The International Academy of Oral Medicine and Toxicology

IAOMT Position Paper on Human Jawbone Osteonecrosis

July 27, 2014

The International Academy of Oral Medicine and Toxicology (IAOMT) is founded upon the belief that "Science" should be the basis upon which all diagnostic and treatment modalities be based. In following that philosophy, this position paper is written utilizing the available information found in textbooks, research papers, and peer reviewed journal articles published throughout the world.

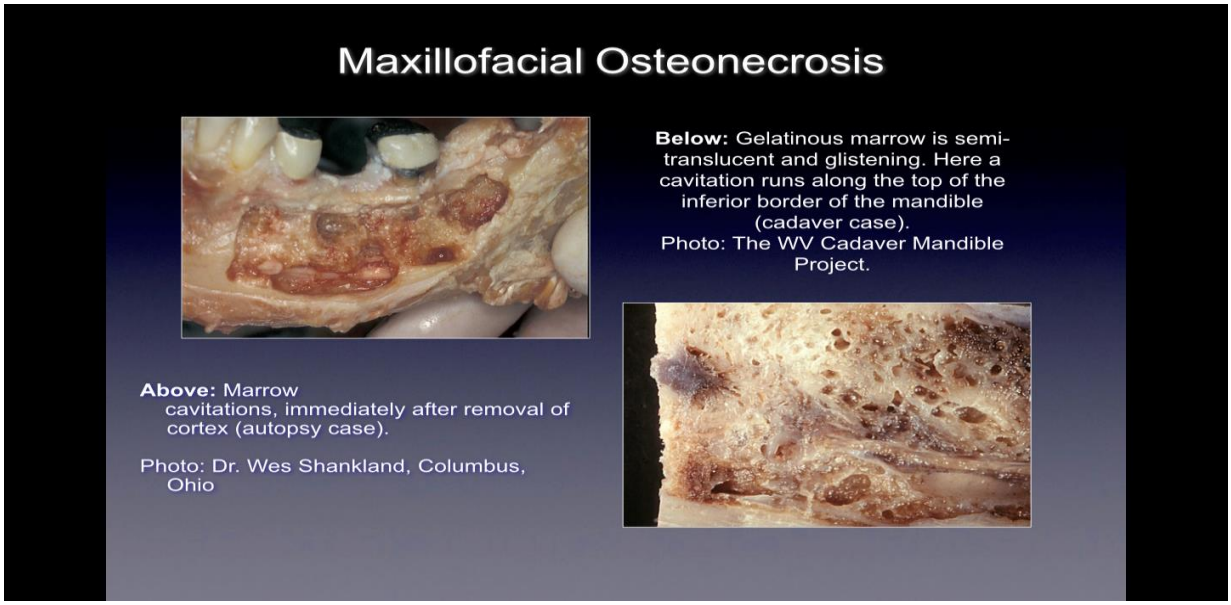
History

A review of the literature relating to the topic of Human Jawbone Osteonecrosis (JON) reveals that information has been researched and presented since the 1860's with Barrett[1] and Noel[2] describing noticeable defects in the jawbone. Noel broke down even further the label of pathological jawbone as either "dead" or the less damaged "reduced vitality". G. V. Black in his 1915 textbook set aside an entire section to describe the usual appearance and treatment of JON.[3] It is unfortunate that this information was seemingly forgotten until the 1970's when others began researching the topic again including information regarding JON in sections of modern oral pathology textbooks.[4, 5] Since that time, articles relative to JON have appeared in peer-reviewed journals including the Journal of Endodontics, the Journal of Periodontics, Oral Surgery-Oral Medicine- Oral Pathology, the AGD's General Dentistry, and the Journal of Craniomandibular Practice, and others. Unfortunately, the topic of JON remains controversial in some dental circles.[6]

Controversy

It is acknowledged that clinically observable and histologically confirmed cases of osteonecrosis pathology exist in almost all other bones in the human body, yet some clinicians still doubt that the same disease occurs in the alveolar processes of the human maxilla and / or mandible.[7] It is our hope that a Pennsylvania action taken against a dentist providing treatment of JON which was later overturned by a hearing examiner for the Pennsylvania State Board of Dentistry will be helpful to advancing the issue. It was the finding of the examiner that 1) JON is accepted as a pathological entity by the majority of dental pathologists, 2) Treatment of the entity is within the standards of care of the State of Pennsylvania, 3) The use of the "thru-transmission ultrasonography" device known Cavitat™ is helpful in the diagnosis of this osseous pathology.[8] The reality that the most widely used oral pathology textbook in the world describes the JON lesion and the treatment thereof, propels the diagnoses and treatment of this disease from a controversial theory to a scientifically recognized fact.[9] The IAOMT hopes national and state

dental regulating entities that have jurisdiction, licensing, and enforcement powers will become familiar with the current body of research regarding JON and base their opinions upon these facts ("Science"), rather than personal opinion or some other agency dictated agenda.



