Osteoporosis and Osteonecrosis of the jaws:

an underestimated problem with multiple ramifications

By Jacques Imbeau
D.M.D., FACNEM (Dent), NZDREX

AS mentioned in Part I, other factors such as toxicants can adversely impact bone cells. Infections, chronic or acute, can affect blood flow by inducing platelet activation and aggregation, contributing to a localized state of hypercoagulability that may contribute to thrombosis, a known cause of bone infarct and ischaemia. Exogenous estrogens have also been linked with thrombophilia and impaired bone healing [57]. Heavy metals such as lead and cadmium have been implicated in osteoporosis and shown to be a cause of hypofibrinolysis. Ethanol both from exogenous and endogenous sources and, its more toxic metabolite, acetaldehyde, have also been implicated in both osteoporosis and osteonecrosis.

BISPHOSPHONATES

In the past few years, thousands of cases of ONj in patients on bisphosphonate therapy have been diagnosed usually following lack of healing after a dental extraction but also in cases of spontaneous exposure of the cortical bone tissue through the gingiva and mucosa [58,59].

TABLE 1 Initiating / predisposing risk factors for ONj other than genetically inherited hypercoagulability.

PHYSICAL TRAUMA	MICROBIAL TRAUMA	TOXIC TRAUMA
Extractions	Periodontal disease	Cadmium, lead
Trauma from drilling	Cyst - granuloma	Root canal toxins
Oral surgery	Abscesses	Anaesthetic by-products
Endodontic therapy	Root canal bacteria/fungi	Vasoconstrictors (epinephrin)
Bruxism	Residual infections	Chemical toxins
Galvanism	Infected impacted teeth	Bacterial/fungal toxins
Radiation therapy	Infected implants	Metallic toxins
Accidents	Infected tooth buds	Thimerosal from vaccines
Deep sea diving	Infected dental alveola	Cigarette smoking
	Improperly cleaned alveola	Chemotherapy
		Alcoholism (ethanol)
		Bisphosphonates drugs

NB: Individual factors may not be enough to initiate cancellous bone damage but a combination of many of the above factors is likely, especially if hypercoagulability is involved. The severity of the damage will vary according to individual susceptibility and the intensity of the above factors.

TABLE 2 – Syndrome, diseases & conditions associated with osteonecrosis

Chronic fatigue syndrome	Irritable bowel syndrome	Myofascial dysfunction syndrome
TMJ syndrome	Micromercurialism	Fibromyalgia
Trigeminal neuralgia	Atypical facial neuralgia / Idiopathic facial neuralgia.	
Migraine headaches	Lupus erythematosus	Hypercorticolism
Hypercoagulation disorders – systemic and/or local (thrombophilia, hypofibrinolysisetc...)		
Intra-osseous inflammation (related to microbial infections, trauma or autoimmunity)		
Oestrogen replacement therapy (HRT) and xeno-oestrogens		
Cardiovascular diseases and homocysteinemia		
Hyperlipidemia & embolic fat	Hypertension	Arthritis
Chronic osteomyelitis	Osteoporosis	Arteriosclerosis
Cirrhosis, pancreatis, fatty liver	Sickle cell anemia	
Cancers (Cancer induced hypercoagulation, lymphoma, carcinoma, radiotherapy induced osteonecrosis)		

The recent increase of such cases has been linked with a major emphasis on the therapeutic use of bisphosphonates for osteoporosis, especially since hormone replacement therapy (HRT) has been shown to increase the risk of breast cancer, clots and cardiovascular disease in women following the 2003 findings of the U.S. Women's Health Initiative study[6]. Two classes of bisphosphonates are presently prescribed:

- Non nitrogen containing bisphosphonates such as Etidronate (Didronel)
- Nitrogen containing such as Alendronate (Fosamax), Pamidronate (Aredia), Zoledronate (Zometa), Risedronate (Actonel) and Ibandronate (Boniva).

The nitrogen containing bisphosphonates are the most potent inhibitors and no case of ONj associated with Etidronate has been reported yet.

