cr(II)), cobalt, copper, lead, mercury, nickel, selenite, tin and vanadate[7] . The effects of combinations of various metals can also be a factor as it has been demonstrated that a particular combination could be synergistic, antagonistic, or additive, depending on the relative doses employed. Generally, a combination was synergistic when the most toxic metal was present at or near its LD1 dose (dose that will kill one cell in a 100) in the presence of the much less toxic metal; the same combination was protective when the least toxic metal was present at or near its LD1 dose [8]. In studies on invertebrates development, it was demonstrated that Hg is three times more toxic than Cu, 20-30 times more than Cd, and 700-1000 times more toxic than Cr[9,10]. Studies on rats, sheep and monkeys implanted with dental amalgam have demonstrated a significant mercury burden in the, kidneys, liver, gut and jawbones of these animals [11,12,13]. So, if the experimental data is similar in humans, in theory a person with oral osteoporosis and mercury and cadmium in her jawbones, the effects of cadmium would be potentiated by mercury if mercury levels are close to a LD1 dose. Of course this is only an assumption and further research is needed before a definite conclusion can be reached in humans.

A strong association between cadmium, lead and osteoporosis has also been established. Low level exposure to cadmium is associated with an increased loss of bone mineral density readily in both genders, leading to osteoporosis and increased risk of fractures, especially in elderly and in females [14,15]. Animal studies have shown cadmium to stimulate the formation and activity of osteoclasts-mediated bone resorption[16]. Recent data demonstrate mild effects of cadmium on both kidney and bone with present environmental exposure levels. Women may be at greater risk than men, because of increased gastrointestinal uptake of cadmium at low iron stores, which is common in women of childbearing age. The same data shows that about 90% of body lead is localised to bone and that there is a significant release of bone lead after the menopause, in association with the acceleration of bone resorption. Thus, postmenopausal women may be at increased risk of adverse effects of lead [17] .

Cadmium and lead also promotes the synthesis of plasminogen activator inhibitor-1 (PAI-1) which is the major inhibitor of fibrinolysis[18]. Persistent blot clots can lead to congestive hyperemia in bone marrow, impaired blood flow and ischaemia in bone tissue resulting in hypoxia, bone cell damage and eventual cell death. Of significance is the fact that the average concentration of cadmium in human bones in the 20th century has increased to about 10 times above the pre-industrial level[19].

Other recent studies have highlighted the potential for adverse effect on bone tissue from certain gut toxins resulting from dysbiosis of the gastro-intestinal (GI) tract, a state of imbalance of the intestinal flora which may lead to excessive bacterial fermentation in the gut and auto-intoxication by microbial toxins, a particular problem in inflammatory bowel diseases[20]. Acetaldehyde, a highly toxic metabolite of ethanol, can play a role in hypoxia and inhibit the osteoblastogenic potential of the bone marrow[21]. Ethanol itself has been shown to alter the epithelial barrier through ethanol oxidation into acetaldehyde by the colonic microflora and downstream mast cell activation. Such alterations that remain for longer periods could result in excessive endotoxin passage into the vascular network[22]. Intracolonic acetaldehyde may also be an important determinant of the blood acetaldehyde level and a possible hepatotoxin[23]. High serum antibody titers against acetaldehyde-protein compounds have been found not only in alcoholics but also in patients with nonalcoholic liver disease, suggesting a contribution of acetaldehyde derived from sources other than exogenous ethanol[24]. In a study on rats the role of intestinal bacterial overgrowth on the production and metabolism of ethanol, rats with a jejunal self-filling diverticulum (blind-loop) were compared to controls with a self-emptying diverticulum. Both endogenous ethanol and acetaldehyde were found in the blind-loop contents. Intragastric administration of sucrose produced a marked increase in acetaldehyde and acetate in the portal venous blood, with only a modest elevation of ethanol. It was concluded that the resulting high concentrations of acetaldehyde, both in the intestinal lumen and the portal blood, may have deleterious effects on the gastrointestinal mucosa and the liver[25]. Another experimental in-vitro study showed the potential of certain bacteria representing normal human colonic flora to produce acetaldehyde under various atmospheric conditions that may ▸

prevail in different parts of the GI tract. This bacterial adaptation may be an essential feature of the bacteriocolonic pathway to produce toxic and carcinogenic acetaldehyde from either endogenous or exogenous ethanol[26]. Many species of gut bacteria, yeast and fungal organisms such as Candida Albicans found in the human GI tract and involved in gut dysbiosis have been shown to significantly increase blood ethanol levels, post-mortem, in individuals who had not consumed any alcohol before death[27,28]. The effects of chronic gut dybiosis and long term exposure to low levels of endogenous acetaldehyde on bone tissue and hepatic function is not yet fully understood. However Cordts et al suggested in 2001 that gut dysbiosis (as indicated by stool yeast) and hepatic detoxification challenge pathway exhaustion may lead to subclinical, systemic inflammation and chronic venous insufficiency (CVI). CVI is a pathological condition caused either by the congenital absence of or damage to venous valves in the superficial and communicating systems. Venous incompetence due to thrombi and formation of thrombi favoured by the Virchow triad (venous stasis, hypercoagulability, endothelial trauma) also can cause CVI[29].