In order to fulfill the mission of educating the practitioner and patients about JON, it is essential to acknowledge the existence of the disease. Also known as Cavitations, Cavitational Osteonecrosis, Ischemic Osteonecrosis, NICO's, and various other labels, the presence of necrotic, or dying bone in the jawbones is well established as a known pathology of mankind.[10] With application of the scientific method, it is clear that pathologically observed areas of JON are found in human jawbones. These bony defects when observed clinically present themselves in numerous ways. Some report that over 75% of lesions are completely hollow or filled with soft, grayish-brown and mushy tissue, often with yellowish oily material (oil cysts) found in the defective areas with surrounding normal bone anatomy.[11] Others report the presence of "cavities" having varying overlying cortical bone density that upon opening appear to have linings with fibrous black, brown or grey filamentous materials.[12] Still others report gross changes variously described as "gritty", "like sawdust", "hollow cavities", and "dry" with occasional sclerotic, tooth-like hardness of the cavity walls. These lesions upon histological examination appear similar to the necrosis in other bones of the body and are histologically different from Osteomyelitis.[13] It is therefore the position of the IAOMT that JON is a diseased state that exists in human jawbones. Recently, DNA analysis of the biopsied contents from JON lesions has become available. Although as yet unpublished, the DNA data clearly demonstrates that JON is colonized with a broad range of potent anaerobic bacteria.

Diagnosis

Diagnosis is difficult due to the fact that some JON is almost invisible on standard radiographic films commonly used in dentistry. Ratner and others have stated that since 40% or more of the bone needs to be altered to show changes on standard dental radiographs, the disease state is

sometimes referred to as "undetectable" on dental films.[14] The interpretation of dental films is subjective and it is not uncommon for many trained researchers and clinicians to review identical films and come away with different interpretations.[15]

For these reasons, Tech 99 scans, MRI with filters, CAT scans, digital radiography, "thru transmission ultrasonography" (Cavitat™),[16] and other methods to visualize these lesions may be necessary. It should be mentioned that although the Cavitat™ ultrasound has been used as a diagnostic aid by some clinicians for many years, it is no longer manufactured.

Cone-Beam Computed Tomography (CBCT) has proven to be a reliable method of identifying and estimating the size and extent of intra-bony defects in the jaws.[17] It also helps to overcome a major limitation of two-dimensional (periapical and panoramic) imaging; the inability to distinguish anatomy in three dimensions. This limitation inherently leads to the superimposition of anatomical structures, which can mask areas of interest and decrease the diagnostic value of an image. In the case of defects or pathology specifically in the mandible, the masking effect of the dense cortical bone on the underlying structures can be significant. Also, CBCT provides the practitioner with a significantly higher diagnostic accuracy (less distortion, less magnification, etc.) than two-dimensional imaging. It also has the ability to view a lesion of interest in three dimensions (frontal, sagittal, coronal), and it employs highly accurate measurement tools and it utilizes advanced software which allows for image manipulation that will further aid in recognition of intra-bony defects.[18,19] Other clinical studies have shown CBCT images are also helpful in determining the contents of a lesion (fluid-filled, granulomatous, solid, etc.), possibly helping to distinguish between inflammatory lesions, odontogenic or non-odontogenic tumors, cysts, and other benign or malignant lesions.[20, 21] Such an image can prove useful in the diagnosis and treatment of JON, in areas such as: 1) Identifying the size, extent and three-dimensional position of a lesion, proximity of a lesion to other nearby vital anatomical structures such as the inferior alveolar nerve, maxillary sinus, or adjacent tooth roots, 2) Determining a

conservative approach to surgical or non-surgical treatment, and 3) Follow-up imaging to determine the possible need to re-treat a lesion. Although there are a lack of clinical studies regarding the use of CBCT specifically for JON lesions, it is clear that using this technology for diagnosis and assessment of other maxillofacial conditions, many of which share very similar physical characteristics to JON, is quickly becoming a valuable diagnostic tool.

