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CONTENTS

THE EFFECT OF ARTIFICIAL INTELLIGENCE ON HEALTH TODAY.....7
Kubilay Ozgur OZTUTUNCU, Ahmet Necati SANLI, Samet YIGMAN

APPLICATIONS AND HURDLES OF GENOME EDITING IN CLINICS 15
Seher YAYLACI

AN OVERVIEW OF THE BIOGENESIS, FUNCTIONS AND POTENTIAL ROLES OF CIRCULAR RNAS.....29
Ilknur ÇINAR AYAN

POLYPHARMACY AND CARDIO-ONCOLOGY: TIME TO PONDER THE ROLE OF CYP450 MRNA.....39
Andleeb SHAHZADI

BIOCHEMICAL TUMOR MARKERS 59
Seyhan TURK

GUT MICROBIOTA AND SCHIZOPHRENIA: EFFECTS OF CLINICAL TREATMENTS AND PROBIOTICS ON GUT MICROBIOTA 71
Irem ALTUNTAŞ, Hatice TURAN PESTEL, Hamideh HAMMAMCHI

OSTEITIS IN CHRONIC RHINOSINUSITIS.....87
Atılay YAYLACI

DO STABILIZATION SPLINT AND BOTOX USED IN BRUXISM TREATMENT CONTRIBUTE TO THE CHANGE IN OCCLUSION 99
Kubra MUMCU, Zuhal GORUS

NUTRITIONAL PROBLEMS IN CHILDREN WITH CEREBRAL PALSY 111
Dilan DEMIRTAS KARAOBA

FOLLICULAR ENVIRONMENT AND OOCYTE MATURATION: ROLES OF VARIOUS FACTORS AND ENERGY METABOLISM 125
Selda KAHVECI

IMPORTANCE OF URINARY INCONTINENCE FOR WOMEN'S HEALTH 137
Semra YILMAZ

THE MOST COMMON CAUSES OF ACUTE ABDOMEN CASES IN INFANCY AND CHIDHOOD; INTUSSUSCEPTION 149
Mehmet UYSAL

OPTICIANRY AND NEXT-GENERATION OPTIC TECHNOLOGIES 161
Sezen TEKIN, Irmak KARADUMAN ER

VALIDATION AND OPTIMIZATION APPLICATIONS IN ELISA METHOD.....171
Faruk DISLI, Sedat YILDIZ

AN ALTERNATIVE APPROACH TO THE PSYCHO-SOCIAL PROBLEMS OF CANCER PATIENTS: MINDFULNESS-BASED PRACTICE.....179
Melike PEHLIVAN

COMPLIANCE OF NURSES WITH STEPS OF DONNING AND DOFFING PERSONAL PROTECTIVE EQUIPMENT DURING THE PANDEMIC; AN OBSERVATIONAL STUDY 197
Selma ATAY , Fatma YILMAZ KURT, Fatma ALDEMIR

OSTEITIS IN CHRONIC RHINOSINUSITIS

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INTRODUCTION

Chronic rhinosinusitis (CRS) is a multifactorial inflammatory disease of the nose and paranasal sinuses. CRS affects approximately 12% of the general population and has a significant impact on quality of life (Fokkens, 2012). Osteitis, defined by increased bone density and irregular thickening of sinus walls, is a common condition in patients with CRS (Georgalas, 2013; Snidvongs et al., 2019). Osteitis has been found to be strongly related to severe sinonasal inflammation and is now considered a contributing factor in recalcitrant and recurrent CRS. It has also been shown that the number and extent of previous surgeries are linked to osteitis, which predicts poorer postoperative outcomes (Telmesani & Al-Shawarby, 2010; Bhandarkar et al., 2013; Leung et al., 2016; Snidvongs et al., 2019). However, it remains uncertain whether surgical intervention and the outcome of osteitis are causally related or simply associated with the common endpoint of persistent disease. Mucosal inflammation is assumed to play a role in initiating osteitis (Georgalas, 2013), but the specific molecular mechanisms underlying osteitis in CRS are still unclear. As of yet, the effectiveness of antibiotics or radical surgery in treating osteitis remains unclear.

