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Incidental sinonasal findings in cone-beam computed tomography imaging of the temporomandibular joints: prevalence and clinical significance

by

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I would like to dedicate this work to my dear father Ailson Guedes, to whom I looked up all my life, as an example of intelligence, determination and amazing strength. Your unconditional support during this past 3 and years meant the world to me. *Obrigada pai!*

ABSTRACT

The objective of this study was to evaluate the prevalence and potential clinical significance of incidental sinonasal findings in cone beam computed tomography (CBCT) scans requested for TMJ diagnostic purposes. This project comprised the retrospective analysis of CBCT images from 500 consecutive scans taken with the original purpose of TMD diagnosis. The assessment of potential clinical significance of incidental sinonasal findings was accomplished by the design of a set of guidelines, which may ultimately lead to a better evaluation of incidental sinonasal CT abnormalities by non-sinus specialists. Our results detected incidental sinonasal findings in 84% of the CBCT scans studied, a considerably higher prevalence than previous estimations using random populations studies. Potentially clinically important variables were detected in approximately one fourth of the scans studied, which potentially requires an otolaryngology evaluation.

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LIST OF ABBREVIATIONS

ABRS = Acute bacterial rhinosinusitis

AFRS = Allergic fungal rhinosinusitis

ARS = Acute rhinosinusitis

CB = Concha bullosa

CBCT = Cone-beam computed tomography

CT = Computed tomography

CNS = Coagulase-negative staphylococci

CRS = Chronic rhinosinusitis

CRSsNP = CRS without nasal polyps

CRSwNP = CRS with nasal polyps

DD = Disc displacement

DDsR = Disc displacement without reduction

DDwR = Disc displacement with reduction

EDI = Edmonton Diagnostic Imaging

EW = Erin Wright (Otolaryngology specialist)

FESS = Functional endoscopic sinus surgery

FDA = United States food and drug administration

IG = Ines Guedes (primary examiner)

MRI = Magnetic resonance imaging

NP = Nasal polyp

OA = Osteoarthritis

OFP = Orofacial pain

OMC = Ostiomeatal complex

P_{absent} = Negative agreement

$P_{overall}$ = Overall agreement

$P_{present}$ = Positive agreement

RC = Retention cysts

RS = Rhinosinusitis

RV = Rae Varughese (dental research assistant)

SAEs = *Staphylococcus aureus* enterotoxins

SPSS = Statistical package for social sciences

TFR = Task Force for Rhinosinusitis

TMJ = Temporomandibular joint

TMD = Temporomandibular disorders

VRS = Viral rhinosinusitis

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

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1.1 INTRODUCTION

Orofacial pain is prevalent within the general population ranging around 17-26%, of which 7-11% are chronic. Diagnosis of orofacial pain is a particularly challenging task as a result of the numerous anatomical structures involved and major psychological importance of this region. Diagnosis and treatment of those may involve a significant interest overlap from many health specialties, including dentistry, otolaryngology, neurology, neurosurgery, psychiatry and psychology [1].

TMD/Orofacial pain comprises issues related to musculoskeletal problems, temporomandibular disorders, headaches and neuropathic pain issues. However; the source of facial pain may also be related with other structures of the craniofacial region, including structures of the sinonasal complex [1].

Diagnosis of orofacial pain involves important steps, including history, physical examination and occasionally imaging studies [2]. Among the most often used radiographic modalities are plain radiographic films, computed tomography and magnetic resonance imaging [3].

Three-dimensional computed tomography has been widely used in the medical field as an essential diagnostic adjunct. However; the application of conventional computed tomography (CT) has a disadvantage, mainly due to high cost of the equipment, large space required for its operation and high dose of radiation exposure. Cone beam computed tomography (CBCT), a technology introduced over the last decade, has dealt with some of the limitations of conventional CT scanning devices. This last generation of CT scanning machines use a source of x-rays that rotates about the patient with no translation components or moving parts to create high quality imaging [4, 5]. CBCT technology has a significantly lower radiation exposure, costs less [6] and produces volume imaging easily and quickly compared to conventional medical CT [7]. In addition, reconstructed images from CBCT are of high diagnostic quality [8-11]. CBCT use has mainly been for orofacial structures, particularly the TMJ, however; the scope of visualization also acquires other head and neck structures including the sinonasal complex [12].

To date there are no studies on the prevalence of sinonasal incidental findings on a TMD/Orofacial pain population. It has also not been determined what may be the clinical significance of sinonasal findings for TMD/orofacial pain patients.

1.2 PROBLEM STATEMENT

Orofacial pain is an unpleasant experience related to the motor and sensory transmission of the trigeminal nerve, with innervation to the hard and soft tissues

of the head, face and neck. When those tissues are damaged - including skin, blood vessels, teeth, glands and muscles – impulses are sent through the trigeminal nerve and are interpreted as pain by brain circuits that are primarily responsible for processing complex behavior [13].

The multifaceted pain pathways related to the trigeminal nerve system explains why the diagnosis and treatment of pain symptoms may require an involvement of different areas of medicine. Pain syndromes affecting the head may be confusing to health professionals and consultation with other specialty areas are often required to avoid unnecessary treatment [13-15].

Orofacial pain includes vascular and non-vascular intracranial disorders, primary headache disorders, neuropathic pain, intraoral pain disorders, temporomandibular disorders, cervicogenic mechanisms of orofacial pain and headaches, extracranial and systemic causes of head and facial pain [13]. Extracranial sources of orofacial pain may include cranial bones, eyes, ears, sinonasal complex, throat, lymphatic system, blood vessels and salivary glands, and require consideration in the diagnostic process [13].

Inflammatory disease affecting the sinonasal complex is not uncommon, it is estimated that it affects more than 50 million people in the United States per year. The diagnosis of inflammatory sinus disease can be difficult, since it involves more than use of radiographic modalities. It requires especially a comprehensive

clinical evaluation, including careful search for etiologic factors and underlying conditions [16].