Techniques as described by Ratner utilizing digital palpation and pressures, diagnostic local anesthetic injections, history and location of radiating pain if present and other manual testing procedures are needed. Complicating the issue is the fact that some JON lesions cause pain, hence the term neuralgia induced cavitational osteonecrosis (NICO) that describes a neuralgia component, and other JON lesions do not cause unprovoked pain, swelling, redness, or even fever.[22] The histological markers are the same but the symptoms differ. We believe that systemic illness previously not attributed to JON needs to be further evaluated.[23]

Systemic Implications

Recent research by Lechner and von Baehr confirm that JON lesions have high levels of inflammatory chemical messengers primarily regulated upon activation, normal T cell expressed, and secreted (RANTES) and fibroblast growth factor (FGF-2). Studies have shown RANTES to be implicated in many systemic illnesses such as arthritis, atopic dermatitis, nephritis, colitis, promotion of multiple sclerosis and Parkinson's disease, alopecia, thyroid disorders, and RANTES has been shown to cause an acceleration of tumor growth. FGF-2 has been shown in prostate cancer to promote tumor and cancer progression. Also, FGF-2 levels have shown direct correlation to the progression, metastasis and prognosis for survival of colorectal cancer patients. Also patients with gastric carcinoma have significantly higher levels of FGF-2 in their serum than that of cancer-free patients. Lechner and von Baehr conclude that RANTES deriving from JON might act as a low level inflammatory signal that leads to up-regulation of RANTES levels in specific organs with deleterious biological effects over the long term. JON can therefore be defined as a sort of inflammatory focus.

Both inflammatory messengers are implicated in many serious illnesses. The excessive levels of RANTES/FGF-2 in JON lesions was compared by Lechner and von Baehr to the levels of these inflammatory messengers that have been observed in other systemic illnesses like amyotrophic lateral sclerosis, multiple sclerosis, rheumatoid arthritis and breast cancer. The levels of these messengers detected in the JONs are higher than in the serum and cerebrospinal fluid of amyotrophic lateral sclerosis and multiple sclerosis patients. Current research by Lechner and von Baehr has demonstrated a five-fold increase in RANTES in the jawbone osteonecrotic lesions of breast cancer patients. They suggest that the JON derived RANTES may serve as an expediter of breast cancer progression.

The most striking discovery of the study was the high levels of RANTES and FGF-2 found in 97% of the tissues investigated. Correlations between levels of RANTES and FGF-2 in NICO tissue were statistically significant. The high levels of RANTES/FGF-2 in JON patients indicate that JON can be described as a derailed metabolic pattern, causing similar and mutually reinforcing pathogenic signaling pathways to other organs. The immune system seems to be

activated in response to danger signals, which evoke various innate molecular pathways that culminate in inflammatory cytokine production and possible activation of the adaptive immune system. The study suggests that JON might serve as a fundamental cause of inflammatory diseases, through RANTES/FGF-2 production. Thus, JON and implicated messengers represent an integrative aspect of inflammatory diseases and serve as a potential etiology of the disease. Removing JONs may be a key to reversing these and other inflammatory diseases.

NICO is a chronic, insidious and subtle process. The absence of acute inflammation or symptoms is supported by the fact that acute pro-inflammatory cytokines, such as TNF-alpha and IL-6 are not seen in increased numbers in the JONs. The absence of acute inflammation denotes that the proliferation of chronic immunological processes associated with JONs are under the guidance of RANTES/FGF-2.[24, 25, 26, 27]