Definition of Osteitis

The term "osteitis" describes an inflammatory condition that affects the bone, specifically the outer layers of bone tissue. Because the flat bones of the paranasal sinuses do not have a marrow space, this terminology is considered more appropriate than "osteomyelitis" in the context of the paranasal region (Kocak et al., 2002). Although the terms "hyperostosis" and "neo-osteogenesis" are frequently used, the presence of these changes may not be the primary or dominant feature of CRS bone inflammation (Georgalas, 2013). In this chapter, "osteitis" refers to inflammation of the bones surrounding the paranasal sinuses that causes radiologically visible changes in the sinonasal bony framework.

Normal Bone Metabolism and Structure

Bone tissue is composed of both organic and inorganic components. The primary organic matrix of bone is type I collagen, which provides tensile strength, and non-collagenous proteins such as osteocalcin and osteopontin that aid in mineralization and cell signaling. The inorganic component of bone is hydroxyapatite, a crystalline calcium phosphate mineral that provides compressive strength and rigidity to the tissue (Bonewald et al., 2011). Bone

tissue comprises three main types of cells: osteoblasts, osteoclasts, and osteocytes. Osteoblasts are specialized types of mesenchymal cells that synthesize organic bone matrix. Additionally, osteoblasts regulate the deposition of hydroxyapatite crystals within the matrix, playing a critical role in mineralization. Osteoclasts, on the other hand, actively participate in bone resorption, allowing for bone tissue remodeling. Osteoclasts secrete acids and enzymes that dissolve the mineral component of bone and also proteases that degrade the organic matrix (Karsenty et al., 2012). Osteocytes are mature osteoblasts that are embedded in the calcified bone matrix. Osteocytes play a pivotal role in maintaining bone health, as they can sense local biomechanical and systemic stimuli and modulate signals arising from mechanical stress or inflammation. Osteocytes can thereby regulate the formation or resorption of bone tissue. Various factors such as hormones, steroids, growth factors, leukotrienes, prostaglandins, and inflammatory cytokines are recognized to affect bone function (Schaffler et al., 2014).

Bone tissue can be classified into two main structural types: woven bone and lamellar bone. Woven bone is an immature type of bone tissue that is rapidly formed during growth or healing. It is characterized by a disorganized arrangement of collagen fibers and randomly arranged mineral crystals. On the other hand, lamellar bone is a more mature type of bone tissue that is formed by the remodeling of woven bone. It is distinguished by an organized arrangement of collagen fibers in parallel sheets, or lamellae, which are interspersed with osteocytes (Kirsch et al., 2006). Despite its seemingly rigid structure, bone is in a state of continuous change referred to as "bone remodeling." Bone remodeling begins during embryonic development and persists throughout an individual's life. (Martin et al., 1998) The majority of the flat bones in the skull are made up of two layers of compact bone known as plates and a layer of spongy bone in between. The flat bones that line the paranasal sinuses, on the other hand, lack this spongy bone layer (Erlebacher et al., 1995).

Histopathology of Osteitis

Based on histological data, pathological alterations observed in rabbits with induced unilateral rhinosinusitis include neo-osteogenesis, periosteal reaction, osteoclastic resorption, fibrosis, and abnormalities in Haversian canals (Norlander et al., 1994; Bolger et al., 1997; Perloff et al., 2000; Khalid et al., 2002; Antunes et al., 2007; Campos et al., 2015). Surprisingly, osteitic alterations detected in specimens from sides with induced rhinosinusitis were

also detected on the contralateral side in nearly half of the cases. This has fostered the hypothesis that disease can spread to distant areas that were not initially involved in the primary infection. The potential causes of the spread of inflammation include the entry of infectious pathogens and inflammation into the underlying bone, the initiation of the remodeling process, and spread through the vascular network or Haversian canals (Khalid et al., 2002). Animal data has several limitations when it comes to studying osteitis in CRS. The induction of unilateral sinusitis with a few bacterial pathogens in animal experiments is not a reliable recreation of the human model of CRS. Because these experiments only represent a single aspect of the disease, which encompasses genetic, environmental, and host factors. Furthermore, methodological issues involving surgical intervention during sampling and inoculation in these studies may lead to direct infection and could be a confounding factor in the bone changes observed. Finally, the short duration of follow-up in animal studies is a major drawback, as osteitis is a temporal sequela of the chronic disease.

