Pathophysiology and Pharmacologic Control of Osseous Mandibular Condylar Resorption

Michael J. Gunson, DDS, MD, G. William Arnett, DDS,† and Stephen B. Milam, DDS, PhD‡*

Purpose: When osseous mandibular condylar resorption occurs there can be many different diagnoses: inflammatory arthritis, TMJ compression, trauma, hormone imbalances, and others. While each diagnosis has its own original inciting event, the pathophysiological pathway for articular bone loss is the same. The aim of this article is to review the relevant literature on condylar resorption and the use of pharmacotherapy to control arthritic erosions and resorption.

Materials and Methods: The literature search was performed using PubMed database with various combinations of related keywords. Preference was given to clinical trials when reviewing articles.

Results: The literature reveals that common cellular level events associated with articular resorption include the activation of osteoblasts by cytokines, free radicals, hormone imbalances and/or potent phospholipid catabolites. The osteoblast then activates the recruitment of osteoclasts and promotes the release of matrix degrading enzymes from the osteoclast.

Research into articular erosions has focused on elucidating the important steps in the bone destructive pathways and interfering with them by pharmacological means. The use of antioxidants, tetracyclines, omega-3 fatty acids, non-steroidal anti-inflammatories and inflammatory cytokine inhibitors to aid in preventing and controlling articular bone loss including osseous mandibular condylar resorption has been successful.

Conclusion: By understanding the known pathways that lead to condylar resorption and the individual patient's susceptibilities, targeted pharmacotherapy might be able to disturb these pathways and prevent further condylar resorption. Basic clinical investigations and randomized clinical trials are still required, but the present science is encouraging.

J Oral Maxillofac Surg 70:1918-1934, 2012

Bone loss at the mandibular condyle has been described as a result of orthognathic surgery, systemic and local arthritides, post-traumatic remodeling, and hormonal imbalance.[1-15] Osseous condylar resorption that occurs without obvious cause is termed idiopathic condylar resorption. The clinical manifestations of condylar resorption are facial imbalance, airway size reduction, and bite disturbances, such as anterior open bite (Fig 1). Although the root causes of osseous condylar resorption differentiate between the diagnoses, all bone loss at the condyle involves a common resorptive pathway: cytokine-activated osteoblasts promote the recruitment and activity of osteoclasts that, in turn, result in the secretion of enzymes that are responsible for the breakdown of hydroxyapatite and collagen (Fig 2).

Rheumatoid arthritis, for example, is caused by a B cell–mediated autoimmune reaction to synovial tissues. As a consequence of this reaction, the local inflammatory cells secrete cytokines that cause the activation of osteoblast-mediated osteoclast catabolism. Whereas the initiating cause is a B-cell antigen-antibody reaction, the end result is promotion of bone breakdown through the common resorptive pathway.

*Private practice, Arnett and Gunson Facial Reconstruction, Santa Barbara, CA.

†Private practice, Arnett and Gunson Facial Reconstruction, Santa Barbara, CA.

‡Dr. Milam is deceased. He was the Chairman of the Oral and Maxillofacial Surgery Department at the University of Texas Health Science Center San Antonio, San Antonio, TX from 1999-2007.

Conflict of Interest Disclosures: None of the authors reported any disclosures.

Address correspondence and reprint requests to Dr Gunson: 9 E Pedregosa St, Santa Barbara, CA 93101. e-mail: gunson@arnettgunson.com

0278-2391/12/7008-0$36.00/0
doi:10.1016/j.joms.2011.07.018

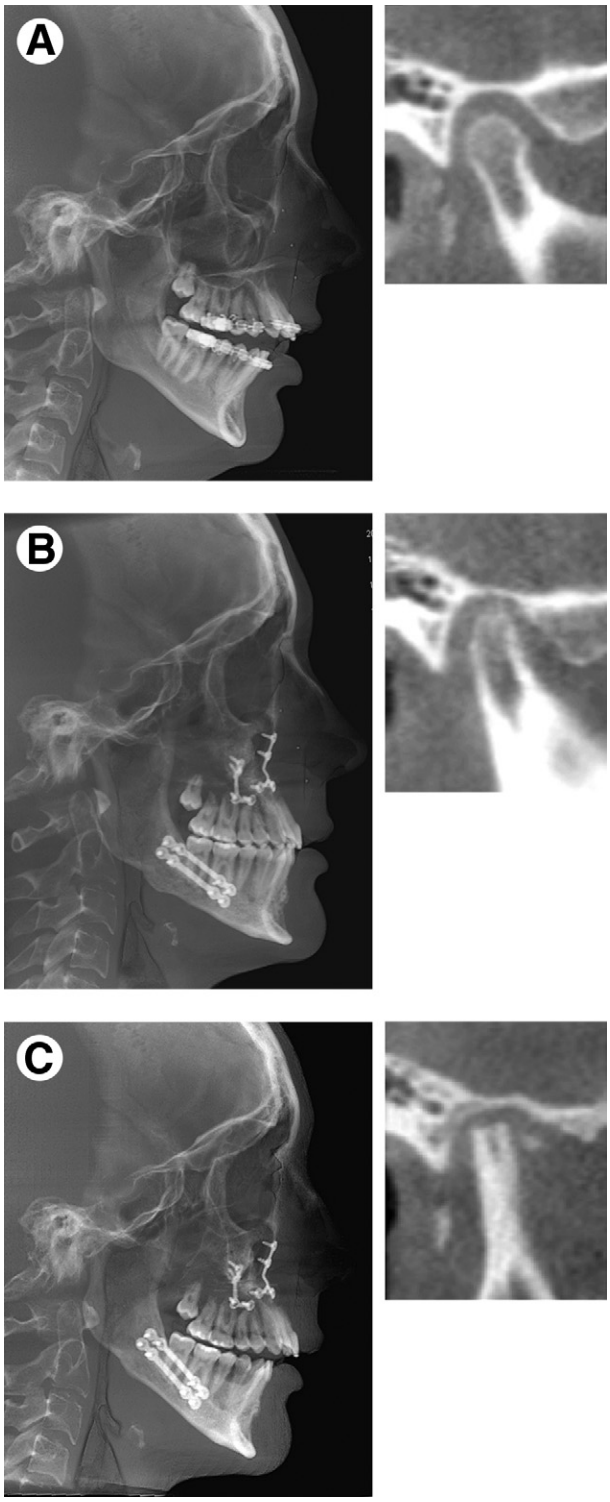

FIGURE 1. A 21-year-old woman who had condylar resorption after orthognathic surgery. History, examination, and blood work showed that the patient did not produce estrogen. The condylar resorption occurred over a 34-month period and resulted in a Class II occlusion with anterior open bite. Sagittal TMJ slices and lateral cephalometric radiographs obtained before surgery (A), 7 months after orthognathic surgery (B), and 34 months after orthognathic surgery (C) are shown.

Gunson, Arnett, and Milam. Pharmacologic Control of Condylar Resorption. J Oral Maxillofac Surg 2012.

The medical approach to minimizing articular bone loss has involved interfering with particular cytokines and enzymes along the common resorptive pathway by pharmacologic means. For example, the use of medications that specifically target the cytokines responsible for osteoblast activation has been quite successful in the treatment of inflammatory arthritis and can decrease the need for surgical intervention in these patients.[16] The use of pharmacologic agents to prevent or slow mandibular condylar resorption is not well described in the oral and maxillofacial literature. Understanding the common bone resorptive pathway and the published success rates of reducing articular erosions through pharmacologic intervention might improve our ability to control mandibular condylar resorption without invasive articular surgery.

In this literature review, the basic cytokines, enzymes, and cellular components that are involved in articular bone loss will be described. A brief review of conditions that activate these pathways is presented. Finally, a review of the medications for which there are published clinical trials of successful articular erosion reduction and a discussion of possible future therapeutic directions are presented.

Pathogenesis of Condylar Resorption

GENESIS OF FREE RADICALS

A free radical is defined as any molecular species capable of independent existence that contains 1 or more unpaired electrons. This particular molecular conformation renders a free radical highly unstable. As a result, free radicals initiate oxidation reactions with adjacent molecules to acquire a paired-electron conformation by reduction. These oxidation reactions can have damaging effects on articular tissues.

It has been proposed that free radicals may be generated in the temporomandibular joint (TMJ) by at least 2 mechanisms, both involving increased mechanical loads.[17] Oxygen-derived free radicals may be generated by a hypoxia-reperfusion mechanism.[18,19] Alternatively, free radicals may be generated by homolytic fission of molecules in articular tissues subjected to shearing forces generated during pathologic compression or joint movement.[18,20,21] Studies have shown elevated oxidative states in TMJ synovial fluid when inflammation and osseous damage are present.[19,22-28]

CYTOKINE SIGNALING

Cytokines are extremely potent molecules that are involved in cell signaling. Cytokines are produced by a variety of cell types present in the TMJ, including

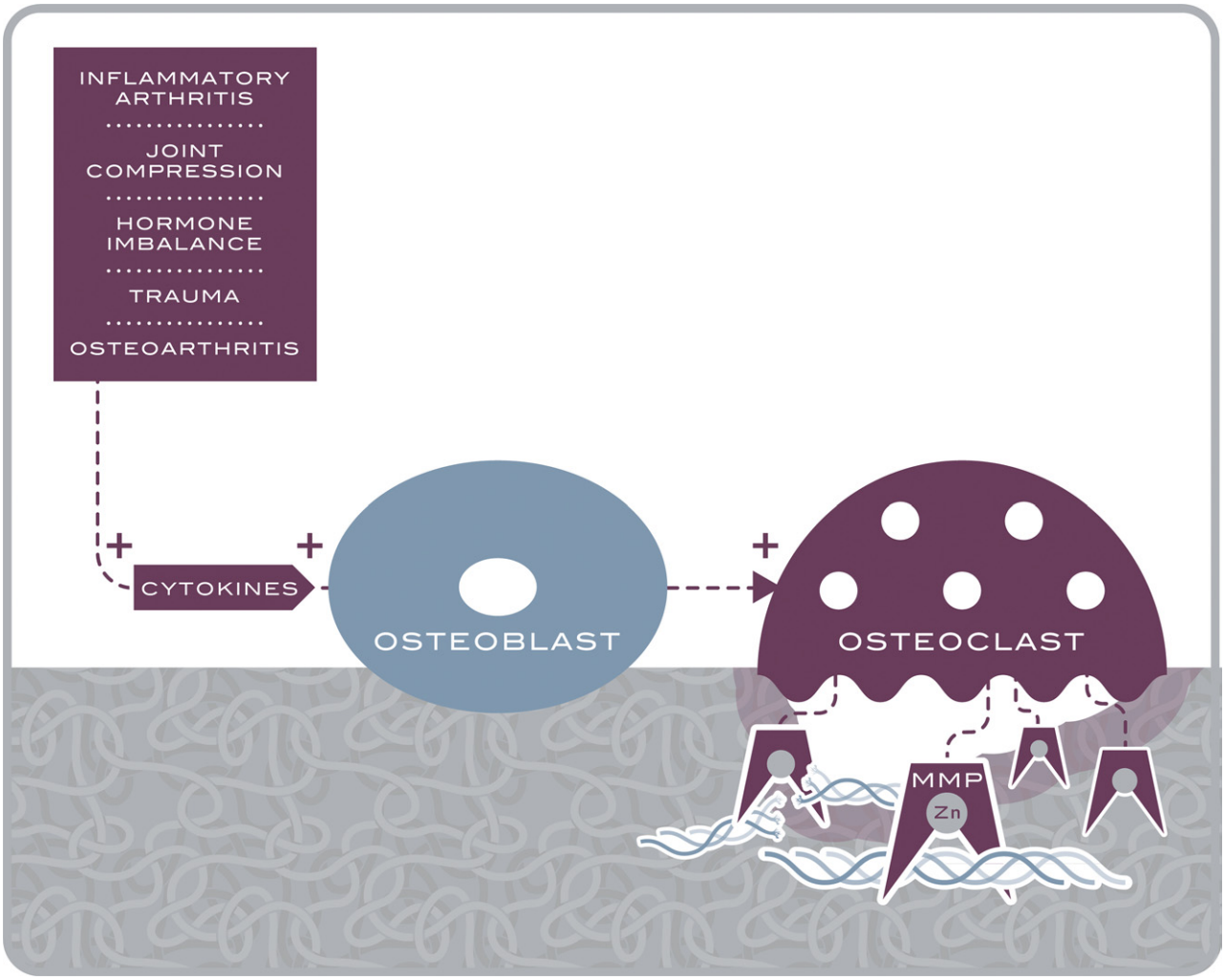

FIGURE 2. The common pathway that is responsible for bone loss at the mandibular condyle consists of the secretion of potent cytokines, which in turn promotes activation of osteoclasts by osteoblasts. The result is the secretion of proteinases by the osteoclast, which in turn causes articular osseous resorption. (Zn, zinc.)