Treatment

Once the location and size of the lesions are determined, treatment modalities are needed. The IAOMT believes that it is generally unacceptable to leave "dead bone" in the human body. It is believed that JON lesions can be the foci for systemic toxins to begin the process for degrading a patient's overall health. Hydrogen sulfide has long been regarded as the most toxic material the human body can produce. Yet the Affinity Labeling Technologies Lab Corporation has found substances that are far more toxic to five essential mammalian enzymes than hydrogen sulfide in JON biopsy samples.[28] Biopsy to confirm the diagnosis of JON and rule out other disease states including cancer is important. Then, treatment to remove or eliminate the involved pathology and stimulate the regrowth of normal, vital bone is necessary. At this time in the peer- reviewed literature, surgical therapy consisting of excising the affected non-vital bone appears to be the favored treatment for JON. The use of epinephrine containing local anesthetics should be avoided due to the already compromised blood flow associated with JON. Following a thorough "surgical decortication and curettage" [29] of the lesion and irrigation with sterile normal saline, healing is enhanced by placement of platelet-rich fibrin (PRF) grafts into the osseous void.[30, 31, 32, 33] The use of platelet-rich fibrin concentrates in surgical procedures is not only beneficial from a clotting standpoint, but also from the aspect of releasing growth factors over a period of up to fourteen days following surgery.[34]

Prior to the use of PRF grafts, relapse of the jawbone osteonecrotic lesion after surgery has been observed to occur in 40% of cases.[35] It should be noted that the 40% rate of surgical failures occurred when no adjunctive healing therapies such as PRF grafts were included as part of the treatment protocol.

Alternative techniques that are used in Europe and other parts of the world as primary or supportive therapies should also be evaluated. These include homeopathy, electrical stimulation, radiation such as laser and infrared, medical grade oxygen/ozone, hyperbaric oxygen, anticoagulation modalities, Sanum remedies, nutrition and nutriceuticals, energy treatments, and others. The IAOMT believes these forms of treatment should be evaluated and confirmed to be viable forms of treatment or shown ineffective and eliminated from use.[36] Standards of care to ensure proper healing and detoxification should be established. Techniques for evaluating success should be tested and standardized. Protocols or procedures to help determine when

treatment is appropriate and when it is not should be put forth for evaluation.

Researchers have shown that JON is a disease associated with reduced blood flow.[37] The sluggish medullary blood flow coupled with the fact that JON lesions maintain a pressure two to four times that of normal marrow challenge the delivery of antibiotics and the delivery of the body's own immune defenses. Genetic predisposition, effects of certain medications, trauma and infections, and other factors like smoking and atmospheric extremes lead to the formation of JON.[38] In no other bone is the potential for trauma and infections as great as in the jawbones. Those with reduced immune function are at increased risk for developing JON.[39]

JON As It Relates To Bisphosphonate Drugs

Of special interest and concern recently pertaining to JON is the increased use of a category of drugs called Bisphosphonates. These drugs are commonly prescribed for osteoporosis and for other diseases such as multiple myeloma and cancers that have metastasized to bone. The bisphosphonate-induced osteonecrosis of the jaw (BIJON) is "characterized by exposure of bone in the mandible or maxilla for more than eight weeks in a patient who has taken or currently is taking a bisphosphonate and who has no history of radiation therapy to the jaws."[40] "The fundamental biologic action of all bisphonates is to inhibit bone resorption and hence bone turnover and renewal, which of course reduces serum calcium levels as well. The reason for this anti-osteoclastic or anti-resorption effect is the inhibition and/or irreversible cell death of the osteoclast. All bisphosphonates have a half-life in bone of more than eleven years and are perhaps even lifelong." [41]

Although all bones are affected by bisphosphonates, the maxilla and mandible have a greater uptake of bisphonates due to the accelerated turnover rate of alveolar bone. Dixon et al. documented the remodeling rate of bone at various sites and found that the alveolar crest remodels at ten times the rate of the tibia.[42] Prolonged use of oral bisphosphonates, the most common of which is alendronate (Fosamax), or short-term use of intravenous bisphosphonates, the most potent of which is zolendronate (Zometa), become lethally toxic to osteoclasts and result in necrotic bone. According to Marx et al. Zometa, when administered at the recommended dose of four milligrams per month, may produce exposed bone within three to twelve months.[43] Once the toxicity of the bisphosphonate has overwhelmed the osteoclasts, necrosis of the bone occurs. The avascular nature of the necrotic bone leads to subsequent necrosis of the overlying tissue, resulting in exposed dead bone.