Human studies on patients with CRS have revealed similar histological findings to animal studies. In these patients, the most significant bony alterations observed were neo-osteogenesis with woven bone formation, osteoblast proliferation, periosteal reaction, osteoclast proliferation and bone resorption, cellular infiltrates, and fibrosis (Biedlingmaier et al., 1996; Kennedy et al., 1998; Giacchi et al., 2001; Lee et al., 2006; Cho et al., 2006; Snidvongs et al.; 2014).

Diagnosis of Osteitis

Histopathological examination of biopsy or surgical specimens is the most accurate method for diagnosing osteitis. In cases for whom surgery is not indicated, computed tomography (CT) offers a minimally invasive option and is currently the preferred modality to assess the presence, severity, and extent of osteitis (Wang et al., 2021). It has been demonstrated that bone changes detected on CT can correlate with histopathologic findings in the bone (Giacchi et al., 2021). Osteitis can be identified on CT scans by the presence of rarefaction and/or irregular thickening of the bone surrounding the sinus walls, as well as the loss of normal structures or landmarks (see Figure 1). These changes are often caused by focal sclerosis, demineralization, cortical destruction, or trabecular loss (Biedlingmaier et al., 1996).

Different staging systems for osteitis have been proposed by various authors. Yet, there is no standardized CT staging methodology for osteitis,

although bone thickness appears to be the most commonly used technique. The Kennedy Osteitis Score graded osteitis as mild (less than 3 mm), moderate (4-5 mm), or severe (greater than 5 mm). (Lee et al., 2006). The Global Osteitis Scoring Scale expanded on previous classification by assessing the pattern of bony involvement in the sinus wall and also including frontal sinus assessment (Georgalas et al., 2010). A different method of CT analysis based on Hounsfield units was also proposed (Cho et al., 2006).

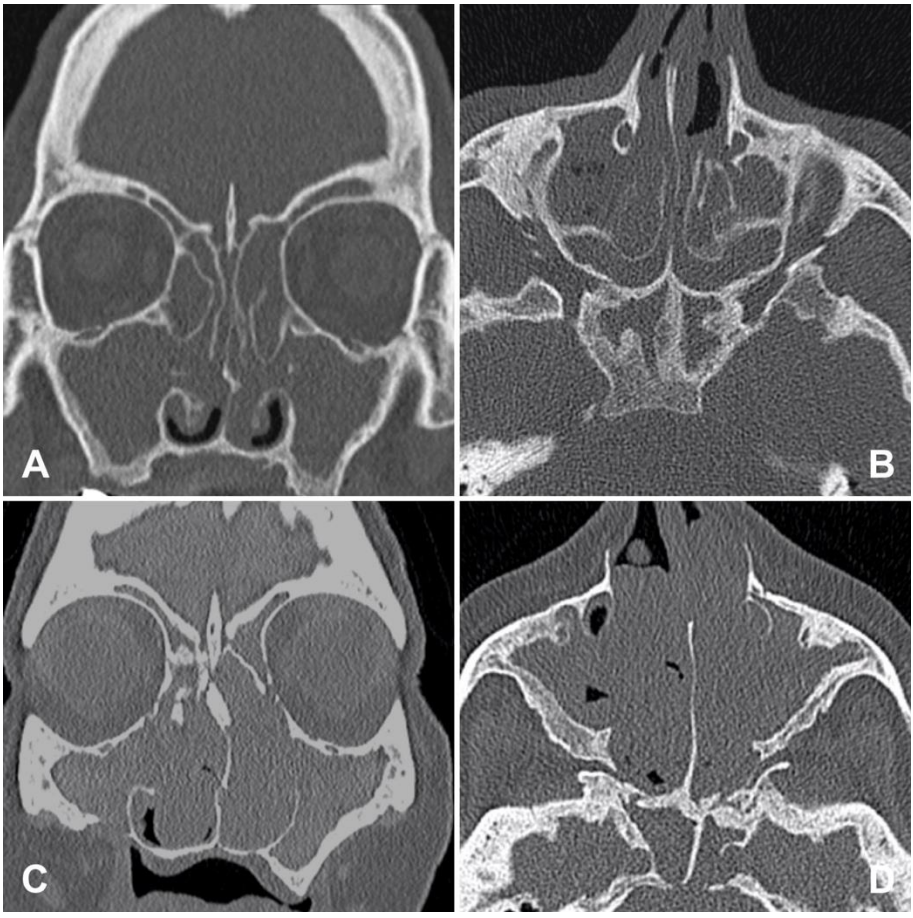


Figure 1. A-B. Bone thickening in the walls of the maxillary and sphenoid sinuses of a patient with chronic rhinosinusitis. **C-D.** Diffuse osteitis in patients who underwent multiple surgeries for chronic rhinosinusitis with nasal polyps