In the past, inflammatory sinus disease was diagnosed based primarily on radiographic findings, however; currently the role of imaging modalities in the diagnosis of rhinosinusitis is restricted to its correlation with clinical signs and symptoms. For that reason, incidental sinonasal findings in images taken for other purposes is challenging, since they cannot be interpreted in the context of clinical variables [16, 17].

It is estimated that approximately one third of asymptomatic adult patients show incidental mucosal changes on computed tomography [17]. Incidental sinonasal findings are commonly seen in CBCT scans taken for TMD purposes due to the reconstruction field used in those cases. Until the beginning of the development of this research there were no studies that assessed the prevalence of incidental sinonasal findings on a TMD/Orofacial pain population. Determining this prevalence on that specific population is especially valuable due to the fact that pathologies related to sinonasal structures may cause facial pain. Therefore, this assessment may be of clinical value to determine a definitive diagnosis and appropriated treatment planning for TMD/Orofacial pain patients.

1.3 RESEARCH QUESTIONS

1. What is the prevalence of incidental sinonasal findings in CBCT scans of a TMD/Orofacial pain patient population?
2. What is the prevalence of potentially clinically important sinonasal findings in CBCT scans of a TMD/ Orofacial pain patient population?

1.4 HIPOTHESES

1.4.1 Null Hypotheses

1. The prevalence of incidental sinonasal findings in CBCT scans of a TMD/Orofacial pain patient population is no different or smaller than prevalence estimations made by previous similar studies for an asymptomatic population.

2. The prevalence of potentially clinically important sinonasal findings in CBCT scans of a TMD/Orofacial pain patient population is no different or smaller than prevalence estimations made by previous similar studies for an asymptomatic population.

1.4.2- Alternate hypotheses

1. The prevalence of incidental sinonasal findings in CBCT scans of a TMD/Orofacial pain patient population is higher than prevalence estimations made by previous similar studies for an asymptomatic population.

2. The prevalence of potentially clinically important sinonasal findings in CBCT scans of a TMD/Orofacial pain patient population is higher than prevalence estimations made by previous similar studies for an asymptomatic population.

1.5 LITERATURE REVIEW

1.5.1 Temporomandibular Disorders

Temporomandibular disorder (TMDs) is a collective term used to describe all functional disturbances of the masticatory system. Multiple etiological factors are involved in their pathogenesis, as a result, no single treatment can affect all the possible etiologies [2].

In a recent article, Laskin [14] discusses the misuse of the term "TMD" in the literature, which often creates diagnostic confusion. He reminds this is a term that

does not refer to a single condition, but a group of disturbances that primarily involve the muscles of mastication, or the temporomandibular joint (TMJ), or both. This author emphasizes the importance of clearly discriminating those conditions in research instead of simply using the broad term "TMD", to clearly defining which condition(s) are being studied.

The American Academy of Orofacial Pain (AAOP) recently published in their guideline textbook the diagnostic classification of TMDs [13]. The two major groups include: 1- TMJ articular disorders, and 2- masticatory muscle disorders. The subclassifications within each of those 2 groups can be seen on table 1.1.

Table 1.1 Diagnostic Classification of TMDs

1. TMJ articular disorders	**2. Masticatory muscle disorders**
1.1 Congenital or developmental disorders	2.1 Local myalgia
1.1.1 Aplasia	2.2 Myofascial pain
1.1.2 Hypoplasia	2.3 Centrally mediated myalgia
1.1.3 Hyperplasia	2.4 Myospasm
1.1.4 Dysplasia	2.5 Myositis
1.1.5 Neoplasia	2.6 Myofibrotic contracture
1.1.5.1 Benign	2.7 Masticatory muscle neoplasia
1.1.5.2 Malignant	
1.2 Disc derangement disorders	
1.2.1 Disc displacement with reduction (DDwR)	
1.2.2 Disc displacement without reduction (DDsR)	
1.3 TMJ dislocation	
1.4 Inflammatory disorders	
1.4.1 Synovitis and capsulitis	
1.4.2 Polyarthritides	
1.5 Noninflammatory disorders	
1.5.1 Primary osteoarthritis (OA)	
1.5.2 Secondary osteoarthritis (OA)	
1.6 Ankylosis	
1.7 Fracture	

de Leeuw [13] – AAOP guidelines

The following sections will discuss the general embryological, anatomical, epidemiological and etiological factors related to TMDs, follow by a discussion of intra-articular TMDs, including disc displacement disorders, and noninflammatory disorders (primary and secondary OA). The final section will review cone-beam computed tomography (CBCT).

1.5.1.1 Embryology of the temporomandibular complex

The embryology of the TMJ occurs in a different fashion then other human synovial joints. The TMJ development starts later, approximately in the 7th week post conception where most of the other joints have already completed their embryologic growth. Another difference is that the TMJ originates from two different blastemata that eventually grow towards each other, rather than a single blastemata origin seen in other human synovial articulations [18].

The preliminary body and ramus of the mandible is formed of membranous bone and grows laterally to the Meckel's cartilage during the 6th week post conception. The accessory mandibular condylar cartilage develops as the first blastema between the 10th and 12th week, this structure grows towards the area that later will develop the temporal blastema. The mesenchyme between the two blastemata becomes smaller due to condylar growth and differentiates into layers of fibrous tissue [18]. The articular compartments are formed during the 10th week with consequent definition of the intervening articular disk. The annexes of the joint

capsules is formed by condensation of mesenchyme, gradually the synovial membrane isolates the joint from the surrounding tissues. The joint capsule is recognizable by the 11th week post conception and subsequently gives origin to the lateral ligaments [18].

The growth of the joint structures is guided by the temporal element following a lateral direction, simultaneously with the widening of the neurocranium. At birth there is no articular tubercle and the glenoid fossa is nearly flat. The tubercle becomes prominent and the fossa increases its concavity when permanent dentition eruption initiates and progresses until the 12th year of life [18].