Initially the exposed bone is not painful because it is necrotic and lacks innervation. However, once the bone becomes infected it often progresses to a painful lesion. Marx details the treatment regimens for various stages of BIONJ involvement. These regimens range from daily oral 12% Chlorhexidine rinses, to long-term antibiotic coverage, to resection of the alveolar bone.[44] Most often the best management practice for treating patients with early stage BIONJ is to leave the exposed bone undisturbed except for removing superficial sharp edges. In cases where patients are able to discontinue bisphosphonate therapy for up to one year, enough osteoclastic activity resumes adjacent to the necrotic bone that fifty percent of patients experience sequestration of the exposed bone with subsequent healing of the soft tissue. In order to expedite

the exfoliation of the diseased bone some practitioners have successfully incorporated the use of oxygen-ozone therapy.[45, 46, 47] Treatments have consisted of injecting oxygen ozone in surrounding tissues on a weekly to monthly basis. In addition, others have encouraged the use of topical applications of ozone that are delivered via ozonated oils. The IAOMT believes that the findings associated with bisphosphonates should be a major concern for the dental profession. Having this knowledge is essential so that dentists will be cognizant of the need to be thorough in checking the medical and pharmacological history of patients prior to performing invasive surgical procedures.

Education

Education of our professional peers is necessary in order to understand the necessity for testing our patients for genetic predisposition of reduced osseous blood flow. Dissemination of information regarding laboratories such as Hemex (Phoenix, Arizona), Thrombocare (Dallas, Texas), and research facilities such as Dr Glueck's lab at the University of Cincinnati Medical Center that provide testing to determine risk factors for increased blood clotting tendencies in the osseous tissues is necessary.[48] Knowing and reviewing risk factors from the environment, medicines, and genetics, as well as previous medical and dental treatments is essential. The need for proper pre and post surgical therapy and proper techniques to be used in performing extractions and other osseous surgeries is indicated. Providing information to the patients regarding post surgical nutrition, blood flow maintenance, and prevention is also needed. Educating our dental boards and national dental agencies regarding the current state of research in JON is essential. If decisions are made using out of date information thus holding practitioners to dated standards of care, then no basis for continuing research, understanding, or treatments will be forth coming for our patients. The IAOMT urges the dental, medical, and research communities to continue applying the scientific method in order to diagnose, treat, educate, and ultimately prevent the occurrence of Human Jawbone Osteonecrosis (JON).

Summary

In summary, jawbone osteonecrosis, whether it is a result of bisphosphonate drugs, use of epinephrine containing local anesthetics, genetic predisposition, or systemic factors, is an insidious disease process. The broad array of DNA verified anaerobic pathogens and their toxins are risk factors for systemic disease. Although most JON lesions are difficult to diagnose with routine radiographs and most are not painful, one should never assume that the disease process does not exist. There are many disease processes that are difficult to diagnose, and many that are not painful. If we used pain as an indicator for treatment, periodontal disease, diabetes and most cancers would go untreated. Today's dental practitioner has a broad spectrum of modalities to successfully treat jawbone osteonecrosis and failure to acknowledge the disease and recommend treatment is no less serious than failure to diagnose and treat periodontal disease. A paradigm shift is in order for the dental profession to follow the lead of the medical profession in the recognition of JON for the health and welfare of its trusting patients.

[1] Barrett WC: Oral Pathology and Practice. Philadelphia, PA, S.S. White Dental Mfg. Co, 1898

[2] Noel HR: A lecture on caries and necrosis of bone. Am J Dent Sci (series 3):189, 1868

[3] Black GV: A work on special dental pathology. Chicago: Medico-Dental Co, 1915; 388-391

[4] Ratner EJ, Person P, Kleinman DJ, et al: Jawbone cavities and trigeminal neuralgia and atypical facial neuralgias. Oral Surg Oral Med Oral Pathol 1979; 48: 3-20

[5] Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and Maxillofacial Pathology. Philadelphia: WB Saunders Co; 2009: 866-869.

[6] Donlon, WC: Invited Commentary on Neuralgia-inducing Cavitational Osteonecrosis. Oral Surg Oral Med Oral Pathol March 1992; 73, no.3: 319-320

[7] Freedman PD, Reich, FR, Steinlauf AF: Letters to the editor. Oral Surg Oral Med Oral Pathol, July 1998; 86 no. 1: 3-4.