The main pharmacological action of bisphosphonates is inhibition of the osteoclast driven bone resorption. This is achieved by shortening osteoclast lifespan by killing them and by inhibiting osteoclast activity and recruitment on the bone surface.[60] When a bisphosphonate binds to bone mineral, osteoclast resorb both bone and the bound bisphosphonate. During bone formation, if any, bisphosphonate remaining on the surface of the bone is covered and remains there until future osteoclastic bone resorption at the site. This explains why inhibition of bone resorption continues long after bisphosphonate treatment has been discontinued [61].

This form of therapy has been shown to prevent loss of BMD as a result of a reduction in bone turnover. However bone health is a lot more than BMD.

In healthy bone tissue there is an homeostasis between bone resorption and bone apposition. Diseased or damaged bone is resorbed through the osteoclasts mediated process while osteoblasts form new bone to replace it, thus maintaining healthy bone density. A process commonly called remodelling.

However osteoporosis is essentially the result of a lack of new bone formation in combination with bone resorption in reactive hyperemia , related to the etiological factors mentioned earlier, and bisphosphonates do not address these etiological factors at all.

An individual who is already having problems with osteoporosis/ osteonecrosis of the jaws due to the effects of these etiological factors will be more susceptible to the adverse effects of bisphosphonates. In theory, by suppressing osteoclastic activity and bone resorption, any ischaemically damaged bone will be left in situ instead of being resorbed. The damaged bone will not be repaired either if the factors already inhibiting osteoblastic activity are still present. Therefore the amount of osteonecrotic tissue should be expected to increase until it reaches a level when any trauma or insult to this necrotic bone will result in extremely poor healing , exposed necrotic bone to the oral environment, development of pain, and increased risks of microbial infection, as effectively seen in bisphosphonates associated cases of ONj.

In a systematic review of cases of bisphosphonates associated ONj up to 2006, it was concluded that the mandible is more commonly affected than the maxilla (2:1 ratio), and 60% of cases are preceded by a dental surgical procedure. According to Woo, Hellstein and Kalmar, oversuppression of bone turnover is probably the primary mechanism for the development of this form of ONj, although there may be contributing co-morbid factors (as discussed elsewhere in this article). It is recommended that all sites of potential jaw infection should be eliminated before bisphosphonate therapy is initiated in these patients to reduce the necessity of subsequent dentoalveolar surgery. The degree of risk for osteonecrosis in patients taking oral bisphosphonates, such as alendronate (Fosamax – Merck), for osteoporosis is uncertain and warrants careful monitoring.[62]

IS OSTEONECROSIS OF THE JAWS A CONTROVERSIAL ISSUE IN DENTISTRY?

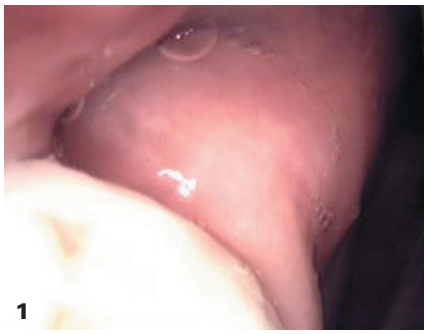
Yes. In our opinion, the controversy is more the result of a lack of understanding of the disease than the lack of prevalence. ONj is not a new disease, around 1850 various forms of "chemical osteomyelitis" resulting from environmental pollutants, such as lead and the white phosphorus used in safety matches, as well as from popular medications containing mercury, arsenic or bismuth, were reported in the literature.[63-69] This disease apparently did not often occur in individuals with good gingival health, and usually targeted the mandible first.[64] It was associated with localized or generalized deep ache or pain, often of multiple jawbone sites. The teeth often appeared sound and suppuration was not present. Even so, the dentist often began extracting one tooth after another in the region of pain, often with temporary relief but usually to no real effect.[65]

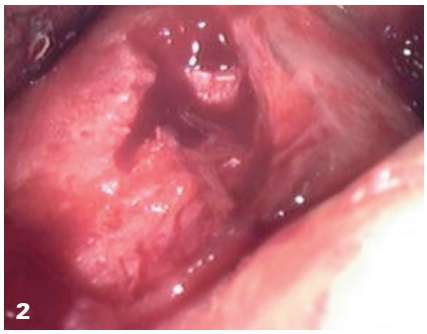
Today a growing body of scientific evidence indicates that this disease process, in the cancellous bone and bone marrow, is caused by bone infarcts mediated by a range of local and systemic factors. And bone infarcts as well as damage to the deeper portion of the cancellous bone is an insidious process. It is certainly not visible clinically and routine imaging techniques such as radiographs are not effective for that sort of damage.