The development of muscles occurs first in the orofacial region, following the cephalocaudal sequence of fetal development. During the 8th and 9th week, the facial pre-muscle masses initiate its formation. Approximately during the 14th week all orofacial muscles have completed their migration reaching their final positions [18]. The four muscles of mastication (masseter, temporalis, lateral pterygoid, and medial pterygoid) are formed from the first pharyngeal arch. That arch was previously invaded by the fourth somitomere myomere and receives innervations by the fifth cranial nerve (trigeminal). These muscles differentiate as individual entities migrating and attaching to their particular sites of origin and insertion in the cranium and mandible respectively [18].

1.5.1.2 Anatomy of the temporomandibular complex

The articulation between the two condylar surfaces of the single mandibular bone with the squamous portion of the temporal bone in the cranium bilaterally forms two of the most complex joints in the body the TMJs [13, 19]. These two synovial joints are able to produce both hinging and gliding movements, and considered a *ginglymoarthrodial joint* [2] or a hinge joint with a movable socket [19].

The vascularization of the TMJ is mainly given by the superficial temporal artery, deep auricular artery and anterior tympanic artery. Venous drainage is provided by the superficial temporal vein and maxillary vein. The auriculotemporal nerve, a branch of the mandibular division of the trigeminal nerve, gives the main sensory innervation of the TMJ [20].

The TMJ consists of the mandible condyle, the squamous portion of the temporal bone, the articular disc contained between these two structures, and ligaments serving as boundaries. The temporal bone mainly encompasses the articular eminence anteriorly, on the base of the zygomatic process; the glenoid fossa, the concavity where lies the mandibular condyle, and the tympanic plate, a vertical plate located anterior to the external auditory meatus [20].

The mandibular condyle has a football shape with main load bearing areas on the lateral aspect. Both the glenoid fossa and the mandibular condyle are lined by

dense, avascular, fibrous connective tissue, unlike other synovial joints that present a hyaline cartilage lining [19, 20]. The articular disc separates the two bone components. The disc is formed by dense fibrous connective tissue, aneural and avascular. In the peripheral areas of the articular disc, where loading is minimal, there is slight vascularization and innervation [2, 20]. The articular disc separates the articular space into two compartments. The superior compartment between the glenoid fossa and the articular disc enables translational movements of the TMJ. The inferior compartment between the articular disc and the condyle enables rotational movements of the TMJ [20].

The articular disc is contiguous posteriorly to a highly vascularized and inervated region of loose connective tissue, referred as the bilaminar zone or retrodiscal tissues, that ultimately blends with the joint capsule. Anteriorly, the disc also blends with the joint capsule. The disc is anchored directly to the condyle both in the medial and lateral aspects by collateral ligaments [13, 19, 20].

The internal surface of the TMJ compartments contains specialized endothelial cells that produce synovial fluid. This fluid functions as a lubricant preventing friction within the joint compartments. As the synovial fluid is forced in and out the articular tissues through joint movement it also enables the occurrence of metabolic exchanges [2, 20].

The muscles involved in mastication include the masseter, temporalis, lateral pterygoid and medial pterygoid muscles. For optimal mechanics during mastication these muscles function in conjunction with other muscle groups of the face, tongue, palate, and hyoid bone [19]. Table 1.2 summarizes the origin and insertion of the masticatory muscles and their specific functions.

Table 1.2 Muscle of mastication – origin, insertion and function

	Origin	Insertion	Function
Masseter - superficial portion - deep portion	Zygomatic process	Lateral aspect of the lower border of the ramus of the mandible	Main: elevation Superficial portion: aids in protrusion
Temporalis - anterior portion - middle portion - posterior portion	Temporal fossa and lateral surface of skull	Coronoid process and anterior border of the ascending ramus	Main: elevation Anterior portion: elevation Middle portion: elevation and retraction Posterior portion: elevation
Medial pterygoid	Pterygoid fossa	Medial surface of the mandibular angle	Main: elevation and protrusion Unilateral: laterality to the opposite side
Lateral pterygoid - Inferior portion	Outer surface of the lateral pterygoid plate	neck of the condyle	Main: depression and protusion Unilateral: laterality to the opposite side
Lateral pterygoid - Superior portion	infratemporal surface of the greater sphenoid wing	articular capsule, disc, and the neck of the condyle	Main: elevation (especially against resistance)

Okeson JP [2]

1.5.1.3 Epidemiology of TMDs

LeResche [21] evaluated 8 studies assessing the epidemiology of TMDs with different sample sizes and different proportions for gender and age. The studies assessed showed prevalence estimations ranging from 6.3% to 24%. Despite the

methodological differences among the evaluated studies the author concluded that TMDs occur in middle aged adults and twice as much in women than men. A study conducted by Johansson et al [22] found similar results when evaluating a population of 12,468 subjects in their 5th and 6th decade of life. TMD pain was reported by 12.1% of the sample, 11.1% reported limitation in range of mouth opening and 19% reported a combination of both. Younger subjects (50-year-old group) and females significantly showed a greater prevalence of TMD symptoms.

A literature review by Carlsson [23] detected a great variation of on TMD prevalence rates. He evaluated 13 articles with different sample sizes and different proportions for gender and age. The prevalence detected ranged from 1.5% to 30%, with a preponderance of women. The author concluded based that the symptomatology of TMD in children was minimal and there is no evidence that it progresses to a more severe condition later in life.

Epidemiological studies on TMD prevalence in children populations have also shown a wide variability. Thilander et al. [24] evaluated 4724 children below 17 years of age and found one or more clinical signs of TMD in 25.5% of that sample, with predominance of females. The majority of the sample (22.8%), however; showed mild signs of TMD. Conti et al [25] evaluated 200 individuals below 20 years of age and found clinical signs of TMD in 37.5% of that sample, with more females than males affected, with the majority of the sample (34%) showing mild signs of TMD. Casanova-Rosado et al [26] assessed 506 individuals

below 25 years of age and 46.1% of that sample exhibited TMD symptoms, with preponderance of women.