Gunson, Arnett, and Milam. Pharmacologic Control of Condylar Resorption. J Oral Maxillofac Surg 2012.

osteoblasts and synoviocytes. To date, major cytokines that have been implicated in the pathogenesis of condylar resorption include tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and receptor activator nuclear factor kappa-beta ligand (RANKL).[29-49] Osteoprotegerin (OPG), which is a RANKL inhibitor, has been found to be more abundant in states of repair and health (Fig 3).[33] Previous clinical trials have shown correlations between concentrations of these cytokines, isolated from diseased human TMJ, and disease severity as assessed during arthroscopic, magnetic resonance imaging (MRI), radiographic, and surgical examination.[50-58] For example, Alstergren and Kopp[30] observed a correlation between TNF-α increases and condylar tissue destruction. Hamada et al[31] showed a decrease in the success of arthrocentesis in treating closed lock of the TMJ when the levels of IL-6 are significantly elevated. Patients with MRI and clinically diagnosed TMJ osteoarthritis had a significantly higher RANKL-OPG ratio than control subjects.[33]

MATRIX METALLOPROTEINASES

Matrix metalloproteinases (MMPs) are endopeptidases that degrade a variety of extracellular matrix molecules (eg, collagen and elastin) found in articular tissues of the TMJ. As the name implies, MMPs require zinc as a cofactor for activity. There is substantial evidence indicating that these enzymes play an important role in bone and cartilage degradation in the TMJ. This evidence supports the presence of 6 of the 28 known MMPs (ie, MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, and MMP-13) in fluid or tissue samples obtained from diseased human TMJ (Fig 4).[52,59-76]

Production of MMPs by resident cell populations, especially the osteoclast, can be induced by TNF-α, IL-6, and RANKL.[60,62,64,68,77] Some MMPs are secreted

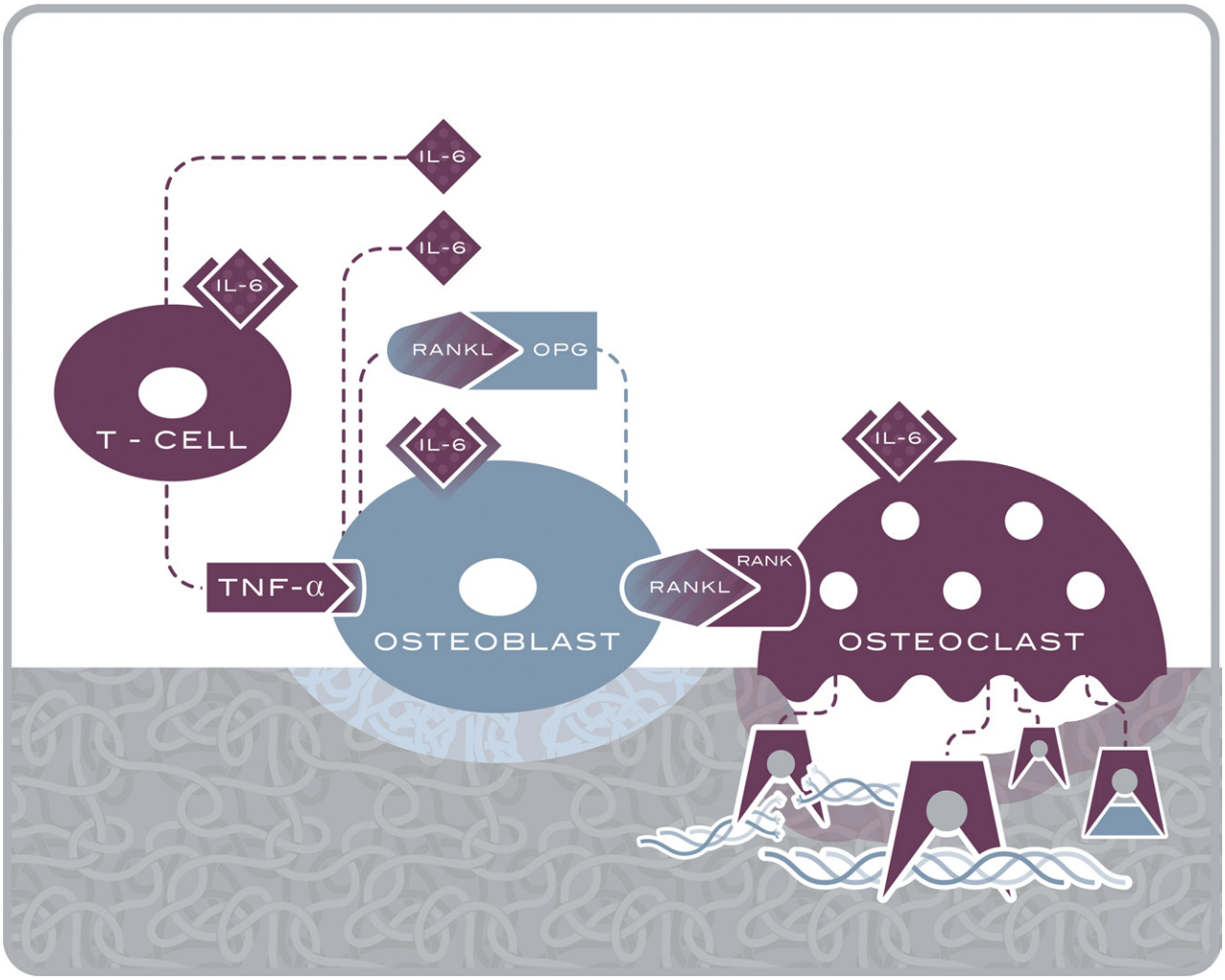

FIGURE 3. TNF-α, IL-6, and RANKL are all cytokines that activate the catabolic pathways of bone resorption (burgundy). OPG is a cytokine/receptor decoy that inhibits bone catabolism (blue) by binding to RANKL. (RANK, receptor activator nuclear factor kappa-beta.)

Gunson, Arnett, and Milam. Pharmacologic Control of Condylar Resorption. J Oral Maxillofac Surg 2012.

by cells in inactive or latent forms and may subsequently be activated by other enzymes or by oxidation reactions initiated by free radicals.[61,66]

Under normal circumstances, the activities of active MMPs are regulated by other molecules, termed tissue inhibitors of metalloproteinases (TIMPs). TIMPs bind to active MMPs and inhibit their activity.[78] Some cases of condylar resorption result from an imbalance between the activities of MMPs and TIMPs, favoring unregulated degradation of tissue by MMPs.[74,79]

LIPID PEROXIDATION AND ARACHIDONIC ACID CATABOLISM

Phospholipids found in cell membranes provide substrates for generation of biologically active molecular species that modulate cellular activities in articular tissues of the TMJ. Arachidonic acid is formed from phospholipids by action of phospholipases. In turn, arachidonic acid is converted to prostanoids by action of cyclo-oxygenases or to leukotrienes by action of lipoxygenases. Alternatively, isoprostanes are generated from phospholipids by oxidation reactions driven by free radicals. Collectively, these phospholipid metabolites play important roles as regulators of chondrogenesis, osteogenesis, and nociception in the TMJ.[23,80,81]

Susceptibility to Condylar Resorption

A number of factors are believed to govern an individual's susceptibility to osseous condylar resorption. These include gender, nutritional status, genetic backdrop, patient's oral habits, and iatrogenic compression.

There is a strong female predilection for condylar resorption.[9,11,12,82-85] Recent evidence suggests that sex hormones, particularly estrogens, play an impor-

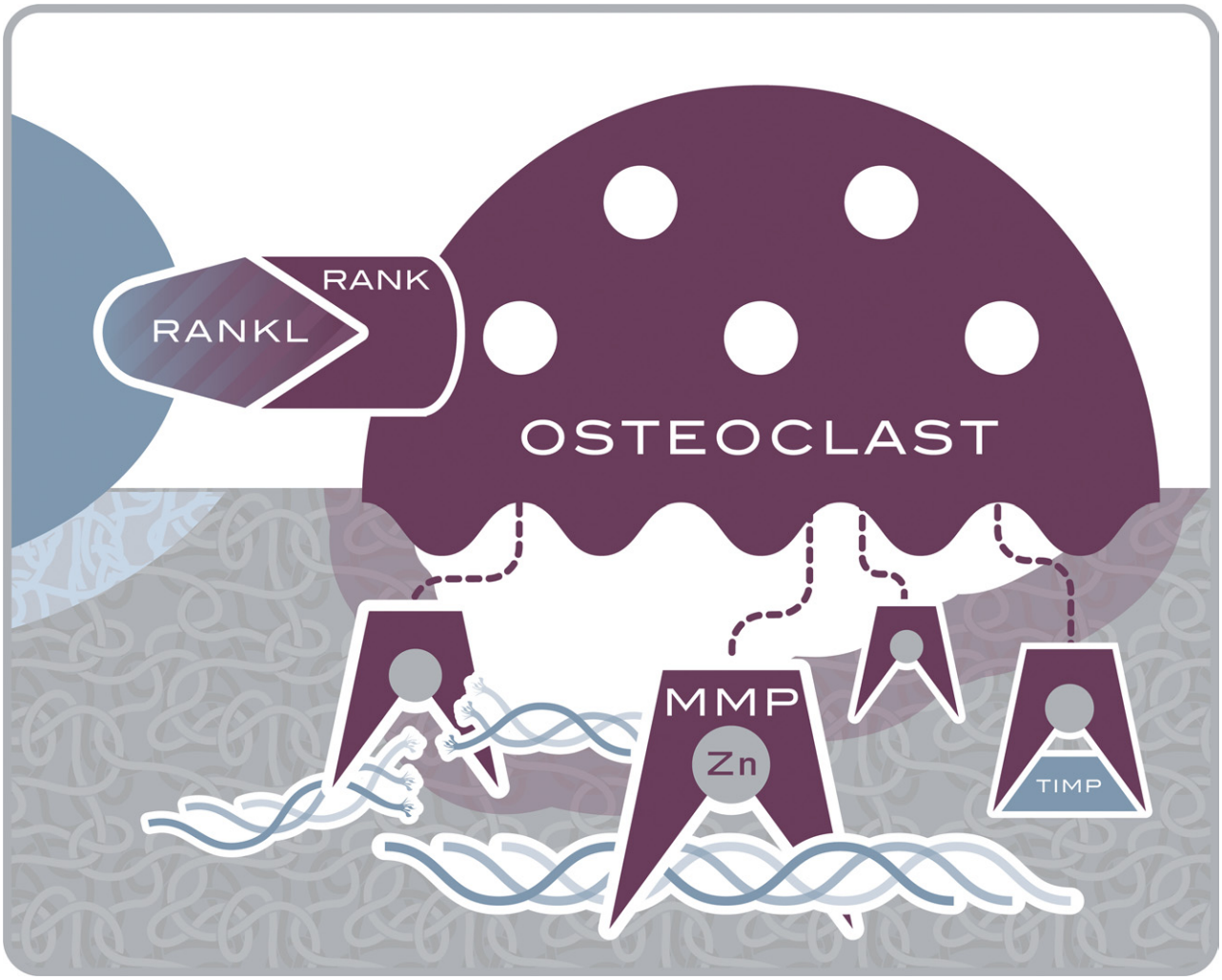

FIGURE 4. MMPs are enzymes that are secreted by local articular cells, particularly osteoclasts, which cut collagen fibers, degrading the extracellular matrix of the condyle. TIMPs control the activity of MMPs by binding them extracellularly. (Zn, zinc; RANK, receptor activator nuclear factor κ.)