[8] Hearing Examiner's Proposed Adjudication and Order, Commonwealth of Pennsylvania, Bureau of Professional and Occupational Affairs v. Stephen R. Evans, DDS, May 10, 2007

[9] IBID 5

[10] Bouquot JE, Roberts, AM, Person P: Neuralgia-inducing Cavitational Osteonecrosis (NICO): Osteomyelitis in 224 jawbone samples from patients with facial neuralgias. Oral Surg Oral Med Oral Pathol 1992; 73: 307-319

[11] Shankland WE, et al: Medullary and Odontogenic Disease in the Painful Jaw: Clinicopathologic Review of 500 Consecutive Lesions. Cranio 2002; 20, no. 4: 295-303

[12] Ratner EJ, Person P, Kleinman DJ, Shklar G, Socranksy SS: Jawbone cavities and trigeminal and atypical facial neuralgias. Oral Surg 19790, 48, no. 1: 3-20

[13] Bouquot JE, Roberts AM, Person P: Neuralgia-inducing cavitational Osteonecrosis (NICO): Osteomyelitis in 224 jawbone samples from patients with facial neuralgias. Oral Surg Oral Med Oral Pathol 1992; 73: 312-315.

[14] Ratner EJ, Person P, Kleinman DJ, et al: Jawbone cavities and trigeminal and atypical facial neuralgias. Oral Surg Oral Med Oral Pathol 1079; 48, mo. 1: 3-20.

[15] Cohen S: Diagnostic procedures. In: Pathways of the pulp. 6th ed. Cohen S. Burns RC (eds). St. Louis: CV Mosby Co; 1994:10.

[16] Imbeau J: Introduction to Through-Transmission Alveolar Ultrasonography (TAU) in Dental Medicine. Cranio April 2005, Vol. 23, No.2: 100-112.

[17] Esposito SA, et al. A Novel Method to Estimate the Volume of Bone Defects Using Cone-Beam Computer Tomography; an In Vitro Study. JOE 2013 Sept; 39(9): 1111-1115.

[18] M. Joujeim, T.J. Prihoda, et al. Evaluation of high-resolution cone-beam computed tomography in the detection of simulated inter-radicular bone lesions. Dentomaxillofacial Radiology (2009) 38, 156-162

[19] B. Felipe, et al. Comparison between cone-beam and multi-slice computed tomography for identification of simulated bone lesions. Braz. oral res. [online]. 2011, vol.25, n.4, pp. 362-368. ISSN 1806-8324.

[20] Tyndall DA, Rathore S. Cone-Beam CT Diagnostic Applications: Caries, Periodontal Bone Assessment, and Endodontic Applications. Dent Clin N Am 52 (2008) 825-841

[21] Patil NA, Gadda R, Salvi R. Cone Beam Computed Tomography: Adding the Third Dimension. J Contemp Dent 2012;2(3):84-88

[22] Bouquot JE, LaMarche MG: Ischemic Osteonecrosis under fixed partial denture pontics: Radiographic and microscopic features in 38 patients with chronic pain. J Prosthetic Dent 81: 148-158.

[23] Bouquot JE: Characterization and identification of chemical toxicants isolated from cavitational material and infected root canalled teeth; in situ testing of teeth for toxicity and infection. Proceedings of Annual Meeting, International Academy of Oral Medicine and Toxicology; San Diego, CA; 1997.

[24] Lechner J, VonBaehr V. Rantes and fibroblast growth factor in jawbone cavitations; Triggers for systemic disease? International Journal of Medicine 2013: 6, 277-290.

[25] Lechner J, Mayer W. Immune messengers in neuralgia inducing cavitational osteonecrosis (NICO) in jawbone and systemic interference. European Journal of Integrative Medicine. 2 (2010) 71-77.

[26] Lechner J. Chronic osteonecrosis of jawbone (NICO): Unknown trigger for systemic disease and a possible new integrative approach? J Altern Med Res 2013;5(3):243-250

[27] Lechner J., von Baehr V. Hyperactive signaling pathways of chemokine RANTES/CCL5 in osteopathies of jawbone in breast cancer patients—case report and research. Breast Cancer: Basic and Clinical Research 2014: 8, 89-96.

