Condylar Resorption, Matrix Metalloproteinases, and Tetracyclines

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Summary
Mandibular condylar resorption occurs as a result of inflammation and hormone imbalance. The cause of the bone loss at the cellular level is secondary to the production of matrix metalloproteinases (MMPs). MMPs have been shown to be present in diseased temporomandibular joints (TMJs). There is evidence that tetracyclines help control bone erosions in arthritic joints by inactivating MMPs. This article reviews the pertinent literature in support of using tetracyclines to prevent mandibular condylar resorption.

Introduction
Orthodontists and maxillofacial surgeons are well acquainted with the effects of condylar resorption (Figure 1).

The clinical outcomes of condylar resorption have been described at length in the literature. The causes, however, have been elusive, hence the common name idiopathic condylar resorption. Over the last several years, the pathophysiology of articular bone erosion secondary to inflammation has been well studied. A number of cytokines and proteases are found in joints that show osseous erosions that are not present in healthy joints, namely TNF-α, IL-1β, IL-6, and RANKL and matrix metalloproteinases.

Matrix Metalloproteinases
MMPs are of interest because they are directly responsible for the enzymatic destruction of extracellular matrix in normal conditions (angiogenesis, morphogenesis, tissue repair) and in pathological conditions (arthritis, metastasis, cirrhosis, endometriosis). MMPs are endopeptidases that are made in the nucleus as inactive enzymes, or zymogens. The zymogens travel to the cell membrane, where they are incorporated. The zymogen is then cleaved into the extracellular matrix as the active enzyme, where it makes cuts into the protein chains (collagen types I through IV, gelatin, etc). These cuts cause the proteins to denature, which results in the destruction of the matrix. The action of the MMP requires the mineral zinc—which is an important part of the MMP’s protein structure; hence the name metalloproteinase (Figure 2).
In joints, MMPs are produced by monocytes, macrophages, polymorphonuclear neutrophils, synoviocytes, osteoblasts, and osteoclasts. MMPs are generally classified by the kind of matrix they degrade; thus collagenase, gelatinase and stromelysin (Figure 3).

The extracellular activity of MMPs is regulated in two ways, by transcription and by extracellular inhibition. The transcription of MMPs in the nucleus is controlled by multiple pathways. MMP transcription is activated by sheer stress to the cell, by free radicals, and by the cytokines TNF-α, IL-1β, IL-6 and RANKL (Figure 4a). Transcription is suppressed by the cytokine osteoprotegerin and by the hormones vitamin D and estradiol (Figure 4b). After transcription, the pro-MMP is then sent to the cell membrane, where it is incorporated. Activation of the MMP occurs when the active side of the MMP is cleaved from the cell and liberated into the extracellular matrix. Extracellular inhibition comes from proteins called tissue inhibitors of metalloproteinases (TIMPs). TIMPs bind to active matrix metalloproteinases and inhibit their activity (Figure 4c). The ratio of MMP:TIMP activity influences the amount of matrix degradation.7-10
This evidence supports the presence of 6 of the known 28 matrix metalloproteinases (MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, and MMP-13) in fluid or tissue samples obtained from diseased human TMJs. Some cases of degenerative joint disease also result from an imbalance between the activities of MMPs and TIMPs, favoring unregulated degradation of tissue by MMPs.

Tetracyclines

Because MMPs are found to be elevated in patients with TMJ arthritis and are so destructive to articular tissues, finding a way to reduce their activity or their production would be helpful in treating patients with arthritis and condylar resorption.

From 1972-1982, at the School of Dental Medicine in Stony Brook New York, Ramurmathy and Golub discovered that tetracyclines have anti-collagenolytic properties. In 1998, Golub and colleagues showed that tetracyclines inhibit bone resorption in two ways—by controlling the expression and activity of MMPs and by regulating osteoclasts and their activity.

Controlling MMPs With Tetracyclines

Tetracyclines inhibit MMPs by chelating zinc and by regulating MMP gene expression. As noted above, 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. In addition, tetracyclines bind to the MMP itself, which causes a conformational change in the enzyme, inactivating it (Figure 5). Tetracyclines have also been shown to decrease the transcription of MMPs by blocking both protein kinase C and calmodulin pathways.

MMPs and Arthritis

The hallmark sign of arthritis is articular bone loss. In the past, clinicians have differentiated between inflammatory arthritis and osteoarthritis (OA). Recently, however, the cellular processes that result in bone and cartilage loss in both forms of arthritis have been shown to be quite similar. While inflammatory arthritis is promoted by a systemic problem, the result is an inflammatory cytokine cascade, which ultimately results in osteoclastic activity and bone loss at the articular surface. OA is not a systemic problem but a local one, secondary to oxidation reactions, free radical production, or shear stress—all three of which result from overuse. Despite the localized nature of OA, the cascade of cellular events that cause articular surface loss is the same as the systemically induced cascade. An increase in TNF-α and IL-1β increases the number of osteoclasts and their activity. TNF-α, IL-1β, IL-6, and RANKL all cause increased expression of the MMP genes. The end result is destruction of cartilage, bone, and connective tissue in both arthritis models.