The Role of Osteitis in Chronic Rhinosinusitis

In patients with CRS, the combination of medical treatment and surgery has been shown to improve quality of life and disease severity measures (Smith et al., 2010). However, despite its effectiveness, there are still a

considerable number of patients who do not improve or experience recurrent exacerbations of the disease even after undergoing such therapy. As potential reasons for treatment failure, ongoing research has predominantly focused on mucosal inflammation and biofilms. However, the role of osteitis has received comparatively little attention.

In CRS, the diseased mucosa can trigger a periosteal reaction and subsequent osteitic changes, indicating that inflammation of the paranasal sinuses involves bone structures as well as mucosa. (Mehta et al., 2008; Snidvongs et al., 2012; Wang et al., 2021). Based on the currently available evidence, patients with CRS frequently exhibit several pathological features, including bone formation, varying degrees of increased osteoblastic-osteoclastic activity, periosteal thickening, fibrosis, and inflammatory cell infiltration, as seen by the loss of organized lamellar bone and the emergence of immature woven bone (Kennedy et al., 1998; Giacchi et al., 2001; Lee et al., 2006; Cho et al., 2006). These bony changes are reported in 5–36% of cases of primary CRS and in 41–88% of revision cases (Lee et al., 2006; Telmesani et al., 2010; Snidvongs et al., 2012; Bhandarkar et al., 2013). These wide ranges in observed incidence rates can be related to discrepancies in osteitis definition methodology (whether histological or radiographic) and the use of different grading systems. However, the data clearly shows that osteitis is more prevalent in cases of revision CRS.

Several authors have identified osteitis as a prevailing factor in recalcitrant CRS and a potential cause of the increased frequency of surgeries. (Lee et al., 2006; Snidvongs et al., 2012; Wang et al., 2021). It is still unclear whether surgical intervention and osteitis outcome have a cause-and-effect relationship or merely share a common endpoint of recalcitrant disease requiring long-term treatment (Snidvongs et al., 2019). Proposed pathoetiologic theories of osteitis in recurrent cases include invasion of bacteria and their toxins in exposed bone during surgery, persistent inflammation in bone tissue, infection or reparative changes in bare bone after mucosal stripping during surgery, or inflammation of bone fragments inadvertently left behind during surgery (Lee et al., 2006; Videler et al., 2007; Snidvongs et al., 2012). However, these explanations do not account for the presence of osteitis in patients who have not undergone surgery and raise the question of different or additional mechanisms that may cause bone changes.

Eosinophilic chronic rhinosinusitis (ECRS) is a subtype of CRS, characterized by refractory nasal polyps with eosinophilic inflammation.

(Fokkens et al., 2020) Recent studies demonstrated higher osteitis scores in patients with CRS with nasal polyposis, as well as eosinophilic inflammation (Mehta et al., 2008; Georgalas et al., 2010; Bhandarkar et al., 2011; Snidvongs et al., 2012; Emre et al., 2015). Further, an association between the severity of osteitis and tissue, sputum, and serum eosinophilia has been reported in patients undergoing primary or revision surgeries. (Bhandarkar et al., 2011; Snidvongs et al., 2012; Tsuda et al., 2022). These findings indicate that osteitis may be the endpoint of a chronic eosinophilic inflammation in ECRS. This data may provide a convincing explanation for the presence of osteitis in patients with CRS who have not undergone surgery.

Several studies have suggested an association between bacteria or biofilm formation and osteitis (Dong et al., 2014; Huang et al., 2015). Furthermore, the presence of biofilm in the CRS has been found to be correlated with a host inflammatory response that involves the recruitment of plasma cells and eosinophils (Arjomandi et al., 2013). Further research is needed to address this unexplained pathophysiology.

The effect of osteitis on the severity of CRS has also been investigated. A number of studies have demonstrated an association between osteitis and the radiological severity of CRS, as measured by the Lund-Mackay grading system (Kacker et al., 2002; Lee et al., 2006; Kim et al., 2006; Georgalas et al., 2010; Bhandarkar et al., 2011; Huang et al., 2015; Tsuda et al., 2022). However, there is little or no association between clinical severity and osteitis, with no evidence of lower baseline quality of life scores in patients with osteitis compared to patients without osteitis (Georgalas et al., 2010; Bhandarkar et al., 2011).