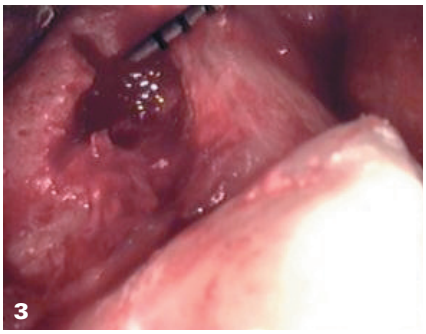
"An important and often incompletely understood principle of radiography is the amount of bone destruction that goes undetected by routine x-rays procedures. This has been demonstrated by numerous investigators... Destruction confined to the cancellous portion of the bone cannot be detected radiographically. Radiolucencies appear only when there is internal or external erosion or destruction of the bone cortex."[70] In fact no radiographic findings are specific for bone infarction / osteonecrosis. A variety of pathologies may mimic bone infarction, including stress fractures, infections, inflammations, and metabolic and neoplastic processes. The limitations apply to all imaging modalities, including plain radiography, radionuclide studies, CT, and MRI. Through-transmission alveolar ultrasound (Cavitat CAV 4000 – Cavitat Medical Technologies, Emory, Texas) based on the principles of quantitative ultrasound (QUS) in combination with dental panoramic radiography is more helpful in assessing changes in jawbone density.[71,72] When health practitioners have an up to date understanding of the disease process and a good anamnesis is combined with detailed clinical findings and course of events, the diagnosis, with the help of various imaging modality, can be achieved earlier, in most patients.

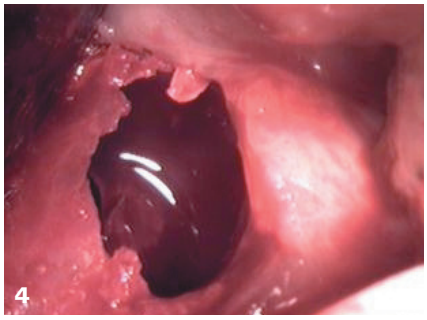
In the modern dental profession, it is only recently when severe cases associated with bisphosphonates came to light, that the issue of ONj has been brought to the attention of a majority of dentists. At present, the focus is mostly on bisphosphonates associated cases. However, the pharmaceutical manufacturers of bisphosphonates drugs such as Merck and Novartis have stated that ONj in patients on this class of drug, can be related to a pre-existing condition, coagulopathy, anemia, infection, use of corticosteroids, alcoholism and other conditions already known to be associated with ONj in absence of bisphosphonate therapy. The implication is that bisphosphonates may not be the initiating cause of ONj and that other pre-existing or concurrent systemic and/or local dental factors are involved.[73,74]

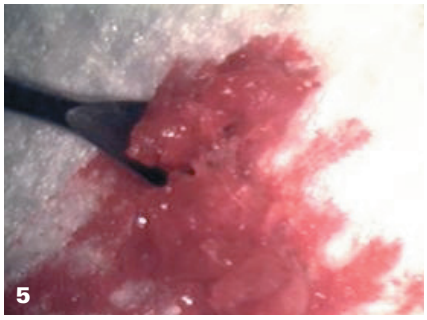
Since ONj has been diagnosed in many patients who did not take bisphosphonates, it is thus logical to assume that bisphosphonates are not the only factor in ONj. While the oversuppression of bone turnover seems to play a major role in aggravating the disease process, other factors can and do initiate the pathophysiological mechanisms responsible for ONj. In non-➲











The photographs are of the left posterior area of the maxilla of a post-menopausal woman diagnosed with systemic osteoporosis who has received IV bisphosphonates. The site corresponds to the location of the upper left third molar and maxillary tuberosity. The patient made no mention of her IV-bisphosphonate injections on her medical questionnaire. She was unaware of the risk of ONj when treated with IV bisphosphonates.