Gunson, Arnett, and Milam. Pharmacologic Control of Condylar Resorption. J Oral Maxillofac Surg 2012.

tant role in the regulation of both discal tissue and osseous and cartilage tissues.[76,86] Estrogens have strong influences on both inflammation and bone and cartilage metabolism.[87] It has been shown that 17β-estradiol has a positive effect on OPG transcription and an inhibitory effect on TNF-α liberation.[88,89] We have previously reported on the presence of estrogen imbalance in a group of female patients with severe condylar resorption.[13]

Evidence also suggests that nutritional status may be an important determinant of an individual's susceptibility to degenerative TMJ disease. For example, the dramatic effects of dietary omega-3 fatty acids on decreasing inflammation have been documented.[90] Much has also been written about the epidemic of low vitamin D levels in our society.[91] Vitamin D not only is known for its role in bone metabolism but also plays an important role in controlling inflammation in arthritis.[92-95] Therefore dietary regulations and monitoring may be important in the control of some degenerative TMJ diseases.

It is becoming increasingly clear that an individual's genetic backdrop may be a primary determinant of susceptibility to osseous changes in the TMJ. For example, MMP, vitamin D receptor, aromatase, and estrogen receptor polymorphisms appear to be associated with higher incidences of articular bone loss, including the TMJ.[96-99] Planello et al[99] reported that MMP-1 polymorphisms were more commonly seen in a large degenerative TMJ population as compared with healthy control subjects.

Bruxism and repetitive oral habits have been shown to lead to condylar bone loss.[100,101] The pathways involved are likely free radical generation through sheer stress and increased metabolic demands.[17-19]

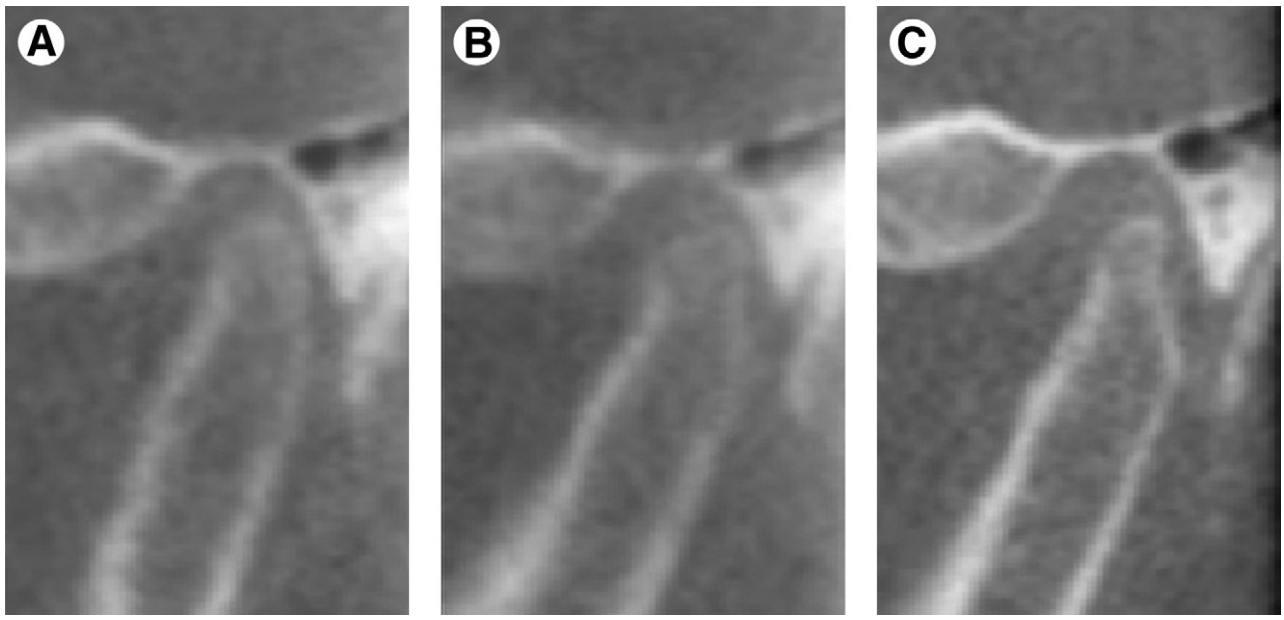

FIGURE 5. The mandibular condyle was posteriorized due to orthognathic surgery. Over several months, the compressed posterior aspect of the condyle has resorbed. The presurgical sagittal tomogram (A), the tomogram obtained 13 days after orthognathic surgery (B), and the tomogram obtained 1 year after orthognathic surgery (C) are shown. This represents one of many possible iatrogenic mechanisms for condylar resorption.

Gunson, Arnett, and Milam. Pharmacologic Control of Condylar Resorption. J Oral Maxillofac Surg 2012.

Finally, we must recognize the clinician's role in producing condylar change through compression. Whether through gross displacement during orthognathic surgery, intermaxillary fixation, improper occlusal splint fabrication, or other means, displacement of the condyle into compressive contact appears to cause activation of the previously mentioned pathologic pathways and osseous condylar resorption (Fig 5).[1-8,102-105]

Pharmacologic Regulation of Pathogenic Mechanisms

FREE RADICAL SEQUESTERING OF ANTIOXIDANTS

As previously mentioned, free radicals may be produced by a variety of mechanisms and are believed to be involved in initiation of condylar resorption in susceptible individuals. It is known, as well, that patients who have inflammatory arthritides have consistently low antioxidant levels.[106] Under normal conditions, free radicals are regulated by free radical scavengers, some of which are also known as antioxidants. Studies have provided evidence that dietary supplementation with antioxidants may have beneficial effects on bony erosions in the management of some inflammatory arthritides, as well as osteoarthritis.[107-120]

CYTOKINE CONTROL

In the arthritis literature, cytokines have emerged as the master controllers of hard tissue degradation in human joint tissues in both osteoarthritis and inflammatory arthritis models. TNF-α, for example, has an immensely negative effect on bone and cartilage through the following pathways: MMP transcription and IL-6–mediated induction of osteoclast progenitor differentiation and osteoclast activity. It is no wonder then that cytokine inhibitor development is so competitively intense. The US Food and Drug Administration has approved 5 agents for treating inflammatory arthritis through TNF-α blockade: etanercept, infliximab, adalimumab, certolizumab, and golimumab. TNF-α inhibitors are the most promising pharmacologic intervention for the control of articular bone loss and erosions and the only cytokine inhibitors for which TMJ studies are available (Fig 6).

There are several studies that show arrestment and even healing of arthritic erosions after patients had been treated with TNF-α inhibitors.[121-123] Døhn et al[122] showed with MRI that etanercept prevented joint surface erosion progression even in the presence of capsular swelling. There are few TNF-α inhibitor studies with regard to TMJ erosions and inflammation. Moen et al[124] showed a decrease in TMJ joint pain and muscle pain and an increase in range of motion in rheumatoid arthritis patients taking infliximab. Finally, a report on using intra-articular injections of a TNF-α inhibitor to stop inflammatory joint erosions in the TMJ was recently published.[125] This would be a promising treatment because the local intracapsular injection could minimize systemic side effects.

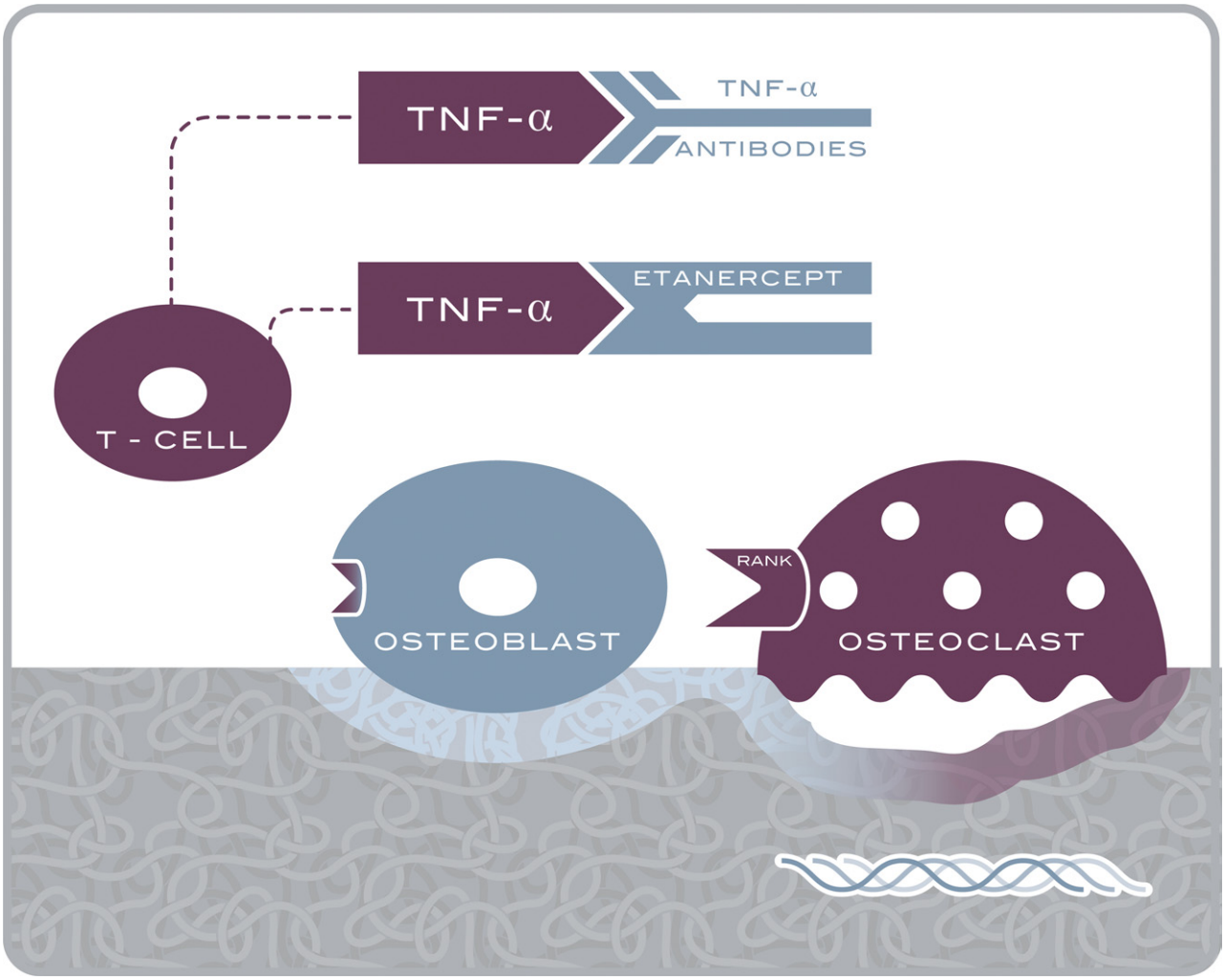

FIGURE 6. Two TNF-α inhibitor types are represented. Etanercept is a soluble receptor analog that binds TNF-α. Infliximab, adalimumab, certolizumab, and golimumab are all monoclonal antibodies to the cytokine TNF-α. (RANK, receptor activator nuclear factor κ.)

Gunson, Arnett, and Milam. Pharmacologic Control of Condylar Resorption. J Oral Maxillofac Surg 2012.

The systemic dosing for etanercept in patients with condylar resorption due to inflammatory arthritis is a 50-mg subcutaneous injection per week. Adalimumab is dosed at 40 mg through 1 subcutaneous injection every 2 weeks. Patients should be monitored closely because the side effect profile of TNF-α inhibitors is not innocuous. Before starting a TNF-α inhibitor, the patient should be screened for tuberculosis and free from active infectious processes. The most common side effect is injection-site reactions. Although it is reported that there can be a worsening or reactivation of infections, this was equal to untreated control subjects with rheumatoid arthritis. The most ominous side effects are the development of demyelinating diseases (<0.1%), lymphoma (0.05 cases per 100 patient-years), and leukemia (0.3 cases per 100 patient-years).[126] These medications are quite costly, and in the patient with inflammatory arthritis, they require constant administration to prevent relapse.