Isong et al [27] conducted a prevalence study based on the results of the 2002 National Health Interview Survey (NHIS) for self-reported symptoms of temporomandibular joint and muscular disorders (TMJMD). This survey included 30,978 people, 17,498 females and 13,480 males, 20,398 non-Hispanic whites and 4179 non-Hispanic blacks. The overall prevalence of TMJMD-type pain was 4.6%, with 6.3% for women and 2.8% for men. That prevalence was greater for non-Hispanic white women below the age of 50 (approximately 8%), whereas non-Hispanic black women had a lower prevalence at ages 25 to 34 years (approximately 4%) increasing only thereafter. This contrast was also detected in men, however age seemed to influence more the prevalence rates within the female group.

1.5.1.4 Etiology of TMDs

The etiology of TMDs is multifactorial, involving variables that may predispose, initiate and/or perpetuate the diseased state [2], with a multitude of conditions concomitantly involved in the cause of TMD needs consideration [28].

Okeson [2] reviewed 57 studies that attempted to look at the relationship between occlusion and TMD signs and symptoms. Twenty-two of the evaluated studies

detected no relationship, whereas 35 studies did find a relationship. However, studies that detected a relationship between occlusion and TMD were inconsistent in the type of occlusal disturbance reported, and additionally these reported issues were commonly found in asymptomatic populations.

Seligman and Pullinger [28] found trauma as a major defining feature of intra-capsular TMD (e.g. DDwR, DDsR, primary and secondary OA). De Boever and Keersmaekers [29] indicated head and neck trauma as a fairly frequent trigger of TMD, as well as that patients with previous history of trauma appear with more prominent symptomatology than patients with absence of that type of history. TMDs related to whiplash injury as a result of a motor vehicle accident (MVA) has also been reported [30]. A study by Visscher et al [31] found a higher prevalence of TMD in individuals with a previous history of whiplash injury, and suggest that this is a more extensive chronic pain condition with marked psychological distress and pain affecting numerous parts of the body.

The possible role of estrogen may explain the increased prevalence of TMD in women [32-34]. A study conducted by De Leeuw et al [35] detected differences in pain sensitivity during the menstrual cycle. This study found the brain areas involved in attention or anticipation of pain to be more activated during the low-estrogen phase. Similar results on TMD pain were detected by Le Resche et al [36], this group found an increase of pain during the low-estrogen phase, as well as during times of rapid estrogen change. Additionally, Ribeiro-DaSilva et al [37] proposed

that a polymorphism in the estrogen receptor may be involved in the higher prevalence of TMD in women, which would explain possible individual differences in the impact of estrogen in females.

Psychological variables have been considered as a factor in the occurrence of TMDs [38, 39]. Ferrando et al [40]detected a diverse psychological profile in TMD patients. Turner et al [41] proposed that there is an empirical indication that psychological variables such as catastrophizing and poor coping strategies are related with chronic disabling TMD. Selaimen et al [28] found depression as a relevant risk indicator for TMD. Post-traumatic stress disorder (PTSD) has also been linked to TMD, De Leeuw et al [42] found PTSD prevalence on TMD patients to be considerably higher than that found in the general population. A study with war veteran population, conducted by Uhac et al [43], found a higher prevalence of TMD in individuals diagnosed with PTSD than in healthy controls. Major traumatic stressors were reported by 49.8% of the TMD patients studied by De Leeuw et al. [44].

Non-functional activity of the jaw (parafunction) is another potential etiological factor for TMDs, these activities include grinding, clenching, oral habits, and may be diurnal and nocturnal. [2]. A study by Winocur suggested that daytime parafunction is a contributing factor to TMD in adolescents, especially in females [45]. In addition a study conducted by Gavish et al [46] with adolescent females found gum chewing as a common oral habit, with positive correlation with muscle

tenderness and joint noises [46]. A study conducted by Galdon et al [47] found TMD of muscular origin to be more related to parafunction than that of articular origin. A study by Israel et al [48] however, found a significant correlation of parafunction and the presence of TMJ osteoarthritis, suggesting that the TMJ overloading triggered by these habits may be closely involved to the development of intra-capsular inflammation and consequent cartilage degradation. However, although studies have found some level of correlation between TMD and daytime parafunction a direct correlation has not been found to date and thus remains speculative. [13]

1.5.1.5 TMJ disc derangement disorders

Many factors have been implicated in the development of disc displacement (DD). Stegenga and de Bont [49] mention trauma as the variable most often linked to DD. A multiple logistic regression analysis carried-out by Pullinger et al [50] suggested that occlusal variables pose a low risk for the development of DD. Tanaka et al [51] found positive evidence that the increased friction between the TMJ articular surfaces caused by clenching habits may ultimately move the articular disc forward. Perrini et al [52] conducted a study that found a positive correlation between generalized joint laxity and the presence of DD. Although many studies have found some level of evidence linking different variables to the development of DD, the full understanding of its etiology remains still not completely clear [53].

Disc displacement with reduction (DDwR) occurs when the TMJ articular disc is displaced anteriorly in closed mouth position and upon mouth opening this disc moves upwards improving its relationship with the mandibular condyle. This process of disc reduction may occur in varying levels, and are responsible for the peculiar joint noises described as clicking or popping. Although DDwR is not necessarily accompanied by symptomatology, pain precipitated by joint movement and mandibular deviation during opening may be found in relation to this condition. Restriction in range of mouth opening is not normally seen in direct relation to DDwR [13].