Photo # 1: *Appearance of soft tissue in the left maxillary tuberosity area – normal clinical appearance with no visible sign of inflammation.*

Photo # 2: *Appearance of bone cortex upon soft tissue flap exposure – note the eroded cortical shell. This is prior to any probing or exploration.*

Photo # 3: *The cortical shell is probed here using a standard periodontal probe. The probe easily penetrated the eroded cortex and there was no resistance to deeper probing in the area of the bone normally occupied by cancellous bone tissue. Photo # 4: A larger window has been prepared in the cortex to expose the medullary area. Note the large osteocavitation filled with some tissue debris at the bottom and the paper thin cortical bone at the margin of the access window. The osteocavitational defect is devoid of any trabecular structure, which has already collapsed, leaving a thinning, partially eroded cortical shell.*

Photo # 5: *The tissue debris removed from the medullary defect. Essentially fragments of necrotic bone trabeculae and necrotic bone marrow, typical of osteonecrosis.*

bisphosphonate cases of ONj, it is mainly the cancellous portion of the bone and it's marrow content that are involved in the disease process. The first stage is an oedema of the bone marrow initiated by a bone infarct, which is itself modulated by numerous etiological factors, leading to fibrous degeneration of the bone marrow as a result of hypoxia and gradual loss of mineral bone density characteristic of ischaemic osteoporosis. Further deterioration can be triggered by additional bone infarcts leading to anoxia and a localized areas of osteonecrosis within the osteoporotic cancellous bone. Secondary events such as dental infection, injection of local anaesthetics with vasoconstrictors such as epinephrine and trauma can add further complications to the disease process and chronic non-suppurative osteomyelitis can also be associated with ONj.[75-87]

However, in patients on bisphosphonates, the cortical bone is also frequently involved as well. Spontaneous exposure of necrotic bone tissue through the oral soft tissues or following non-healing bone exposure after routine dental surgery, characteristics of this form of ONj , may be the result of late diagnosis of a disease process that has been masked by the oversuppression of osteoclastic activity, allowing pre-existing etiological factors to further aggravate bone damage.

RECOMMENDED TREATMENTS:

The treatment should be tailored to the individual patient according to the etiological factors involved and the severity of the disease process. With oral osteoporosis the emphasis should be on good nutrient absorption and metabolic wastes elimination through a healthy gastro-intestinal function, effective hepatic metabolism of toxicants such as exogenous oestrogens, endogenous acetaldehyde and heavy metals, a balanced diet, healthy lifestyle, assessment of factors related to potential coagulopathies, and treatment of periodontal diseases and other oral and dental infections. If patients are on bisphosphonates, the need for this form of therapy should be re-assessed in light of the most recent research.

In cases of advanced oral ischaemic osteoporosis and/or ONj that are not bisphosphonates related, clinical evidence has shown that surgically removing the damaged marrow, usually by curettage and decortication, will eliminate the problem (and the pain) in 74% of patients with jaw involvement.[88] Repeat surgeries, usual-

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ly smaller procedures than the first, may be required, and almost a third of jawbone patients will need surgery in one or more other parts of the jaws because the disease so frequently present multiple lesions, i.e. multiple sites in the same or similar bones, with normal marrow in between. In the hip, at least half of all patients will get the disease in the opposite hip over time; this pattern occurs in the jaws as well. Recently, it has been found that some osteonecrosis patients respond to anticoagulation therapies alone. The earlier the diagnosis the better the prognosis. Research is ongoing on other non-surgical therapeutic modalities that could alone or in combination with surgery further improve the prognosis and reduce the morbidity of ONj. A greater emphasis on minimizing or correcting known etiological factors is necessary while further research is conducted on CIBD such as oral osteoporosis and ONj.