MMPs also respond to systemic hormones such as estrogen, vitamin D, and parathyroid hormones. We found an association between low estrogen levels and low vitamin D levels in patients with severe condylar resorption. All of these hormones and cytokines are intimately involved in osteoclast differentiation and activation. This makes sense: MMPs are osteoclast produced and are responsible for bone and cartilage destruction.

MMPs and the TMJ

There is substantial evidence indicating that MMPs play an important role in bone and cartilage degradation associated with degenerative temporomandibular joint (TMJ) arthritis.
Regulating Osteoclasts With Tetracyclines
Osteoclasts are responsible for the breakdown of bone and cartilage. Their activity is tightly controlled by cytokines such as IL-6, TNF-α, nitric oxide, and IL-1β. Tetracyclines have been shown to prevent the liberation of these cytokines, diminishing the activity of osteoclasts.42-46 Tetracyclines also prevent the differentiation of osteoclast precursor cells into osteoclasts.47 Finally, tetracyclines promote the programmed cell death (apoptosis) of osteoclasts.48, 49 All these actions result in a decrease of bone and cartilage loss secondary to osteoclast activity when tetracyclines are present.

Tetracyclines and Arthritis
In short, 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 encouraging.

In the animal model of arthritis, tetracyclines have been shown to inhibit MMPs and to prevent the progression of osseous disease.50-52 Yu et al52 induced knee arthritis in dogs by severing the anterior cruciate ligament. Half the dogs were pretreated with doxycycline. Doxycycline prevented the full-thickness cartilage ulcerations that were seen in the untreated group.

In human studies, tetracyclines have been successfully used to diminish bone erosions in patients with inflammatory arthritis. One meta-analysis of 10 clinical trials that used tetracycline for rheumatoid arthritis (RA) showed significant improvement in disease activity with no side effects.53 In a single-blinded controlled study, doxycycline was shown to be as effective as methotrexate in treating inflammatory arthritis.54

Israel et al reported that doxycycline administered at a dose of 50 mg twice daily for 3 months significantly suppressed MMP activity in three patients diagnosed with advanced osteoarthritis of the TMJ. Two of the three patients reported marked improvement in symptoms, including improved mandibular range of motion. One patient did not experience symptomatic relief despite a marked reduction in MMP activity.55 While symptomatic relief would be important, it must be noted that inhibition of MMPs has a direct effect on bony resorption, which is often unrelated to TMJ symptoms. Clinicians need to keep this in mind when reviewing the literature.

Dosing
At present, there are no definitive studies demonstrating the efficacy of tetracycline therapy for degenerative TMJ arthritides. However, based on the available information, tetracyclines may be considered for the treatment of rapidly progressive condylar resorption, and in patients with degenerative TMJ disease. They may also be used in patients at increased risk for resorption. This includes patients with bruxism, inflammatory arthritis, or a past history of resorption who are undergoing occlusal treatment. Of all the available tetracyclines, Golub et al found that doxycycline was the most effective at suppressing MMP activity.56 Appropriate studies to determine effective dose schedules have not been conducted to date. However, based on the limited clinical data, it is reasonable to consider doxycycline at a dose of 50 mg twice daily.

Side Effects
The adverse effects of tetracyclines are well known. They include allergic reactions; gastrointestinal symptoms (ulcers, nausea, vomiting, diarrhea, 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, potentiate lithium toxicity, increase digoxin availability and toxicity, and decrease prothrombin activity.57

If tetracycline therapy is initiated, the patient should be advised of the potential for reduced efficacy of oral contraception. In addition, the patient should be cautioned against sun exposure, and should be monitored for other side effects. If surgery is contemplated, the patient’s coagulation status should be evaluated.

There is some question as to whether bacterial resistance may develop with the chronic use of antibiotics. Studies show that long-term low-dose doxycycline (20 mg twice daily) does not lead to a significant increase in bacterial resistance or to a change in fecal or vaginal flora.58, 59

Other Medications to Control MMPs
Tetracyclines are not the only medications that can prevent MMP-induced bone erosions. There are promising studies that show the benefits of TNF-α inhibitors; osteoprotegerin analogues; HMG-CoA reductase inhibitors (eg, simvastatin); and hormone replacement therapies, including vitamin D and estradiol.60-61 These medications, along with doxycycline, show great promise in controlling articular bone loss in the face of inflammation.

Conclusion
When patients present with condylar resorption, clinicians have long been resigned to two choices: watch and wait or surgical resection with the resulting disability and deformity. Doxycycline is just one pharmacological intervention that...
shows promise in curbing the bone loss associated with arthritis and condylar resorption (Figures 6-a, b, c, d, e).

**Figure 6-a, b, c, d, e** This is a 31-year-old patient with condylar resorption secondary to rheumatoid arthritis. She was treated with orthognathic surgery to correct her malocclusion. The effects of MMPs were controlled pre- and postoperatively by prescribing the following medications: doxycycline, simvastatin, Enbrel, Feldene, vitamin D, and omega-3 fatty acids. She is 10 months postsurgery with minimal osseous change to her condyles and a stable class I occlusion with good overbite and overjet.
References