Disc displacement without reduction (DDsR) occurs when the TMJ articular disc is displaced anteriorly and this misalignment is not improved upon mandibular movement. This mechanism is also usually referred as "closed lock". In this case the disc maintains its anterior displaced location despite condylar translation, which frequently causes mouth-opening limitation with deflection to the affected side, particularly in cases of sudden onset. Pain triggered by forced mouth opening and a past history of TMJ clicking sounds that ceased with jaw locking may also be present in patients with DDsR [13].

1.5.1.6 TMJ osteoarthritis

Osteoarthritis (OA), also referred as degenerative joint disease (DJD) [13], is a term used to define the disturbance that affects synovial joints leading to erosion and

fibrillation of the articular cartilage and ultimate degeneration of adjacent subchondral bone [54]. This condition mostly affects the articular cartilage but it may also affect the TMJ, an atypical synovial joint covered by fibrocartilage [55].

OA is subdivided into primary and secondary based on the presence or not of a clearly identifiable causative event. Patients suffering from primary OA have no previous history of a major precipitating event. Its symptomatology includes TMJ pain upon function and palpation; and limitation in mouth opening, and/or joint crepitation may also be present. Those suffering from secondary OA present a previous disease or event in relation to the development of OA, such as direct trauma, local TMJ infection, and systemic arthritis (eg. rheumatoid arthritis). The symptomatology of secondary OA is similar to that found on its primary counterpart [13].

It has been widely debated whether TMJ disc derangement would be connected with the presence of OA. De Leeuw [13] classifies this event among those in relation with the development of secondary OA, although other authors believe that there is not enough evidence to clearly link these two conditions [56, 57].

The disease mechanism of TMJ OA is not yet completely understood. It has been proposed different theories including direct mechanical injury, hypoxia-reperfusion injury, and neurogenic inflammation [58]. Those models consider direct or indirect mechanical stress as the central cause for the subsequent degenerative

changes seen in TMJ OA [59]. An additional model has been proposed by Milam et al [59] that hypothesizes that the free-radical produced by mechanical stress may be accounted for the launching of a cascade of molecular events that ultimately leads to degenerative joint disease.

The risk factors for the occurrence of OA in general include two essential events: the presence excessive loading on normal cartilage, and normal loading on an abnormal cartilage. This decreased tissue capacity to endure and adapt to loading may be seen in relation to the aging process, and sometimes it can also be related to genetic factors [60].

The treatment goal in TMJ OA is to diminish the disease's normal route and/or enable less discomfort during its course. During the period of OA acute symptoms the main objective is to provide pain control, followed by maintenance/recuperation of a normal functioning of the TMJ. Avoiding or at least minimizing the potential for joint deformity it is also important during phase. Subsequently to symptom stabilization, treatment is directed with self care management tools to minimize TMJ loading [61].

1.5.1.7 CBCT technology

Cone beam computed tomography (CBCT) was introduced in the 1990's and it has been widely applied in different areas of Dentistry as an option to the lower

quality images produced by two-dimensional (2D) imaging modalities [62]. This technology also enables lower dose and lower cost imaging when compared with conventional CT scanners [6].

Sir Godfrey Hounsfield initially introduced CT technology in the 1960's. Five generations have followed its initial development, always aiming to improve the quality and accuracy of the final images. These machines, however, still require considerable time for imaging reconstruction, a large physical space, and demand higher cost compared to 2D imaging modalities [5].

CBCT technology provides imaging in a faster fashion than conventional CT [7]. This occurs due to the images being captured by a rotating gantry to which an x-ray source and detector are fixed. A divergent cone-shaped source of ionizing radiation is then directed through the center of the area of interest, the x-ray source-detector system rotates 360 degrees and a series of exposures of approximately one for each degree is attained. These steps enable the capture of data with only one rotational sequence of the gantry, which can be successfully used for subsequent image reconstruction [7, 62]. In conventional CT, a fan-shaped x-ray beam is used in a helical progression that captures images in individual slices, which are subsequently linked to each other to form a 3D image. The drawback is that each of these slices requires an individual 2D reconstruction, demanding time to acquire the final image [62].

A systematic review carried out by De Vos et al [63] encountered the following as the main clinical applications of CBCT technology: dento-alveolar and maxillofacial surgery, implantology, orthodontics, endodontics, periodontics, forensic dentistry and otolaryngology. Where the most common application involved the detection of impacted teeth and implantology.

Ludlow et al [6] studied the effective radiation dose used by different CBCT units. Their results uncovered a radiation dose that may be of 2% to 23% of that found for conventional CT scanners. On the other hand, the CBCT radiation dose may be of several to many times greater that that found for a single panoramic 2D image. These results corroborate with those found by Schulze et al [64]. Their results detected radiation exposure levels of the CBCT systems lying between conventional CT and conventional radiography.

The quality and accuracy of the images provided by CBCT technology have been discussed by several studies. Michkowski et al [11] reported satisfactory information of linear distances and volumes provided by CBCT, with not relevant differences to multidetector row CT. Those results agree with those found by Hashimoto et al [65], as their subjective evaluation of image validity of CBCT scans proved superior to that found for multidetector row helical CT. Pinsky et al [66] considered CBCT technology to be an accurate, non-invasive method to reliably assess size and volume of osseous lesions. Stratemann et al [67] found the images provided by the

CBCT system was highly accurate when compared with physical measures directly from the skulls, with less than 1% relative error.

Suomalainen et al [68] studied the reliability of CBCT in implant-planning measurements when compared with multislice CT and consider the CBCT system as a reliable tool on that matter. Marmulla et al [69] reported images produced by CBCT NewTom 9000 machine as geometrically correct and suitable for 3D implant planning.

Honda et al [8] studied the diagnostic reliability of CBCT and helical computed tomography for the detection of osseous abnormalities of the mandibular condyle. They detected no differences between these two systems when compared to macroscopic observations as the gold standard. Kamburoglu et al [70] assessed the accuracy and reproducibility of CBCT measurements of specific distances around the mandibular canal in comparison with direct digital caliper measurements. Their results detected comparable measurements between the two systems.