Since reactive bone marrow hyperemia has been implicated in osteoporosis and hyperemia has been associated with a venous outflow problem, the relationship between gut dysbiosis, hepatic dysfunction and endogenous acetaldehyde production in CIBD warrants further attention.

THE MOUTH AND BODY CONNECTION

Further investigations have demonstrated a significant association between bone mineral density (BMD) of the mandible and the peripheral skeleton in postmenopausal women. Some studies also have linked low BMD of the mandible and the peripheral skeleton with alveolar bone loss of the mandible and tooth loss.

In a review of the literature in 1997, Hildebolt concluded that an association between osteoporosis and oral bone loss existed while recommending additional longitudinal studies. He suggested that inexpensive methods must be developed for sensitive and specific measures of oral bone loss[30].

More recent studies have cited osteoporosis as a risk factor for periodontal disease even while their association is still not well understood[31]. There is evidence that patients with systemic osteoporosis are likely to have decreased oral bone density, which may affect treatment decisions. Further, patients with decreased bone mineral density, indicative of osteoporosis, may be at a higher risk for periodontitis. Therefore, osteoporosis, could be considered a risk factor for periodontitis[32].

Numerous researchers have also established an association between periodontal diseases and various systemic diseases including cardio-vascular diseases. For example DeStefano et al. focused on the contribution of periodontitis and analyzed coronary heart disease and mortality outcomes in nearly 10,000 subjects followed for 14 years longitudinally in the NHANES I study. Periodontitis for this cohort study was assessed with the periodontal index. Overall, subjects with periodontitis had a 25% increased risk for coronary heart disease relative to those with minimal periodontal disease. This association occurred after adjustments for potential confounders like age, sex, race, education, marital state, systolic blood pressure, total cholesterol levels, body mass index, diabetes, physical activity, alcohol consumption, poverty and cigarette smoking. For males younger than 50 years, periodontitis more strongly affected the incidence of coronary heart disease with a relative risk of 1.72[33].

Lately, data regarding the periodontal microbial challenge support the biological plausibility of the associations seen in human population studies. **Hertzberg et al. have reported that two oral microbes, Streptococcus sanguis and P. gingivalis, express a collagen-like platelet aggregation-associated protein that can stimulate thrombotic events**[34,35]. Genco et al. presented preliminary data that suggest an odds ratio of 2.8 for subjects harboring P. gingivalis in periodontal pockets and exhibiting a myocardial infarction[36]. In addition, Zambon et al. recently isolated DNA sequences specific for periodontal pathogens like P. gingivalis and A. actinomycetemcomitans from human atheroma specimens using polymerase chain reaction (PCR) techniques[37]. Other non periodontal infectious agents like Clamydia pneumoniae, Heliobacter pylori, herpes simplex and cytolomegalovirus have been previously detected in atheromatous lesions using similar methods, and further support an infectious aetiology for cardiovascular disease[38].

The available evidence points to adverse impact on bone nutrition and impaired elimination of metabolic waste and xeno-toxicants because of altered blood flow to the affected bone areas.

In spite of the above scientific evidence, osteoporosis, including oral osteoporosis, is underdiagnosed[39] because diagnosis of osteoporosis is complicated by the fact that osteoporotic cancellous bone cannot be easily detected by routine clinical examination, even with the help of routine blood tests or x-rays[2]. Special investigations using dual x-ray absorptiometry (DEXA) and Quantitative Ultrasounds (QUS) are necessary[40].

OSTEOCROSIS:

Osteonecrosis is a severe bone disease that is also caused by ischaemia. It means literally, "dead bone from poor blood flow." It may have either necrotic bone or bone marrow that has been slowly strangulated or nutrient-starved. Bone with chronically poor blood flow develops either a fibrous marrow since fibres can more easily live in nutrient starved areas, a greasy, dead fatty marrow (wet rot), a very dry, sometimes leathery marrow (dry rot), or a completely hollow marrow space (osteocavitation), also typical of ONj. The blood flow mpairment occurs following a bone infarct, a blood clot

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forming inside the smaller blood vessels of cancellous bone tissue.