[28] Haley B. Characterization and identification of chemical toxicants isolated from cavitational

material and infected root canalled teeth; in situ testing of teeth for toxicity and infection; Proceedings of Annual meeting, International Academy of Oral medicine and Toxicology; San Diego, California; 1997

[29] IBID 5

[30] L. He, Y. Lin, X. Hu, Y. Zhang, and J. We, "A comparative study of platelet-rich fibrin (PRF) and platelet-rich plasma (PRP) on the effect of proliferation and differentiation of rat osteoblasts in vitro." Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009 Nov;108(5):707-13

[31] M. Thorat, A.R. Pradeep, and B. Pallavi, "Clinical effect of autologous platelet-rich fibrin in the treatment of intra-bony defects; a controlled clinical trial," Journal of Clinical Periodontology, vol. 38, no, 10, pp. 925-932, 2011

[32] D.M. Dohan, J. Choukroun, A. Diss et al., "Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Art I: technological concepts and evolution," Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology, vol. 101, no 3, pp. 37-44.

[33] J.M. Karp, F. Sarraf, M.S. Shoichet, and J. E. Davies, "Fibrin filled scaffolds for bones-tissue engineering: an in vivo study," Journal of Biomedical Materials Research A, vol. 71, no. 1, pp. 162-171, 2004.

[34] D.M.S. Ehrenfest, G. M. de Peppo, P. Doglioli, and G. Sammartino, "Slow release of growth factors and thrombospondin-1 in Choukroun's platelet-rich fibrin (PRF): a gold standard to achieve for all surgical platelet concentrates technologies," Growth Factors, vol. 27, no. 1, pp. 63-69, 2009.

[35] Bouquot, J.E, and McMahon, R.E. Ischemic osteonecrosis in facial pain syndromes; a review of NICO (neuralgia-inducing cavitational osteonecrosis) based on experience with more than 2,000 patients TM Diary 1996; 8:32-39).

[36] Ali M, et al. Curriculum for Doctorate of Integrative Medicine. Capital University of Integrative Medicine: Washington DC: 2000.

[37] Glueck CJ, McMahon RE, Bouquot JE, Rabinovich B: Thrombophilia, hypofibrinolysis, and osteonecrosis of the jaws. Oral Surg Oral Med Oral Path 1996; 81:557-566.

[38] Bouquot, JE, McMahon RE: Neuropathic pain in maxillofacial osteonecrosis. J Oral Maxillofac Surg 2000; 58:1003-1020.

[39] Brown P, Cran L: Avascular necrosis of bone in patients with human immunodeficiency virus infection: report of 6 cases and review of the literature. Clinical Infectious Diseases 2001; 32:1221-1226.

[40] Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehotra B (Task Force on Bisphophonate-Related Osteonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons). American Association of Oral and Maxillofacial Surgeons position pater on bisphosphonate-related osteonecrosis of the jaw-2009 update. Aust Endod J 2009; 35:119-130.

[41] Marx, R.E. Oral and Intravenous bisphosphonate-induced osteonecrosis of the jaws. Chicago: Quintessence. 2011: 11-12.

[42] Dixon RB, Tricker ND, Garetto LP. Bone turnover in elderly canine mandible and tibia [abstract 2579]. J Dent Res 1997; 76: 336.

[43] Marx RE, Swatari Y, Fortin M, Broumand V. Bisphophonate-induce exposed bone (osteonecrosis/osteopetrosis) of the jaws: Risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg 2005;63: 1567-1575.

[44] Marx, R.E. Oral and Intravenous bisphosphonate-induced osteonecrosis of the jaws. Chicago: Quintessence. 2011: 59-66.

[45] Cole, G. Treatment of bisphosphonate related osteonecrosis of the jaw (BRONJ) with oxygen-ozone therapy: a case report. J of Implant and Advanced Clinical Dentistry, Vol 5, No. 5, May 2013

[46] Ripamonti, CI, Maniezzo M, Pessi, MA, Boldini, S. Treatment of osteonecrosis of the jaw (ONJ) by medical ozone gas insufflation. A case report. Tumori 2012. May-June; 98(3): 72-75.

[47] Agrillo, A et al. Bisphosphonate-related osteonecrosis of the jaw (BRONJ): five year experience in the treatment of 131 cases with ozone therapy. Eur Rev Med Pharmacol Sci. 2012 Nov:16(2): 1741-1747.

[48] Bick RL: Disorders of Thrombosis and Hemostasis. Clinical and Laboratory Practice. Roger Bick (ed). Third ec., Philadelphia, PA: Lippincott Williams and Williams; 2002