MMP INACTIVATION BY TETRACYCLINES

Tetracyclines inhibit the actions of MMPs by chelating zinc and by regulating MMP gene expression. Periodontists were among the first researchers to explain these mechanisms by using the periodontal disease model. As explained previously, MMPs need zinc to actively cleave collagen proteins. Tetracyclines bind divalent ions, such as zinc. By reducing the amount of free zinc in tissues, tetracyclines reduce the number of MMPs available.[127] In addition, tetracyclines bind to the MMP itself, which causes a conformational change in the enzyme, inactivating it.[128] Tetracyclines also decrease the transcription of MMPs by blocking both the protein kinase C and the calmodulin pathways.[129,130]

Tetracyclines also prevent the liberation of cytokines IL-6 and TNF-α, which in turn diminishes the differentiation of osteoclast progenitor cells and

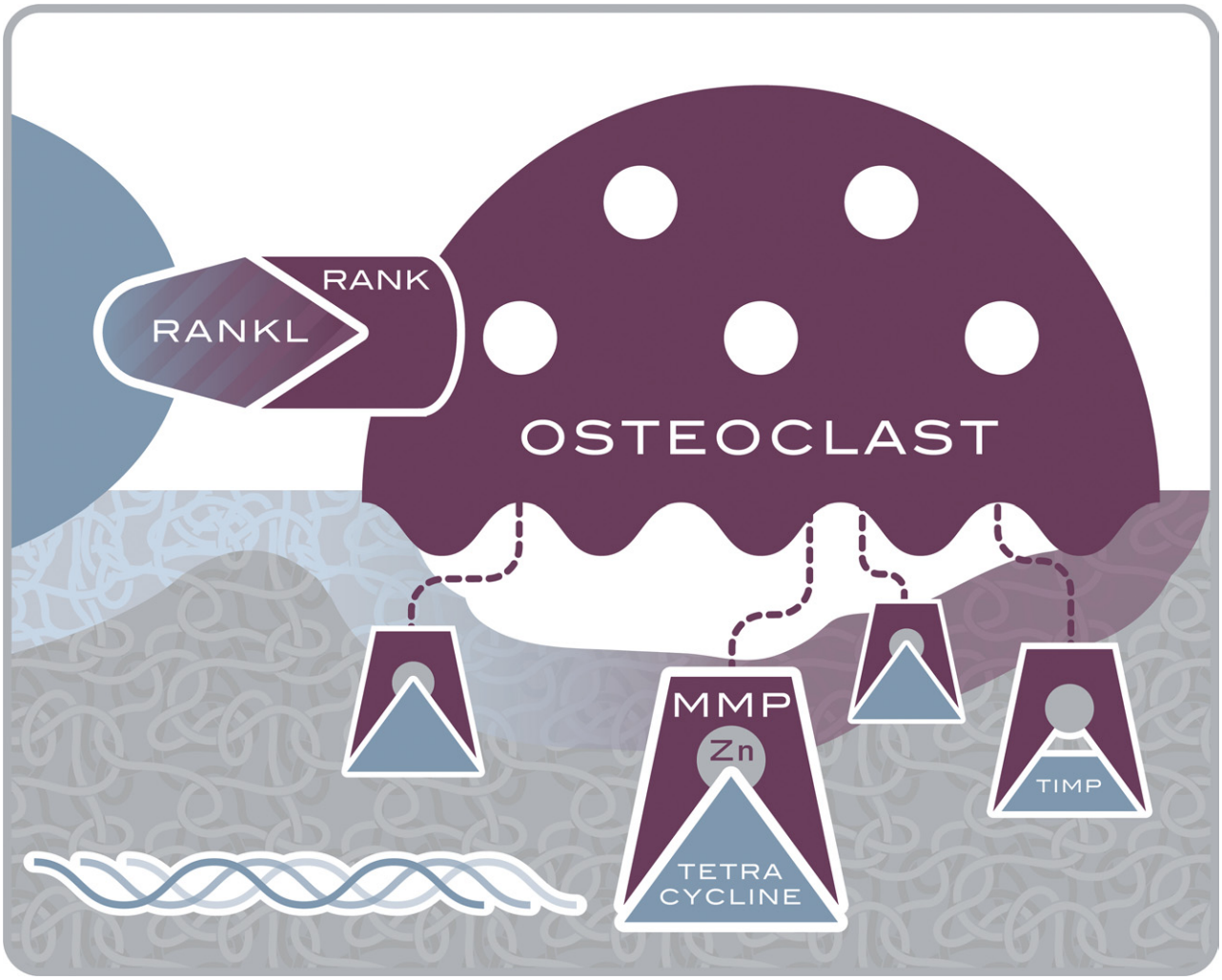

FIGURE 7. Doxycycline decreases MMP activity in several ways. It decreases the liberation of osteoclast-stimulating cytokines TNF-α, IL-6, and interleukin 1β; it binds zinc (Zn), making it unavailable for MMP transcription; and it also binds directly to the MMP, preventing the enzyme's ability to destroy extracellular matrix (collagen fibers). (RANK, receptor activator nuclear factor κ.)

Gunson, Arnett, and Milam. Pharmacologic Control of Condylar Resorption. J Oral Maxillofac Surg 2012.

osteoclast resorptive activity.[131-136] Finally, tetracyclines promote the programmed cell death (apoptosis) of osteoclasts.[137,138] All these actions result in a decrease of bone and cartilage loss due to decreased osteoclast activity when tetracyclines are present (Fig 7).

It is obvious that the literature shows that tetracyclines exert control over MMP transcription and activity and regulate osteoclast activity as well. The clinical evidence supporting the use of tetracyclines to protect articular bone and cartilage from arthritic inflammation is promising.

Tetracyclines have been successfully used to diminish bone erosions in patients with rheumatoid arthritis. A meta-analysis of 10 clinical trials that used tetracycline for rheumatoid arthritis showed significant improvement in disease activity with no side effects.[139] In a single blinded controlled study, doxycycline was shown to be as good as methotrexate in treating rheumatoid arthritis.[140] Brandt et al[141] showed that doxycycline limited erosion progression in the osteoarthritis model as well. Other clinical trials show a clinically measurable reduction in MMP-8 and inflammatory cytokine levels.[142,143] Israel et al[144] reported that doxycycline administered at a dose of 50 mg twice daily for 3 months significantly suppressed MMP activity in patients diagnosed with advanced osteoarthritis of the TMJ.

Adverse effects of tetracyclines are well known. They include gastrointestinal symptoms (ie, nausea, vomiting, diarrhea, esophageal ulcers, and *Candida* superinfection), photosensitivity, vestibular toxicity with vertigo and tinnitus, decreased bone growth in children, and discoloration of teeth if administered during tooth development. Tetracyclines may also reduce the effectiveness of oral contraceptives, po-

tentiate lithium toxicity, increase digoxin availability and toxicity, and decrease prothrombin activity.

INHIBITION OF PROSTANOIDS AND LEUKOTRIENES BY OMEGA-3 FATTY ACIDS

Over the past 2 decades, evidence has emerged suggesting that dietary modifications can influence prostanoids and leukotriene synthesis. Omega-3 fatty acids found in fish oils are incorporated in cell membranes after ingestion. These fatty acids provide substrates (eg, eicosapentaenoic acid and docosahexaenoic acid) that yield novel prostanoids and leukotrienes by actions of cyclooxygenases and lipoxygenases. In some instances, it appears that these novel prostanoid and leukotriene species either are less potent with respect to inflammatory properties or are anti-inflammatory in nature.[145] Thus dietary supplementation with omega-3 fatty acids may reduce inflammation (pain, swelling, edema) by enhanced production of prostanoids and leukotrienes that do not evoke strong inflammatory responses.[146]

Randomized clinical trials examining the effects of dietary supplementation with omega-3 fatty acids in rheumatoid arthritis patients have shown beneficial effects.[147-149] These beneficial effects are produced when plasma phospholipid eicosapentaenoic acid content exceeds 3.2% of total fatty acid levels. This may be produced by daily intake of 2.6 to 7.1 g of omega-3 fatty acids. It should be noted that the beneficial effects of omega-3 fatty acids are rapidly reversed with withdrawal of dietary intake. Omega-3 fatty acids potentiate anticoagulants and could prolong bleeding times.

INHIBITION OF PROSTANOIDS AND LEUKOTRIENE PRODUCTION BY CYCLOOXYGENASE AND LIPOXYGENASE INHIBITORS

The pharmacology of nonsteroidal anti-inflammatory drugs is complex. Contrary to popular belief, some nonsteroidal anti-inflammatory drugs can exert a multitude of biologic effects beyond cyclooxygenase or lipoxygenase inhibition. Other known effects produced by some nonsteroidal anti-inflammatory drugs include uncoupling mitochondrial oxidative phosphorylation, activation of cyclic adenosine monophosphate–dependent phosphokinase A, inhibition of interleukin-1 and interleukin-1 receptor synthesis, free radical scavenging, and inhibition of MMPs.[150,151] Through these multiple biologic effects, it is now known that nonsteroidal anti-inflammatory drugs protect bone and cartilage from breakdown and relieve pain and effusion.[152,153] In addition, some nonsteroidal anti-inflammatory drugs appear to stimulate cartilage matrix synthesis (eg, tolmetin and tenidap), whereas others may inhibit cartilage matrix synthesis (eg, ibuprofen, naproxen, and indomethacin) or have neutral effects on cartilage matrix synthesis (eg, piroxicam and aspirin).[154,155]

When TMJ inflammation is suspected (eg, joint effusion, slight posterior open bite with localized preauricular pain, and rapidly progressive condylar resorption), then initiation of a nonsteroidal anti-inflammatory drug therapy should be considered. On the basis of current information, 20 mg of piroxicam daily is appropriate unless contraindicated.

Nonsteroidal anti-inflammatory drugs should be avoided in patients with known drug hypersensitivity, some gastrointestinal disorders, renal dysfunction, or bleeding disorders. During therapy, patients should be monitored for side effects including gastrointestinal distress, renal dysfunction, bronchospasm, thrombocytopenia, and Stevens-Johnson syndrome/erythema multiforme–like syndrome. Potential drug interactions with nonsteroidal anti-inflammatory drugs include renal toxicity with angiotensin converting enzyme inhibitors and acetaminophen and gastrointestinal bleeding with selective serotonin reuptake inhibitors. Bleeding risk is increased because of platelet inhibition.

Future Directions

STATINS

A plethora of studies shows that 3-hydroxy-3-methyl-glutaryl–coenzyme A reductase inhibitors or statins reduce the risk of myocardial infarction by lowering cholesterol levels and through anti-inflammatory mechanisms. The discovery that statins control inflammatory pathways separate from their cholesterol level–lowering mechanisms led to numerous other studies in the fields of autoimmune disease, arthritis, and tissue injury. In all these areas statins have shown significant promise as anti-inflammatory agents.[156-160]

Statins seem to modulate T-cell cytokine and MMP production in the articular model.[158,161-163] The ability of statins to reduce MMP and inflammatory cytokine activity might imply a role for 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors to control condylar resorption.

Although no research has been performed regarding the effect of statins on TMJ arthritides, 2 studies have evaluated the effect of statins on arthritis.[164,165] The controlled trial of McCarey et al[165] showed decreases in disease activity scores, C-reactive protein levels, and swollen joint counts greater than placebo in patients with rheumatoid arthritis taking atorvastatin.

The side effect profile of statins is low and often equal to placebo. The most important side effects, however, are liver dysfunction and muscular symptoms related to rhabdomyolysis.