A technical report article published by Tsiklakis et al [4] considered CBCT technology the imaging technique of choice for bony changes in the TMJ. The image quality of CBCT has been researched in the TMJ region. Honey et al [10] detected a superior reliability and greater accuracy of CBCT images when compared to corrected angle linear tomography and TMJ panoramic projections in the detection of condylar cortical erosions. Hintze et al [9] found no differences in

diagnostic accuracy between CBCT and conventional tomograms in detecting bone changes of the articular TMJ tubercle and condyle.

Rafferty et al [71] presented the first publication on the application of the CBCT technology in image-guided surgery of the frontal recess. These authors conducted an investigation of 12 cadavers that demonstrated the immense potential of this technology in sinus surgery. They demonstrated that the CBCT system enabled an increase in surgical confidence in the access of the frontal recess, as well as it resolved ambiguities with anatomical variations. These advantages were possible as this technology enabled sufficiently high resolution of both bone and soft tissue structures at an acceptable low radiation dose to be used repeatedly in the intraoperative setting.

A latter study by Zoumalan et al [72] assessed the image quality and potential diagnostic accuracy of the CBCT system in sinus imaging. The authors considered that the data acquired by this technology, in addition to clinical impression and endoscopy, provides useful radiologic documentation for the diagnosis of chronic sinusitis. As a result, this system was considered a reasonable alternative to traditional multidetector scanners, with the advantage of decreased radiation exposure an in office clinical availability.

1.5.2 The sinonasal complex

1.5.2.1 Embryology of the nasal cavity and paranasal sinuses

The embryologic formation of the nasal cavity occurs during the fourth and eighth gestational week. During that period the medial nasal prominence and the maxillary process join to form the upper maxilla and philtrum of the upper lip. The frontonasal and maxillary processes come together forming the nasal cavities. The nasal septum is then formed from the growth of the frontonasal process and midline extensions of mesoderm from the maxillary processes. The primary and secondary palatal shelves join in an axial plane to separate the nasal cavity and nasopharynx from the oral cavity and oropharynx. The septum finally merges with the fused palate, which leads to the final separation of the nasal cavities. During the sixth week post-conception the mesenchyme forms a simple lateral nasal wall that subsequently invaginates to create complex folds, known as turbinals and recesses, which subsequently give rise to mature structures in the form of turbinates and meati [73].

The development of the four paranasal sinuses initiate approximately at the end of the third gestational month. It occurs from the middle and superior nasal meatus, and the sphenoethmoidal recesses. The mucous membranes located on those areas form outpouchings that grow in a process known as primary pneumatization. It expands the cartilage walls and roof of the nasal fossae into the maxillary,

sphenoid, frontal and ethmoid bones. The secondary pneumatization occurs enlarging the sinuses further into bone, the communication between nose and the sinus is maintained through the ostial passage [18].

The timelines of pneumatization varies among the sinuses. The maxillary sinus starts first, it is estimated that its pneumatization initiates as early as the tenth gestational week, and the secondary approximately during the fifth month. The sphenoidal sinus start developing at the fourth gestational month and the secondary pneumatization only occurs at 6 to 7 years. The development of the ethmoid sinus begins at the fourth month post-conception. The secondary pneumatization occurs from birth and 2 years to form groups of 3 to 15 air cells known as the ethmoid labyrinth. Finally, the frontal sinus starts its growth at 3 to 4 months post conception. The secondary pneumatization only starts between 6 months to 2 years and is generally not complete until early adulthood. The growth of the paranasal sinuses seems to persist in a smaller rate later in life [18].

1.5.2.2 Anatomy of the nasal cavity and paranasal sinuses

The anatomy of the paranasal sinuses is complex and highly variable, particularly when it comes to the ethmoid structures. The ethmoid sinus is commonly referred as “the labyrinth” due to the several cells present in its structure [74]. This sinus is the central part of the nose, where its lateral portions, called lamina papyracea,

form the medial walls of the orbit. The posterior part faces the sphenoid, and the superior surface relates to the base of the anterior cranial fossa [73].

The ethmoid is organized into lamellae obliquely oriented and organized in parallel. The first lamella is the uncinate process, the second the ethmoid bulla, the third is the basal or ground lamella of the middle turbinate, the fourth is the lamella of the superior turbinate and fifth is the lamella of the supreme turbinate. The third lamella divides the anterior and posterior ethmoids, the anterior drains into the middle meatus and the posterior into the superior and supreme meati [73, 74].

The anterior ostiomeatal complex comprises the frontal recess together with the anterior ethmoid air cells (agger nasi, supraorbital ethmoid air cells, ethmoid bulla and frontal cells), frontal sinus ostium, maxillary sinus ostium, middle meatus and infundibulum [16]. This group of structures is also referred as the ostiomeatal unit or simply the ostiomeatal complex (OMC) [73, 74].

The frontal sinus is a pneumatized cavity, variable in size and located anterosuperior to the nasal cavity. The anterior table relates to the forehead, the posterior table to the anterior cranial fossa, and the floor functions as the supraorbital roof [73]. The frontal recess, formerly named nasal frontal duct, refers to the air space connecting the inferiomedial frontal sinus and the anterior middle meatus. The mucociliary drainage of the frontal and anterior ethmoid is made through that recess to the middle meatus and infundibulum [16].

The agger nasi is situated below the frontal sinus and formed from aeration of the ethmoid sinuses that projects anterior to the attachment of the middle turbinate [16, 73]. The middle meatus refers to the area flanked by the middle turbinate medially and laterally by the medial walls of the uncinate process and ethmoid bulla. The uncinate process can be seen either as the most superior and medial wall of the maxillary sinus or the superior extension of the lateral nasal wall. The infundibulum is the space delineated by the inferior medial orbital wall and the uncinate process [16].