In patients with bisphosphonates-associated ONj, the response to surgical treatment is usually poor.[89] Conservative debridement of necrotic bone, pain control, infection management, use of antimicrobial oral rinses, and withdrawal of bisphosphonates are preferable to aggressive surgical measures for treating this form of ONj.[90] Although an effective treatment for bisphosphonate-associated bone lesions has not yet been established,[91] and this is unlikely to occur until this form of ONj is better understood, there as been clinical reports of some improvement after 6 months or more of complete cessation of bisphosphonate therapy.[92]

PREVENTION:

An ounce of prevention is worth a pound of cure. This is particularly true in CIBDs which are by nature hidden into the deepest and least easily visible part of our body, the trabecular bone tissue.

- Prevention of CIBD involves the elimination or appropriate modification of factors that can initiate, predispose or increase the likelihood of CIBD occurring.
- Implementing of good oral hygiene programs to avoid dental caries and gum disease in order to avoid infection and potential trauma.
- The use of biocompatible, non-metallic, dental materials. Manufacturers should provide written results of biocompatibility testing according to ANSI / ISO standards. Avoidance of vasoconstrictors such as epinephrine in patients at risk. In routine dental surgery for exodontia, complete removal of infected periradicular tissue should be emphasized.
- If decay is present, early diagnosis and interception is indicated.
- Inclusion of chronic radicular infection in the assessment of treatment outcome in endodontic therapy, in addition to symptomatology and radiographic criterion. Full informed consent on the potential implications of chronic dental infections .
- The use of minimally invasive techniques whenever possible (minimally invasive dental medicine).
- Dietary and lifestyle choices such as organic foods, reduction of refined and processed foods such as sucrose and bleached flour which are a known cause of dental diseases. Avoidance of source of heavy metals such as cadmium, lead and mercury. Superphosphate fertilizers and tobacco are a known source of cadmium exposure in humans,[93,94,95] dental amalgams are the main source of mercury exposure for the non-industrially exposed population.[96] Some brands of dental amalgams have also been shown to be a source of other toxic metals such as cadmium, indium, lead and in some case antimony. These metals, released from amalgam particles in the GI tract, were found in the liver, kidneys, lungs and blood or research animals.[97,98,99]
- Emphasis on healthy gastro-intestinal and hepatic function, especially in patients with multiple metallic restorations such as amalgam or/and chronic infections such as gum disease or devitalized teeth. An important reminder is that patients cannot efficiently detoxify if the two major organs of detoxification and elimination are dysfunctional.

CONCLUSION:

There is still much to be learned about osteoporosis / osteonecrosis of the jaws. Health professionals have a duty of care to their patients in the prevention and early diagnosis of jaw osteoporosis and/ or earlier stages of ONj. The quality of the prognosis is inversely related to the severity of the disease process. Greater awareness allows early diagnosis and early treatments, especially non surgical modalities to reduce coagulopathy, improve bone nutrition and reduce bone heavy metals content. Etiological factors have to be considered carefully in determining the best course of action in the diagnosis and treatment of ONj. In patients with CIBD, more attention should be paid to GI tract health and hepatic function. The key role of the gut in nutrients absorption and toxins elimination in combination with the liver cannot be overemphasized, especially in ONj.

Dentists, physicians, and natural health practitioners need to collaborate in an integrative manner in the treatment and management of jaw osteoporosis / osteonecrosis since such CIBD have both dental and systemic components that can have severe consequences on health as well as dental treatment decisions.

ABOUT THE AUTHOR: *Dr. Imbeau has received his doctorate in dental medicine (D.M.D.) from the Faculty of Dental Medicine, University of Montreal in 1980. From 1980 to 1982, he was a clinical instructor on the same Faculty. He received his New Zealand dental registration in 1994 and was director of dental services at the Bay of Plenty Environmental Health Clinic until 2003. He is presently director of Parkview Centre for Integrative Dental Medicine in Auckland and a fellow of the Australasian College for Nutritional and Environmental Medicine as well as a certified instructor in alveolar jawbone ultrasonography.*

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