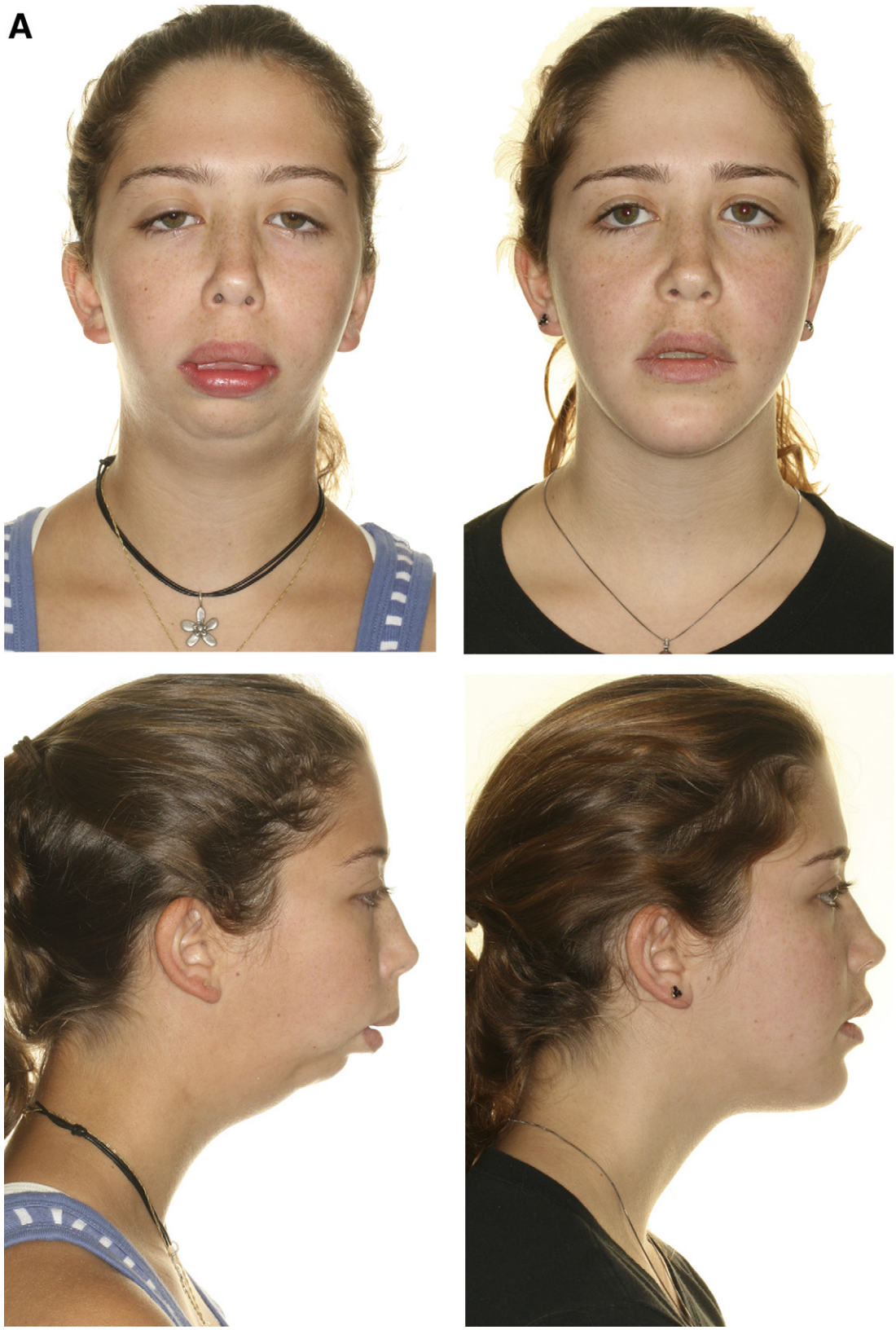

FIGURE 8. An 18-year-old woman who had severe condylar resorption due to inflammatory arthritis. She was prescribed doxycycline, omega-3 fatty acids, and etanercept before and immediately after orthognathic surgery. Her condylar resorption remitted and her occlusion was stable at 29 months after surgery. Facial photos before orthognathic surgery and 29 months after orthognathic surgery (A), occlusal photos (B), condylar photos (C), and the cephalometric treatment plan (D) are shown. (**Figure 8 continued on next page.**)

Gunson, Arnett, and Milam. Pharmacologic Control of Condylar Resorption. J Oral Maxillofac Surg 2012.

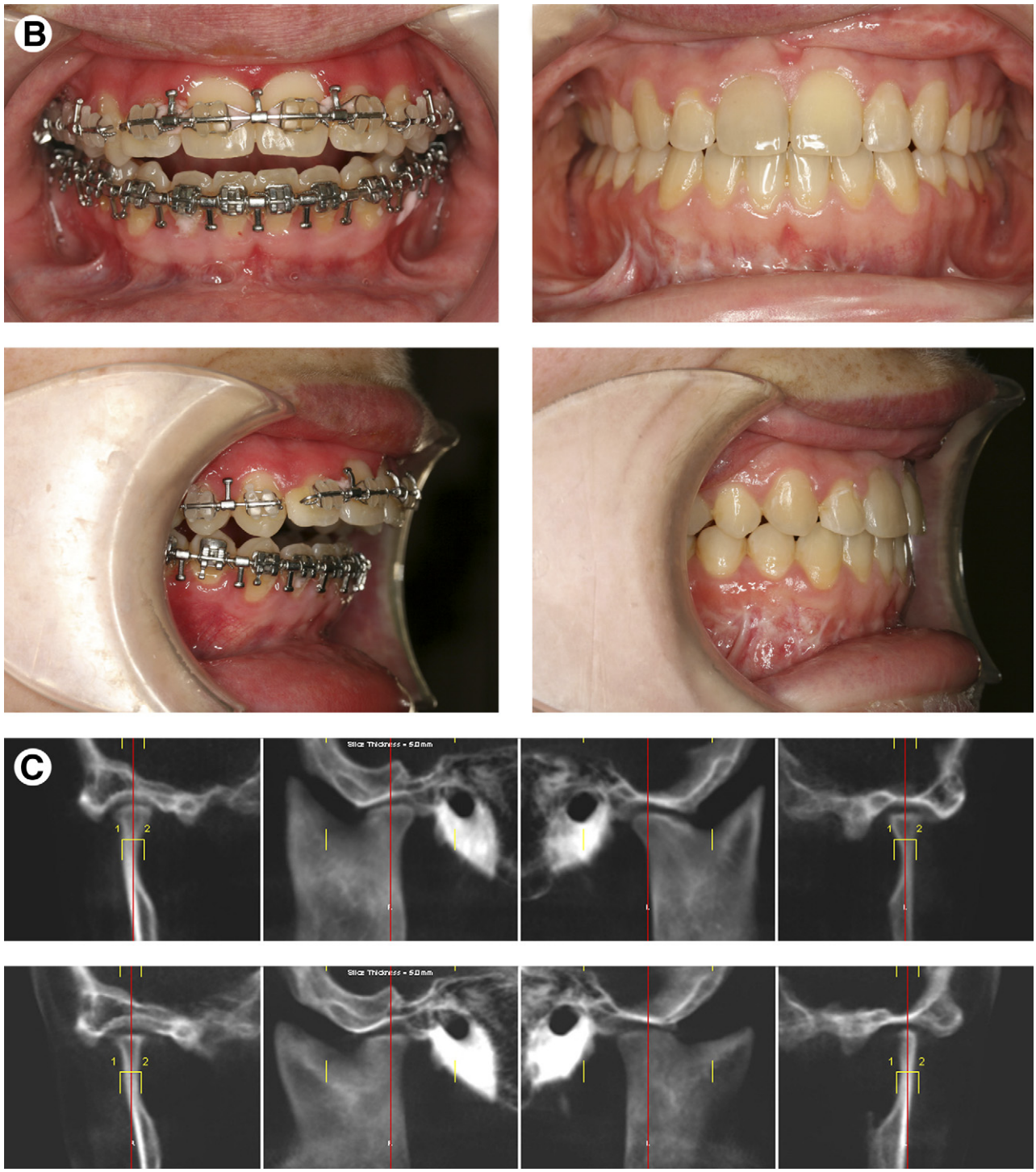

FIGURE 8. (Cont'd) (Figure 8 continued on next page.)

Gunson, Arnett, and Milam. Pharmacologic Control of Condylar Resorption. J Oral Maxillofac Surg 2012.

Obviously, further study is necessary with randomized placebo-controlled trials to evaluate the effect of statins on joint arthritides.

RANKL INHIBITOR

OPG has positive effects on bone preservation by blocking RANKL activation of osteoclast differentiation and osteoclast resorption activity. With this understanding, a human monoclonal antibody was developed that binds to RANKL in much the same way that OPG does. In phase 2 trials, denosumab was shown not only to prevent rheumatoid arthritis articular erosions on MRI but also to maintain bone mineral density in those who were treated compared

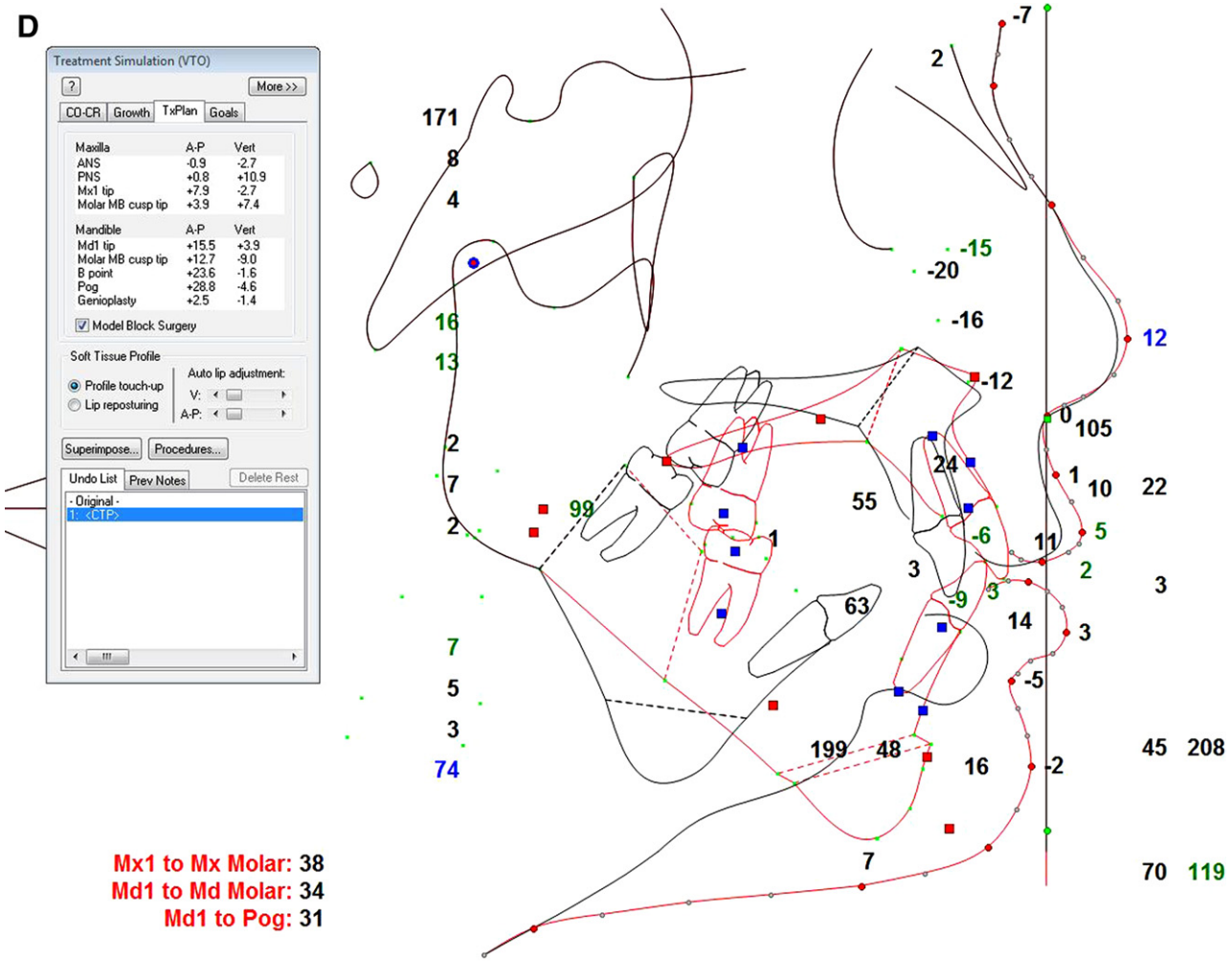

FIGURE 8. (Cont'd)

Gunson, Arnett, and Milam. Pharmacologic Control of Condylar Resorption. J Oral Maxillofac Surg 2012.

with control subjects.[166] There are, however, reports that denosumab risks causing oral osteonecrosis much like bisphosphonate therapy does.[167,168] Denosumab is administered intravenously. There are no TMJ studies available at present.

IL-6 RECEPTOR INHIBITOR

IL-6 promotes osteoclastogenesis and activation of osteoclast bone resorption. An IL-6 receptor monoclonal antibody was developed that prevents the binding of IL-6 to its receptor. There are 4 published clinical trials using tocilizumab, all of which show prevention of erosions with a low side effect profile.[169-172] Like denosumab, tocilizumab is administered intravenously, and no TMJ studies have been performed.