The hiatus semilunaris inferioris is a small crescent-shaped space delineated by the anterior medial wall of the ethmoid bulla and the posterior-free margin of the uncinate process. The ethmoid bulla is an air cell located posterolaterally to the uncinate process and demarked laterally by the lamina papyracea. It communicates to the middle meatus through an ostium [16, 74].

The maxillary sinus is the largest paranasal sinus. It is a bilateral, large, pneumatized space localized within the maxillary bone. This sinus is most often seen as a single chamber and is demarked by the facial surface of the maxilla anteriorly; infratemporal and pterygopalatine fossa posteriorly; the orbital floor superiorly; hard palate, alveolar process and dental portion of the maxilla inferiorly; zygomatic process laterally; uncinate process, fontanelles and inferior turbinate medially [73, 74]. This sinus drains into the ethmoid infundibulum through an ostium located superiorly in the medial wall[73].

The posterior ostiomeatal complex refers to the posterior ethmoid and sphenoid sinus. The most posterior ethmoid air cells, usually a collection of one to five, is demarked anteriorly by the basal lammela of the middle turbinate, posteriorly by the anterior wall of the sphenoid sinus, laterally by the lamina papyracea, medially by the superior and supreme turbinates and superiorly by the ethmoid roof that has close relation with the skull base and optic nerve [16, 74]. The posterior ethmoid drains into the superior and supreme meati to the correspondent turbinates [74].

The sphenoid sinus has an inferior and posterior location when visualized in comparison to the nasal cavity. It is encountered surrounded into the clivus, and the sella turcica is found superoposteriorly. Drainage goes into the sphenoethmoid recess through an ostium located anterosuperior to the nasal septum. This recess lies between the anterior wall of the sphenoid sinus and the posterior ethmoid [16].

1.5.2.3 Physiology of the nasal cavity and paranasal sinuses

The main function of the nose is obviously its role in the respiratory process. It also has a sensorial aspect being involved with the sense of olfaction. Additionally, the nose acts as a protective device filtering, warming and humidifying the air that goes to the lower airways. The capacity to perform those duties is enabled by the complex anatomy of the nasal cavity [73].

The coarse nasal hairs located at the nasal fossa aid the filtering process, capturing large particles entering the nose. The smaller particles are trapped by the nasal mucus due to the turbulence created during the air passage through the nasal structures. Those particles are then expelled out the nose and the sinuses through mucociliary clearance. The nasal mucosa acts as the primary defense upon the external environment and its possible invading pathogens, including bacteria, viruses and fungi [73].

The actual function of the paranasal sinuses is still uncertain. It has been discussed that the sinuses may be involved in the process of humidification and warming of the inspired air as well as to add resonance to the voice. It has also been proposed that the pneumatization of bone that gives origin to the sinus ultimately leads to a reduction in bone mass and weight of the skull [75]. In the following topic it will be discussed the pathological processes that lead to inflammation of the sinonasal mucosa causing disturbances on the normal physiology of those structures. Subsequently a separate section will be dedicated to discuss computed tomography of sinonasal structures.

1.5.2.4 Rhinosinusitis

1.5.2.4.1 Introduction

The group of disorders that have as its main characteristic the inflammation of the mucosa of the nose and paranasal sinuses are defined as rhinosinusitis (RS). The previous use of the term sinusitis was exchanged to rhinosinusitis due to the fact that in almost all cases it occurs with concomitant inflammation of the nasal mucosa [76].

RS is a very prevalent disease in the general population. It has been estimated that approximately 26 million Americans suffer from pathologies affecting the sinuses [77]. In 2006 this group of diseases was involved in 12.9 millions visits to office-based physicians [78] and 1.4 million of hospital outpatient visits [79]. It is also estimated that the direct medical costs implicated in the diagnosis and treatment of rhinosinusitis in the US may be in the order of 2 billion dollars anually [80].

This very common condition affects significantly the quality of life of the affected individuals, triggers important physical symptoms and consequently influences negatively routine daily functioning [76]. The general symptomatology of RS frequently appears as facial pain, headache and nasal congestion often accompanied by anterior and posterior purulent nasal drainage and hyposmia/anosmia (diminishing and loss of the sense of smell, respectively) [81].

There is a general agreement in this field of expertise that no etiologic fact accounts alone for the pathogenesis of RS. It is a multifactorial problem with numerous possible causes including environmental factors such as genetic and congenital conditions, allergic causes, anatomical abnormalities and systemic diseases. Host factors are also extremely important in the etiology of RS, including infectious agents (viral, bacterial and fungal), trauma, noxious chemicals and iatrogenic causes [76, 81].

It is very important to remember that rhinosinusitis may also have a non-inflammatory source or component in a select subset of patients. There are several conditions that may predispose to RS symptoms such as the following: overactivity and underactivity of autonomic nerve pathways, abnormalities in leukotriene production or responsiveness, nociceptive dysfunction, gastroesophageal reflux, defects in mucociliary clearance, antibody deficiency syndromes and aspirin-associated respiratory disease [76] .

The most common and accepted classification of RS is into acute and chronic forms. In summary acute RS (ARS) is defined as inflammation of the nasal passages and paranasal sinuses mucosa with signs and symptoms that last for a minimum of 10 days to up to 4 weeks [81, 82] . Chronic rhinosinusitis (CRS), on the other hand, refers to an inflammatory condition of the nasal cavity and sinuses that has been persisting with or without treatment for 12 weeks or more [76, 82, 83] .

Other possible classifications include subacute RS (signs and symptoms that last from 4 to 12 weeks) and recurrent acute rhinosinusitis [84].

In a recent consensus among specialists involved in the diagnosis and treatment of CRS [76] it was determined that the presence or absence of nasal polyps (NP) is a crucial finding in the determination of prognosis and treatment of that disease. Therefore; it was agreed upon a subclassification of chronic rhinosinusitis as chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP) [76, 82, 85].