Specific Treatments for CRS with Osteitis

The presence of concurrent osteitis in patients with CRS has prompted the development of novel therapeutic strategies. However, there is an ongoing debate surrounding the optimal management of osteitic bone in these patients.

Surgical therapy

The most commonly used treatment for osteitis is surgery, based on the concept that removing the bone eliminates the source of ongoing inflammation. Professional opinion recommends the removal of osteitic bone wherever possible (Chiu, 2005; Lee et al., 2006). However, the extent to which osteitic bone removal from different sinuses should be addressed in endoscopic sinus surgery is unclear, as is the extent to which more aggressive

removal might correlate with a clinically relevant improvement in symptoms or inflammation in patients with osteitis. In fact, almost complete removal of osteitic bone is only feasible for the ethmoid sinuses, as the non-ostial regions of the maxillary, frontal, and sphenoid walls are not easily accessible during endoscopic sinus surgery.

Radical surgeries, including the Denker procedure and the Draf 3 frontal sinusotomy, are appealing options based on the idea that removing bone as the source of ongoing inflammation (Chiu, 2005; Lee et al., 2006; Georgalas et al., 2010). Although these procedures have been advocated for patients with recalcitrant CRS, their role in patients with osteitis is not well defined. When contemplating radical surgery as an option for recalcitrant CRS, it is essential to recognize that the surgery itself can provoke an osteitic bone reaction (Moreno et al., 2008). Moreover, there is evidence showing a direct correlation between the number of surgeries and osteitis (Georgalas et al., 2010). A study has revealed worse outcomes for patients with osteitis who undergo radical surgery (Bhandarkar et al., 2011). In contrast, Wang et al. discovered that radical endoscopic sinus surgery, which included extended bilateral sinus opening and complete removal of the osteitic bony tissue (the ethmoid sinus, middle turbinate, and superior turbinate), was more effective in reducing the inflammatory load (eosinophils in the mucosa, osteitic bony lamella, superantigen, bacterial load, and biofilm) of the sinuses with osteitis (Wang et al., 2021).

Medical therapy

Regrettably, there is even less evidence available regarding the use of long-term antibiotics for osteitis. Some authors have suggested intravenous administration of long-term antibiotics at levels sufficient to reach the bone in order to eliminate bone involvement, similar to osteomyelitis treatment (Tovi et al., 1992; Schaberg et al., 2010). Nonetheless, both studies have methodological flaws, small sample sizes, and no control group. Moreover, there is a lack of conceptual support for such an intervention, as no group has yet identified bacteria within bone specimens that are associated with osteitis. In the absence of evidence indicating an ongoing bacterial infection in the sinus bone, there is limited justification for the use of prolonged antibiotic therapy. A further challenge associated with systemic medical treatment is the relatively avascular and ischemic nature of the infected area, along with the fibrosis of the haversian canals, which can impede the penetration of medications into the osteitic bone (Videler et al., 2007). Macrolide antibiotics,

which have both anti-inflammatory and antibacterial properties, were thought to be a promising remedy for osteitis (Park et al., 2007), until recent evidence proved otherwise. In conclusion, although nasal antimicrobial therapy holds promise, its role has not been firmly established.

Alternative medical approaches such as long-term systemic steroid treatment could be considered if the role of the inflammatory pathway is determined to be more significant than that of the infectious pathway in the bone involvement in CRS (Videler et al., 2007). Snidvongs et al. (2012) recommended an intensive post-operative corticosteroid therapy regimen for individuals with elevated eosinophilia levels to address systemic mediators. Additional research in this area has investigated the effectiveness of topical steroids in animal models (Antunes et al., 2007) and the development of innovative drug delivery systems to address the issue of limited bone penetration (Beule et al., 2008).

CONCLUSION

Osteitis is linked to severe mucosal inflammation and recurrent sinus surgery; however, its role in the pathophysiology of CRS is uncertain. Therefore, a thorough understanding of the immune system's involvement, as well as the molecular triggers for bony remodeling in CRS, would greatly aid in the development of targeted therapies. Further studies are necessary to investigate the outcomes of patients treated exclusively for the removal or modification of osteitis in CRS.

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