OTHER BIOLOGIC AGENTS

There are many other biologic agents in clinical trials that appear to have a significant positive effect on articular bone loss. Rituximab is a monoclonal antibody against the CD20 protein on the surface of B cells. Blockage of the CD20 protein has shown improvement in bony erosions in refractory rheumatoid arthritis patients.[173] Abatacept is a fusion protein directed at cytotoxic T-lymphocyte antigen 4 (CTLA-4) and as such inhibits costimulation of T cells. Abatacept reduces TNF-α release and has improved symptoms in psoriatic arthritis patients.[174]

In conclusion, when patients present with bone loss at the mandibular condyle, clinicians have long been resigned to 2 choices: watch and wait or perform surgical resection and reconstruction with their resulting disability and deformity. By understanding the known pathways that lead to condylar resorption and the individual patient's susceptibilities, targeted pharmacotherapy might be able to disturb these pathways and prevent further condylar resorption. If such stability is achievable, the surgeon can then, through orthognathic surgery, restore facial esthet-

ics, airway patency, and occlusal harmony without the risk of further degradation or invasive condylar surgery (Fig 8). Basic clinical investigations and randomized clinical trials are still required, but the present science is encouraging.

References

1. Arnett GW, Milam SB, Gottesman L: Progressive mandibular retrusion—Idiopathic condylar resorption. Part II. Am J Orthod Dentofacial Orthop 110:117, 1996
2. Arnett GW, Milam SB, Gottesman L: Progressive mandibular retrusion—Idiopathic condylar resorption. Part I. Am J Orthod Dentofacial Orthop 110:8, 1996
3. Arnett GW, Tamborello JA, Rathbone JA: Temporomandibular joint ramifications of orthognathic surgery, *in* Bell WH (ed): Modern Practice in Orthognathic and Reconstructive Surgery (ed 1). Philadelphia, PA, Saunders, 1992, pp 522-593
4. Arnett GW: A redefinition of bilateral sagittal osteotomy (BSO) advancement relapse. Am J Orthod Dentofacial Orthop 104: 506, 1993
5. Arnett GW, Tamborello JA: TMJ dysfunction from transorally placed lag screws: Fact or fiction? J Oral Maxillofac Surg 46:625, 1988
6. Arnett GW, Milam SB: The unfavorable long-term result in orthognathic surgery II: Injury to the temporomandibular joint and trigeminal nerve, *in* Kaban LB, Pogrel MA, Perrott DH (eds): Complications in Oral and Maxillofacial Surgery (ed 1). Philadelphia, PA, Saunders, 1997, pp 265-277
7. Arnett GW, Milam SB, Gottesman L, et al: Morphologic changes of the temporomandibular joint associated with orthognathic surgery, *in* Fonseca RJ (ed): Oral and Maxillofacial Surgery. Philadelphia, PA, Saunders, 2000, pp 245-249
8. Arnett GW, Tamborello JA: Progressive class II development—Female idiopathic condylar resorption, *in* West RA (ed): Oral and Maxillofacial Surgery Clinics of North America. Philadelphia, PA, Saunders, 1990, pp 699-716
9. Moore KE, Gooris PJ, Stoelinga PJ: The contributing role of condylar resorption to skeletal relapse following mandibular advancement surgery: Report of five cases. J Oral Maxillofac Surg 49:448, 1991
10. De Clercq CA, Neyt LF, Mommaerts MY, et al: Condylar resorption in orthognathic surgery: A retrospective study. Int J Adult Orthodon Orthognath Surg 9:233, 1994
11. Hoppenreijs TJ, Freihofer HP, Stoelinga PJ, et al: Condylar remodelling and resorption after Le Fort I and bimaxillary osteotomies in patients with anterior open bite. A clinical and radiological study. Int J Oral Maxillofac Surg 27:81, 1998
12. Wolford LM: Idiopathic condylar resorption of the temporomandibular joint in teenage girls (cheerleaders syndrome). Proc (Bayl Univ Med Cent) 14:246, 2001
13. Gunson MJ, Arnett GW, Formby B, et al: Oral contraceptive pill use and abnormal menstrual cycles in women with severe condylar resorption: A case for low serum 17beta-estradiol as a major factor in progressive condylar resorption. Am J Orthod Dentofacial Orthop 136:772, 2009
14. Cutbirth M, Van Sickels JE, Thrash WJ: Condylar resorption after bicortical screw fixation of mandibular advancement. J Oral Maxillofac Surg 56:178, 1998
15. Mercuri LG: Osteoarthritis, osteoarthrosis, and idiopathic condylar resorption. Oral Maxillofac Surg Clin North Am 20:169, 2008
16. Sano H, Arai K, Murai T, et al: Tight control is important in patients with rheumatoid arthritis treated with an anti-tumor necrosis factor biological agent: Prospective study of 91 cases who used a biological agent for more than 1 year. Mod Rheumatol 19:390, 2009
17. Milam SB, Schmitz JP: Molecular biology of temporomandibular joint disorders: Proposed mechanisms of disease. J Oral Maxillofac Surg 53:1448, 1995
18. Milam SB, Zardeneta G, Schmitz JP: Oxidative stress and degenerative temporomandibular joint disease: A proposed hypothesis. J Oral Maxillofac Surg 56:214, 1998
19. Zardeneta G, Milam SB, Schmitz JP: Iron-dependent generation of free radicals: Plausible mechanisms in the progressive deterioration of the temporomandibular joint. J Oral Maxillofac Surg 58:302, 2000
20. Symons MC: Formation of radicals by mechanical processes. Free Radic Res Commun 5:131, 1988
21. Chandra H, Symons MC: Sulphur radicals formed by cutting alpha-keratin. Nature 328:833, 1987
22. Cai HX, Luo JM, Long X, et al: Free-radical oxidation and superoxide dismutase activity in synovial fluid of patients with temporomandibular disorders. J Orofac Pain 20:53, 2006
23. Arinci A, Ademoglu E, Aslan A, et al: Molecular correlates of temporomandibular joint disease. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 99:666, 2005
24. Tomida M, Ishimaru JI, Murayama K, et al: Intra-articular oxidative state correlated with the pathogenesis of disorders of the temporomandibular joint. Br J Oral Maxillofac Surg 42:405, 2004
25. Takahashi T, Kondoh T, Ohtani M, et al: Association between arthroscopic diagnosis of temporomandibular joint osteoarthritis and synovial fluid nitric oxide levels. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 88:129, 1999
26. Suenaga S, Abeyama K, Hamasaki A, et al: Temporomandibular disorders: Relationship between joint pain and effusion and nitric oxide concentration in the joint fluid. Dentomaxillofac Radiol 30:214, 2001
27. Aghabeigi B, Cintra N, Meghji S, et al: Measurement of nitric oxide in temporomandibular joint saline aspirates. Int J Oral Maxillofac Surg 32:401, 2003
28. Lee MC, Kawai Y, Shoji H, et al: Evidence of reactive oxygen species generation in synovial fluid from patients with temporomandibular disease by electron spin resonance spectroscopy. Redox Rep 9:331, 2004
29. Sato J, Segami N, Nishimura M, et al: Expression of interleukin 8 in synovial tissues in patients with internal derangement of the temporomandibular joint and its relationship with clinical variables. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 103:467, 2007
30. Alstergren P, Kopp S: Insufficient endogenous control of tumor necrosis factor-alpha contributes to temporomandibular joint pain and tissue destruction in rheumatoid arthritis. J Rheumatol 33:1734, 2006
31. Hamada Y, Kondoh T, Holmlund AB, et al: Inflammatory cytokines correlated with clinical outcome of temporomandibular joint irrigation in patients with chronic closed lock. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 102:596, 2006
32. Matsumoto K, Honda K, Ohshima M, et al: Cytokine profile in synovial fluid from patients with internal derangement of the temporomandibular joint: A preliminary study. Dentomaxillofac Radiol 35:432, 2006
33. Wakita T, Mogi M, Kurita K, et al: Increase in RANKL: OPG ratio in synovia of patients with temporomandibular joint disorder. J Dent Res 85:627, 2006
34. Ogura N, Tobe M, Sakamaki H, et al: Tumor necrosis factor-alpha increases chemokine gene expression and production in synovial fibroblasts from human temporomandibular joint. J Oral Pathol Med 34:357, 2005
35. Nishimura M, Segami N, Kaneyama K, et al: Comparison of cytokine level in synovial fluid between successful and unsuccessful cases in arthrocentesis of the temporomandibular joint. J Oral Maxillofac Surg 62:284, 2004
36. Ogura N, Tobe M, Sakamaki H, et al: Interleukin-1beta increases RANTES gene expression and production in synovial fibroblasts from human temporomandibular joint. J Oral Pathol Med 33:629, 2004
37. Tominaga K, Habu M, Sukedai M, et al: IL-1 beta, IL-1 receptor antagonist and soluble type II IL-1 receptor in synovial fluid of patients with temporomandibular disorders. Arch Oral Biol 49:493, 2004