Under ischaemic conditions numerous pathological changes in the bone marrow and trabeculae of oral cancellous bone have been documented. Microscopically, areas of "apparent fatty degeneration and/or necrosis, often with pooled fat from destroyed adipose cells (oil cysts) and with marrow fibrosis (reticular fatty degeneration)" are seen. These changes are present even if "most bony trabeculae appear at first glance viable, mature and otherwise normal, but closer inspection demonstrates focal loss of osteocytes and variable micro cracking (splitting along natural cleavage planes). The microscopic features are similar to those of ischaemic or aseptic osteonecrosis of long bones, corticosteroid-induced osteonecrosis, and the osteomyelitis of caisson (deep-sea diver's) disease"[41].

In the cancellous portion of femoral head it is not uncommon to find trabeculae with apparently intact osteocytes which seem to be "alive" but are no longer synthetizing collagen[42]. This appears to be consistent with the findings in alveolar cancellous bone.

Any bone can be affected, but the hips, knees and jaws are most often involved. Pain can often be severe, especially if teeth and/or a branch of the trigeminal nerve is involved, but many patients do not experience pain, at least in the earlier stages. When severe facial pain is involved, the term NICO, for Neuralgia-Inducing Cavitational Osteonecrosis, is frequently used.

ONj , even in its mild or minor forms, creates a marrow environment that is conducive to bacterial growth. Since many individuals have low-grade infections of the teeth and gums, this probably is one of the major mechanisms by which the marrow blood flow problem can worsen (any local infection / inflammation will cause increased pressures and clotting in the area involved). No other bones have this mechanism as a major risk factor for osteonecrosis. A wide variety of bacteria have been cultured from ONj lesions. Typically, they are the same microorganisms as those found in periodontitis or devitalized teeth. However, according to special staining of biopsied tissues, bacterial elements are rarely found in large numbers. So while ONj is not primarily an infection, many cases have a secondary, very low-level of bacterial infection and chronic non-suppurative osteomyelitis can be associated with ONj. Fungal infections in the involved bone do not seem to be a problem, but viral infections have not been studied. Some viruses, such as the smallpox virus (no longer existent) can produce osteonecrosis in at least 5% of infected persons, usually in the leg bones[43].

The effects of persistent ischaemia on bone cells

Cortical bone is well vascularized by the surrounding soft tissues thus less susceptible to ischaemic damage. Cancellous bone, with it's mesh like structure and spaces filled with marrow tissue is more prone to damage by bone infarcts, leading to anoxia and premature cell apoptosis[44-47]. The mean life-span of osteocytes has been estimated to be 15 years in cancellous bone[48] and 25 years in cortical bone[49] while the average lifespan of human osteoclasts is about 2 to 6 weeks and the average lifespan of osteoblasts is approximately 3 months([50]. In healthy bone these cells are constantly replaced by differentiation of bone marrow mesenchymal stem cells (MSCs)[51]. However in both nontraumatic osteonecrosis and alcohol-induced osteonecrosis of the femoral head, a decrease in the differentiation ability of mesenchymal stem into bone cells has been demonstrated [52,53] and altered osteoblastic function plays a role in ON of the femoral head[54]. If these results are extrapolated to ONj the altered differentiation potential of bone marrow MSCs combined with the altered osteoblastic activity and premature death of existing bone cells would explain the failed attempts at repair seen in ischaemically damage cancellous bone tissue in ONj.

The rapidity with which premature cell death can occur depends on the cell type and the degree and duration of the anoxia. Hematopoietic cells, in bone marrow, are sensitive to anoxia and are the first to die after reduction or removal of the blood supply. In anoxic conditions they usually die within 12 hours. Experimental evidence suggests that bone cells composed of osteocytes, osteoclasts, and osteoblasts die within 12-48 hours, and marrow fat cells die within 120 hours[55]. The death of bone does not alter its radiographic opacity nor it's mineral density. Necrotic bone cannot undergo resorption; therefore, it appears relatively more opaque.

Attempts at repair of ischaemically damaged bone will usual occur in 2 phases. First, when dead bone abuts live marrow, capillaries and undifferentiated mesenchymal cells grow into the dead marrow spaces, while macrophages degrade dead cellular and fat debris. Second, mesenchymal cells differentiate into osteoblasts or fibroblasts. Under favorable conditions, layers of new bone form on the surface of dead spongy trabeculae. If sufficiently thickened, these layers may increase the radiopacity of the bone; therefore, the first radiographic evidence of previous osteonecrosis may be patchy sclerosis resulting from repair. Under unfavorable conditions repeated attempts at repair in ischaemic conditions can be seen histologically and are characterized by extensive delamination or microcracking along cement lines as well as the formation of excessive cement lines[56]. Ultimate failure of repair mechanisms due to persistent and repeated ischaemic events is manifested as trabecular fractures that occur in the dead bone under functional load. Later followed by cracks and fissures leading to structural collapse of the area involved [55] (osteocavitation). ■

To be continued in the next issue.