38. Alstergren P, Benavente C, Kopp S: Interleukin-1beta, interleukin-1 receptor antagonist, and interleukin-1 soluble receptor II in temporomandibular joint synovial fluid from patients with chronic polyarthritides. J Oral Maxillofac Surg 61:1171, 2003
39. Sato J, Segami N, Nishimura M, et al: Expression of interleukin 6 in synovial tissues in patients with internal derangement of the temporomandibular joint. Br J Oral Maxillofac Surg 41:95, 2003
40. Kaneyama K, Segami N, Nishimura M, et al: Importance of proinflammatory cytokines in synovial fluid from 121 joints with temporomandibular disorders. Br J Oral Maxillofac Surg 40:418, 2002
41. Ogura N, Tobe M, Sakamaki H, et al: Interleukin-1 beta induces interleukin-6 mRNA expression and protein production in synovial cells from human temporomandibular joint. J Oral Pathol Med 31:353, 2002
42. Suzuki T, Segami N, Nishimura M, et al: Co-expression of interleukin-1beta and tumor necrosis factor alpha in synovial tissues and synovial fluids of temporomandibular joint with internal derangement: Comparison with histological grading of synovial inflammation. J Oral Pathol Med 31:549, 2002
43. Tobe M, Ogura N, Abiko Y, et al: Interleukin-1beta stimulates interleukin-8 production and gene expression in synovial cells from human temporomandibular joint. J Oral Maxillofac Surg 60:741, 2002
44. Emshoff R, Puffer P, Strobl H, et al: Effect of temporomandibular joint arthrocentesis on synovial fluid mediator level of tumor necrosis factor-alpha: Implications for treatment outcome. Int J Oral Maxillofac Surg 29:176, 2000
45. Alstergren P, Kopp S, Theodorsson E: Synovial fluid sampling from the temporomandibular joint: Sample quality criteria and levels of interleukin-1 beta and serotonin. Acta Odontol Scand 57:16, 1999
46. Suzuki T, Bessho K, Segami N, et al: Bone morphogenetic protein-2 in temporomandibular joints with internal derangement. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 88:670, 1999
47. Alstergren P, Ernberg M, Kvarnström M, et al: Interleukin-1beta in synovial fluid from the arthritic temporomandibular joint and its relation to pain, mobility, and anterior open bite. J Oral Maxillofac Surg 56:1059, 1998
48. Fu K, Ma X, Zhang Z, et al: Tumor necrosis factor in synovial fluid of patients with temporomandibular disorders. J Oral Maxillofac Surg 53:424, 1995
49. Shafer DM, Assael L, White LB, et al: Tumor necrosis factor-alpha as a biochemical marker of pain and outcome in temporomandibular joints with internal derangements. J Oral Maxillofac Surg 52:786, 1994
50. Emshoff R, Puffer P, Rudisch A, et al: Temporomandibular joint pain: Relationship to internal derangement type, osteoarthrosis, and synovial fluid mediator level of tumor necrosis factor-alpha. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 90:442, 2000
51. Kaneyama K, Segami N, Sun W, et al: Levels of soluble cytokine factors in temporomandibular joint effusions seen on magnetic resonance images. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 99:411, 2005
52. Kubota E, Imamura H, Kubota T, et al: Interleukin 1 beta and stromelysin (MMP3) activity of synovial fluid as possible markers of osteoarthritis in the temporomandibular joint. J Oral Maxillofac Surg 55:20, 1997
53. Nishimura M, Segami N, Kaneyama K, et al: Proinflammatory cytokines and arthroscopic findings of patients with internal derangement and osteoarthritis of the temporomandibular joint. Br J Oral Maxillofac Surg 40:68, 2002
54. Nordahl S, Alstergren P, Eliasson S, et al: Interleukin-1beta in plasma and synovial fluid in relation to radiographic changes in arthritic temporomandibular joints. Eur J Oral Sci 106:559, 1998
55. Sandler NA, Buckley MJ, Cillo JE, et al: Correlation of inflammatory cytokines with arthroscopic findings in patients with temporomandibular joint internal derangements. J Oral Maxillofac Surg 56:534, 1998
56. Segami N, Miyamaru M, Nishimura M, et al: Does joint effusion on T2 magnetic resonance images reflect synovitis? Part 2. Comparison of concentration levels of proinflammatory cytokines and total protein in synovial fluid of the temporomandibular joint with internal derangements and osteoarthrosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 94:515, 2002
57. Voog U, Alstergren P, Eliasson S, et al: Inflammatory mediators and radiographic changes in temporomandibular joints of patients with rheumatoid arthritis. Acta Odontol Scand 61:57, 2003
58. Voog U, Alstergren P, Eliasson S, et al: Progression of radiographic changes in the temporomandibular joints of patients with rheumatoid arthritis in relation to inflammatory markers and mediators in the blood. Acta Odontol Scand 62:7, 2004
59. Muroi Y, Kakudo K, Nakata K: Effects of compressive loading on human synovium-derived cells. J Dent Res 86:786, 2007
60. Puzas JE, Landeau JM, Tallents R, et al: Degradative pathways in tissues of the temporomandibular joint. Use of in vitro and in vivo models to characterize matrix metalloproteinase and cytokine activity. Cells Tissues Organs 169:248, 2001
61. Miyamoto K, Ishimaru J, Kurita K, et al: Synovial matrix metalloproteinase-2 in different stages of sheep temporomandibular joint osteoarthrosis. J Oral Maxillofac Surg 60:66, 2002
62. Yamaguchi A, Tojyo I, Yoshida H, et al: Role of hypoxia and interleukin-1beta in gene expressions of matrix metalloproteinases in temporomandibular joint disc cells. Arch Oral Biol 50:81, 2005
63. Tiilikainen P, Pirttiniemi P, Kainulainen T, et al: MMP-3 and −8 expression is found in the condylar surface of temporomandibular joints with internal derangement. J Oral Pathol Med 34:39, 2005
64. Lai YC, Shaftel SS, Miller JN, et al: Intraarticular induction of interleukin-1beta expression in the adult mouse, with resultant temporomandibular joint pathologic changes, dysfunction, and pain. Arthritis Rheum 54:1184, 2006
65. Yoshida K, Takatsuka S, Hatada E, et al: Expression of matrix metalloproteinases and aggrecanase in the synovial fluids of patients with symptomatic temporomandibular disorders. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 102:22, 2006
66. Mizui T, Ishimaru J, Miyamoto K, et al: Matrix metalloproteinase-2 in synovial lavage fluid of patients with disorders of the temporomandibular joint. Br J Oral Maxillofac Surg 39:310, 2001
67. Srinivas R, Sorsa T, Tjäderhane L, et al: Matrix metalloproteinases in mild and severe temporomandibular joint internal derangement synovial fluid. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 91:517, 2001
68. Ijima Y, Kobayashi M, Kubota E: Role of interleukin-1 in induction of matrix metalloproteinases synthesized by rat temporomandibular joint chondrocytes and disc cells. Eur J Oral Sci 109:50, 2001
69. Tanaka A, Kumagai S, Kawashiri S, et al: Expression of matrix metalloproteinase-2 and −9 in synovial fluid of the temporomandibular joint accompanied by anterior disc displacement. J Oral Pathol Med 30:59, 2001
70. Tanaka A, Kawashiri S, Kumagai S, et al: Expression of matrix metalloproteinase-2 in osteoarthritic fibrocartilage from human mandibular condyle. J Oral Pathol Med 29:314, 2000
71. Kubota T, Kubota E, Matsumoto A, et al: Identification of matrix metalloproteinases (MMPs) in synovial fluid from patients with temporomandibular disorder. Eur J Oral Sci 106: 992, 1998
72. Zardeneta G, Milam SB, Lee T, et al: Detection and preliminary characterization of matrix metalloproteinase activity in temporomandibular joint lavage fluid. Int J Oral Maxillofac Surg 27:397, 1998
73. Kubota E, Kubota T, Matsumoto J, et al: Synovial fluid cytokines and proteinases as markers of temporomandibular joint disease. J Oral Maxillofac Surg 56:192, 1998
74. Kanyama M, Kuboki T, Kojima S, et al: Matrix metalloproteinases and tissue inhibitors of metalloproteinases in synovial

fluids of patients with temporomandibular joint osteoarthritis. J Orofac Pain 14:20, 2000
75. Marchetti C, Cornaglia I, Casasco A, et al: Immunolocalization of gelatinase-A (matrix metalloproteinase-2) in damaged human temporomandibular joint discs. Arch Oral Biol 44:297, 1999
76. Kapila S, Wang W, Uston K: Matrix metalloproteinase induction by relaxin causes cartilage matrix degradation in target synovial joints. Ann N Y Acad Sci 1160:322, 2009
77. Abramson SB, Yazici Y: Biologics in development for rheumatoid arthritis: Relevance to osteoarthritis. Adv Drug Deliv Rev 58:212, 2006
78. Milner JM, Rowan AD, Cawston TE, et al: Metalloproteinase and inhibitor expression profiling of resorbing cartilage reveals pro-collagenase activation as a critical step for collagenolysis. Arthritis Res Ther 8:R142, 2006
79. Shinoda C, Takaku S: Interleukin-1 beta, interleukin-6, and tissue inhibitor of metalloproteinase-1 in the synovial fluid of the temporomandibular joint with respect to cartilage destruction. Oral Dis 6:383, 2000
80. Alstergren P, Kopp S: Prostaglandin E2 in temporomandibular joint synovial fluid and its relation to pain and inflammatory disorders. J Oral Maxillofac Surg 58:180, 2000
81. Nishimura M, Segami N, Kaneyama K, et al: Relationships between pain-related mediators and both synovitis and joint pain in patients with internal derangements and osteoarthritis of the temporomandibular joint. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 94:328, 2002
82. Merkx MA, Van Damme PA: Condylar resorption after orthognathic surgery. Evaluation of treatment in 8 patients. J Craniomaxillofac Surg 22:53, 1994
83. Abubaker AO, Raslan WF, Sotereanos GC: Estrogen and progesterone receptors in temporomandibular joint discs of symptomatic and asymptomatic persons: A preliminary study. J Oral Maxillofac Surg 51:1096, 1993
84. Aufdemorte TB, Van Sickels JE, Dolwick MF, et al: Estrogen receptors in the temporomandibular joint of the baboon (Papio cynocephalus): An autoradiographic study. Oral Surg Oral Med Oral Pathol 61:307, 1986
85. Yamashiro T, Takano-Yamamoto T: Differential responses of mandibular condyle and femur to oestrogen deficiency in young rats. Arch Oral Biol 43:191, 1998
86. Hajati AK, Alstergren P, Näsström K, et al: Endogenous glutamate in association with inflammatory and hormonal factors modulates bone tissue resorption of the temporomandibular joint in patients with early rheumatoid arthritis. J Oral Maxillofac Surg 67:1895, 2009
87. Liang L, Yu JF, Wang Y, et al: Estrogen regulates expression of osteoprotegerin and RANKL in human periodontal ligament cells through estrogen receptor beta. J Periodontol 79:1745, 2008
88. Galal N, El BW, Deyama Y, et al: Effect of estrogen on bone resorption and inflammation in the temporomandibular joint cellular elements. Int J Mol Med 21:785, 2008
89. Mitani M, Miura Y, Saura R, et al: Estrogen specifically stimulates expression and production of osteoprotegerin from rheumatoid synovial fibroblasts. Int J Mol Med 15:827, 2005
90. Simopoulos AP: Omega-3 fatty acids in inflammation and autoimmune diseases. J Am Coll Nutr 21:495, 2002
91. Holick MF: The vitamin D epidemic and its health consequences. J Nutr 135:2739S, 2005
92. Heidari B, Hajian-Tilaki K, Heidari P: The status of serum vitamin D in patients with rheumatoid arthritis and undifferentiated inflammatory arthritis compared with controls. Rheumatol Int 2011 [Epub ahead of print]
93. Heidari B, Heidari P, Hajian-Tilaki K: Association between serum vitamin D deficiency and knee osteoarthritis. Int Orthop 2010 [Epub ahead of print]
94. Bergink AP, Uitterlinden AG, Van Leeuwen JP, et al: Vitamin D status, bone mineral density, and the development of radiographic osteoarthritis of the knee: The Rotterdam Study. J Clin Rheumatol 15:230, 2009
95. Lane NE, Gore LR, Cummings SR, et al: Serum vitamin D levels and incident changes of radiographic hip osteoarthritis: A longitudinal study. Study of Osteoporotic Fractures Research Group. Arthritis Rheum 42:854, 1999
96. Peterson CA, Heffernan ME: Serum tumor necrosis factor-alpha concentrations are negatively correlated with serum 25(OH)D concentrations in healthy women. J Inflamm (Lond) 5:10, 2008
97. Riancho JA, García-Ibarbia C, Gravani A, et al: Common variations in estrogen-related genes are associated with severe large-joint osteoarthritis: A multicenter genetic and functional study. Osteoarthritis Cartilage 18:927, 2010
98. Hernández JL, Garcés CM, Sumillera M, et al: Aromatase expression in osteoarthritic and osteoporotic bone. Arthritis Rheum 58:1696, 2008
99. Planello AC, Campos MI, Meloto CB, et al: Association of matrix metalloproteinase gene polymorphism with temporomandibular joint degeneration. Eur J Oral Sci 119:1, 2011
100. Güler N, Yatmaz PI, Ataoglu H, et al: Temporomandibular internal derangement: Correlation of MRI findings with clinical symptoms of pain and joint sounds in patients with bruxing behaviour. Dentomaxillofac Radiol 32:304, 2003
101. Yamada K, Hanada K, Fukui T, et al: Condylar bony change and self-reported parafunctional habits in prospective orthognathic surgery patients with temporomandibular disorders. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 92:265, 2001
102. Ellis E III, Carlson DS: The effects of mandibular immobilization on the masticatory system. A review. Clin Plast Surg 16:133, 1989
103. Ellis E III, Hinton RJ: Histologic examination of the temporomandibular joint after mandibular advancement with and without rigid fixation: An experimental investigation in adult Macaca mulatta. J Oral Maxillofac Surg 49:1316, 1991
104. Bouwman JP, Kerstens HC, Tuinzing DB: Condylar resorption in orthognathic surgery. The role of intermaxillary fixation. Oral Surg Oral Med Oral Pathol 78:138, 1994
105. Sindelar BJ, Edwards S, Herring SW: Morphologic changes in the TMJ following splint wear. Anat Rec 266:167, 2002
106. Paredes S, Girona J, Hurt-Camejo E, et al: Antioxidant vitamins and lipid peroxidation in patients with rheumatoid arthritis: Association with inflammatory markers. J Rheumatol 29:2271, 2002
107. Bae SC, Kim SJ, Sung MK: Inadequate antioxidant nutrient intake and altered plasma antioxidant status of rheumatoid arthritis patients. J Am Coll Nutr 22:311, 2003
108. Eldin AA, Hamdy MA, Shaheen AA, et al: Effect of vitamin C administration in modulating some biochemical changes in arthritic rats. Pharmacol Res 26:357, 1992
109. Tarp U, Stengaard-Pedersen K, Hansen JC, et al: Glutathione redox cycle enzymes and selenium in severe rheumatoid arthritis: Lack of antioxidative response to selenium supplementation in polymorphonuclear leucocytes. Ann Rheum Dis 51:1044, 1992
110. Mahmud Z, Ali SM: Role of vitamin A and E in spondylosis. Bangladesh Med Res Counc Bull 18:47, 1992
111. McAlindon TE, Jacques P, Zhang Y, et al: Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? Arthritis Rheum 39:648, 1996
112. Edmonds SE, Winyard PG, Guo R, et al: Putative analgesic activity of repeated oral doses of vitamin E in the treatment of rheumatoid arthritis. Results of a prospective placebo-controlled double blind trial. Ann Rheum Dis 56:649, 1997
113. Venkatraman JT, Chu WC: Effects of dietary omega-3 and omega-6 lipids and vitamin E on serum cytokines, lipid mediators and anti-DNA antibodies in a mouse model for rheumatoid arthritis. J Am Coll Nutr 18:602, 1999
114. Helgeland M, Svendsen E, Førre O, et al: Dietary intake and serum concentrations of antioxidants in children with juvenile arthritis. Clin Exp Rheumatol 18:637, 2000
115. Tiku ML, Shah R, Allison GT: Evidence linking chondrocyte lipid peroxidation to cartilage matrix protein degradation. Possible role in cartilage aging and the pathogenesis of osteoarthritis. J Biol Chem 275:20069, 2000

116. Helmy M, Shohayeb M, Helmy MH, et al: Antioxidants as adjuvant therapy in rheumatoid disease. A preliminary study. Arzneimittelforschung 51:293, 2001
117. Darlington LG, Stone TW: Antioxidants and fatty acids in the amelioration of rheumatoid arthritis and related disorders. Br J Nutr 85:251, 2001
118. Canter PH, Wider B, Ernst E: The antioxidant vitamins A, C, E and selenium in the treatment of arthritis: A systematic review of randomized clinical trials. Rheumatology (Oxford) 46: 1223, 2007
119. Wang Y, Hodge AM, Wluka AE, et al: Effect of antioxidants on knee cartilage and bone in healthy, middle-aged subjects: A cross-sectional study. Arthritis Res Ther 9:R66, 2007
120. Abate A, Yang G, Dennery PA, et al: Synergistic inhibition of cyclooxygenase-2 expression by vitamin E and aspirin. Free Radic Biol Med 29:1135, 2000
121. Ahn IE, Ju JH, Park SH, et al: Radiologic observation: Repair of focal bone erosions after humanized antitumor necrosis factor antibody adalimumab therapy in a patient with rheumatoid arthritis. Clin Rheumatol 29:211, 2010
122. Døhn UM, Skjødt H, Hetland ML, et al: No erosive progression revealed by MRI in rheumatoid arthritis patients treated with etanercept, even in patients with persistent MRI and clinical signs of joint inflammation. Clin Rheumatol 26:1857, 2007
123. Møller Døhn U, Boonen A, Hetland ML, et al: Erosive progression is minimal, but erosion healing rare, in patients with rheumatoid arthritis treated with adalimumab. A 1-year investigator-initiated follow-up study using high-resolution computed tomography as the primary outcome measure. Ann Rheum Dis 68:1585, 2009
124. Moen K, Kvalvik AG, Hellem S, et al: The long-term effect of anti TNF-alpha treatment on temporomandibular joints, oral mucosa, and salivary flow in patients with active rheumatoid arthritis: A pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 100:433, 2005
125. Alstergren P, Larsson PT, Kopp S: Successful treatment with multiple intra-articular injections of infliximab in a patient with psoriatic arthritis. Scand J Rheumatol 37:155, 2008
126. Weinblatt ME, Bathon JM, Kremer JM, et al: Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and long-standing rheumatoid arthritis. Arthritis Care Res (Hoboken) 2010 [Epub ahead of print]
127. Golub LM, Lee HM, Greenwald RA, et al: A matrix metalloproteinase inhibitor reduces bone-type collagen degradation fragments and specific collagenases in gingival crevicular fluid during adult periodontitis. Inflamm Res 46:310, 1997
128. Smith GN Jr, Mickler EA, Hasty KA, et al: Specificity of inhibition of matrix metalloproteinase activity by doxycycline: Relationship to structure of the enzyme. Arthritis Rheum 42:1140, 1999
129. Schlondorff D, Satriano J: Interactions with calmodulin: Potential mechanism for some inhibitory actions of tetracyclines and calcium channel blockers. Biochem Pharmacol 34:3391, 1985
130. Webster GF, Toso SM, Hegemann L: Inhibition of a model of in vitro granuloma formation by tetracyclines and ciprofloxacin. Involvement of protein kinase C. Arch Dermatol 130:748, 1994
131. Kirkwood K, Martin T, Andreadis ST, et al: Chemically modified tetracyclines selectively inhibit IL-6 expression in osteoblasts by decreasing mRNA stability. Biochem Pharmacol 66: 1809, 2003
132. Arner EC, Hughes CE, Decicco CP, et al: Cytokine-induced cartilage proteoglycan degradation is mediated by aggrecanase. Osteoarthritis Cartilage 6:214, 1998
133. Amin AR, Attur MG, Thakker GD, et al: A novel mechanism of action of tetracyclines: Effects on nitric oxide synthases. Proc Natl Acad Sci U S A 93:14014, 1996
134. Borderie D, Hernvann A, Hilliquin P, et al: Tetracyclines inhibit nitrosothiol production by cytokine-stimulated osteoarthritic synovial cells. Inflamm Res 50:409, 2001
135. Shlopov BV, Stuart JM, Gumanovskaya ML, et al: Regulation of cartilage collagenase by doxycycline. J Rheumatol 28:835, 2001
136. Holmes SG, Still K, Buttle DJ, et al: Chemically modified tetracyclines act through multiple mechanisms directly on osteoclast precursors. Bone 35:471, 2004
137. Bettany JT, Peet NM, Wolowacz RG, et al: Tetracyclines induce apoptosis in osteoclasts. Bone 27:75, 2000
138. Bettany JT, Wolowacz RG: Tetracycline derivatives induce apoptosis selectively in cultured monocytes and macrophages but not in mesenchymal cells. Adv Dent Res 12:136, 1998
139. Stone M, Fortin PR, Pacheco-Tena C, et al: Should tetracycline treatment be used more extensively for rheumatoid arthritis? Metaanalysis demonstrates clinical benefit with reduction in disease activity. J Rheumatol 30:2112, 2003
140. Sreekanth VR, Handa R, Wali JP, et al: Doxycycline in the treatment of rheumatoid arthritis—A pilot study. J Assoc Physicians India 48:804, 2000
141. Brandt KD, Mazzuca SA, Katz BP, et al: Effects of doxycycline on progression of osteoarthritis: Results of a randomized, placebo-controlled, double-blind trial. Arthritis Rheum 52: 2015, 2005
142. Kloppenburg M, Dijkmans BA, Verweij CL, et al: Inflammatory and immunological parameters of disease activity in rheumatoid arthritis patients treated with minocycline. Immunopharmacology 31:163, 1996
143. Lauhio A, Konttinen YT, Tschesche H, et al: Reduction of matrix metalloproteinase 8-neutrophil collagenase levels during long-term doxycycline treatment of reactive arthritis. Antimicrob Agents Chemother 38:400, 1994
144. Israel HA, Ramamurthy NS, Greenwald R, et al: The potential role of doxycycline in the treatment of osteoarthritis of the temporomandibular joint. Adv Dent Res 12:51, 1998
145. Sundrarjun T, Komindr S, Archararit N, et al: Effects of n-3 fatty acids on serum interleukin-6, tumour necrosis factor-alpha and soluble tumour necrosis factor receptor p55 in active rheumatoid arthritis. J Int Med Res 32:443, 2004
146. Wall R, Ross RP, Fitzgerald GF, et al: Fatty acids from fish: The anti-inflammatory potential of long-chain omega-3 fatty acids. Nutr Rev 68:280, 2010
147. Berbert AA, Kondo CR, Almendra CL, et al: Supplementation of fish oil and olive oil in patients with rheumatoid arthritis. Nutrition 21:131, 2005
148. Kremer JM, Lawrence DA, Petrillo GF, et al: Effects of high-dose fish oil on rheumatoid arthritis after stopping nonsteroidal antiinflammatory drugs. Clinical and immune correlates. Arthritis Rheum 38:1107, 1995
149. Goldberg RJ, Katz J: A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. Pain 129:210, 2007
150. Barracchini A, Franceschini N, Amicosante G, et al: Can nonsteroidal anti-inflammatory drugs act as metalloproteinase modulators? An in-vitro study of inhibition of collagenase activity. J Pharm Pharmacol 50:1417, 1998
151. Mouithys-Mickalad AM, Zheng SX, Deby-Dupont GP, et al: In vitro study of the antioxidant properties of non steroidal anti-inflammatory drugs by chemiluminescence and electron spin resonance (ESR). Free Radic Res 33:607, 2000
152. Ayral X, Mackillop N, Genant HK, et al: Arthroscopic evaluation of potential structure-modifying drug in osteoarthritis of the knee. A multicenter, randomized, double-blind comparison of tenidap sodium vs piroxicam. Osteoarthritis Cartilage 11:198, 2003
153. Ravaud P, Auleley GR, Ayral X, et al: Piroxicam therapy: A double blind, randomized, multicenter study comparing 2 versus 4 week treatment in patients with painful knee osteoarthritis with effusion. J Rheumatol 25:2425, 1998
154. Blanco FJ, Guitian R, Moreno J, et al: Effect of antiinflammatory drugs on COX-1 and COX-2 activity in human articular chondrocytes. J Rheumatol 26:1366, 1999
155. Dingle JT: The effects of NSAID on the matrix of human articular cartilages. Z Rheumatol 58:125, 1999
156. Novack V, Eisinger M, Frenkel A, et al: The effects of statin therapy on inflammatory cytokines in patients with bacterial infections: A randomized double-blind placebo controlled clinical trial. Intensive Care Med 35:1255, 2009

157. Naidu BV, Woolley SM, Farivar AS, et al: Simvastatin ameliorates injury in an experimental model of lung ischemia-reperfusion. J Thorac Cardiovasc Surg 126:482, 2003
158. Leung BP, Sattar N, Crilly A, et al: A novel anti-inflammatory role for simvastatin in inflammatory arthritis. J Immunol 170: 1524, 2003
159. McCarey DW, McInnes IB, Sattar N: The antiinflammatory effects of statins. N Engl J Med 345:1209, 2001
160. Campese VM, Hadaya B, Chiu J: HMG-CoA reductase inhibitors and the kidney. Curr Hypertens Rep 7:337, 2005
161. Thunyakitpisal PD, Chaisuparat R: Simvastatin, an HMG-CoA reductase inhibitor, reduced the expression of matrix metalloproteinase-9 (gelatinase B) in osteoblastic cells and HT1080 fibrosarcoma cells. J Pharmacol Sci 94:403, 2004
162. Lazzerini PE, Capecchi PL, Nerucci F, et al: Simvastatin reduces MMP-3 level in interleukin 1beta stimulated human chondrocyte culture. Ann Rheum Dis 63:867, 2004
163. Barsante MM, Roffê E, Yokoro CM, et al: Anti-inflammatory and analgesic effects of atorvastatin in a rat model of adjuvant-induced arthritis. Eur J Pharmacol 516:282, 2005
164. Abud-Mendoza C, de la Fuente H, Cuevas-Orta E, et al: Therapy with statins in patients with refractory rheumatic diseases: A preliminary study. Lupus 12:607, 2003
165. McCarey DW, McInnes IB, Madhok R, et al: Trial of atorvastatin in rheumatoid arthritis (TARA): Double-blind, randomised placebo-controlled trial. Lancet 363:2015, 2004
166. Deodhar A, Dore RK, Mandel D, et al: Denosumab-mediated increase in hand bone mineral density associated with decreased progression of bone erosion in rheumatoid arthritis patients. Arthritis Care Res (Hoboken) 62:569, 2010
167. Aghaloo TL, Felsenfeld AL, Tetradis S: Osteonecrosis of the jaw in a patient on Denosumab. J Oral Maxillofac Surg 68:959, 2010
168. Stopeck AT, Lipton A, Body JJ, et al: Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: A randomized, double-blind study. J Clin Oncol 28:5132, 2010
169. Smolen JS, Beaulieu A, Rubbert-Roth A, et al: Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): A double-blind, placebo-controlled, randomised trial. Lancet 371:987, 2008
170. Genovese MC, McKay JD, Nasonov EL, et al: Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: The tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum 58:2968, 2008
171. Emery P, Keystone E, Tony HP, et al: IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: Results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis 67:1516, 2008
172. Jones G, Sebba A, Gu J, et al: Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. Ann Rheum Dis 69:88, 2010
173. Tak PP, Rigby WF, Rubbert-Roth A, et al: Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: The IMAGE trial. Ann Rheum Dis 70:39, 2011
174. Mease P, Genovese MC, Gladstein G, et al: Abatacept in the treatment of patients with psoriatic arthritis: Results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. Arthritis Rheum 63:939, 2011