Another CRS subclassification has been proposed and involves those cases where patients have a positive evidence of pathologic fungal colonization and allergy to the fungus colonizing nasal and sinus mucus. That condition is defined as Allergic Fungal Rhinosinusitis (AFRS) and deserved a separated classification within CRS because it produces remarkable radiographic and physical findings that affect prognosis and treatment decisions[76, 82].

The Sinus and Allergy Health Partnership presented a consensus on the research definitions and clinical trial guidelines related to RS (table 1.3) [82]. During the following topics it will be discussed in more details the four main subclassifications of RS: ARS, CRSwNP, CRSsNP and AFRS.

Table 1.3 Rhinosinusitis consensus research definitions and clinical guidelines

	Type of rhinosinusitis			
Criteria for diagnosis	**ABRS**	**CRSsNP**	**CRSwNP**	**AFRS**
Pattern of symptoms	• Symptoms present for a minimum of 10 d up until a maximum of 28 d OR • Severe disease (presence of purulence for 3-4 d with high fever) OR • Worsening disease (symptoms that initially regress but worsen within the first 10 d)	Symptoms present for ≥ 12 wks	Symptoms present for ≥ 12 wks	Symptoms present for ≥ 12 wks
Symptoms for diagnosis	Requires: • Anterior and/or posterior mucopurulent drainage PLUS • Nasal obstruction OR • Facial pain/pressure/fullness	Requires ≥ 2 of the following: • Anterior and/or posterior mucopurulent drainage • Nasal obstruction • Facial pain/pressure/fullness	Requires ≥ 2 of the following: • Anterior and/or posterior mucopurulent drainage • Nasal obstruction • Decreased sense of smell	Requires ≥ 1 of the following: • Anterior and/or posterior drainage • Nasal obstruction • Decreased sense of smell • Facial pain/pressure/fullness
Objective documentation	Requires either: • Nasal airway examination for mucopurulent drainage OR • Radiographic evidence of acute RS	Requires both: • Endoscopy to exclude the presence of polyps in the middle meatus and document presence of inflammation, AND • Evidence of RS on imaging by CT	Requires both: • Endoscopy to confirm presence of bilateral polyps in the middle meatus AND • Imaging by CT with confirmation of bilateral mucosal disease	Requires: • Endoscopy to document presence of allergic mucin and inflammation, • Evidence of RS by CT or MRI • Evidence of fungal specific IgE • No histologic evidence of fungal invasion when risk factors for invasive fungal disease are present.

Modified from Meltzer et al [76]

1.5.2.4.2 Acute Rhinosinusitis

Acute rhinosinusitis (ARS) refers to the inflammation of the nasal and paranasal mucosa that leads to a self-limited period of upper respiratory symptoms that usually last for up to 4 weeks. The signs and symptoms often include nasal discharge, nasal obstruction and facial pain, pressure or fullness. It is a condition that is generally infectious in nature, in contrast to its chronic counterpart where other different pathogenesis pathways can be involved [76, 82, 84] .

ARS is often a sequela of a viral upper respiratory infection, with or without an allergic component [76] . Although the most common cause of ARS is a community acquired viral infection, bacterial infections and complications of viral disease leading to bacterial infection also have a significant frequency [84, 86] .

The epithelium within the paranasal sinuses is pseudostratified ciliated and interspersed by goblet cells, that continuously secret mucus creating a thin layer covering the sinus mucosa. In normal situations that superficial layer traps inhaled particles and the unremitting ciliary movement continuously moves that superficial layer of mucus away from the sinus cavities through the ostial opening, keeping the sinus epithelium free of pathogens [87, 88].

Disturbance in production and clearance of the mucus within the sinuses affects the normal functioning of the epithelial cells leading to accumulation and

stagnation of secretion [87, 88]. A viral infection may disrupt that balance by triggering swelling of the nasal membranes, obstructing drainage of the sinus outflow tract, and predisposing mucus accumulation. Ultimately, this pool of retained secretions is a favorable environment for microorganism proliferation, which may lead to congestion and inflammation of the sinus mucosa [87].

A study by Gwaltney et al (1999) examined the effects of usual symptoms of the common cold in order to determine how the nasal fluid would be propelled into the paranasal sinuses. Intranasal pressures were measured in 4 healthy adults during nose blowing, sneezing and coughing. It was found that only the pressures created by nose blowing would propel viscous fluid into paranasal sinuses. A CT scan experiment was also performed, where contrast medium was placed in the pharynx and then the subjects were asked to perform sneezing, coughing and nose blowing. That test showed contrast in one or more sinuses, again, only as a result of nose blowing [89].

Those findings corroborate with the hypothesis that the contamination of the otherwise virtually sterile paranasal sinuses might happen due to the propelling of infectious nasal fluid produced during a cold into those anatomical structures. That fluid may contain viruses, bacteria and inflammatory mediators that produce inflammation, infection or both. The infectious colonization leads to mucosal edema, cellular infiltration and mucus thickened by means of exocytosis of mucin

from the numerous globet cells in the sinus epithelium that is ultimately joined together to form an exudate [76].

The current criteria to differentiate acute viral rhinosinusitis (VRS) and acute bacterial rhinosinusitis (ABRS) are mainly based on illness pattern and duration, since the symptoms profile is quite similar in both cases. When symptoms or signs of ARS are present for less than 7-10 days and are not worsening the diagnosis of VRS is the most appropriate. In contrast, ABRS is diagnosed when signs or symptoms of acute rhinosinusitis are present for 7-10 days and beyond the onset of upper respiratory symptoms or worsened within 10 days after an initial improvement [84].

An allergic component is also proposed considering that allergies often create a proper inflammatory environment for bacterial infection. It is suggested that persistent allergic rhinitis can be a predisposing condition in the development of ARS[76]. In order to distinguish if there is an allergic factor implicated in the pathogenesis of ARS, three specific points related to the patient's signs and symptoms are important to note: 1 – Allergy predisposition alone often does not trigger purulent nasal discharge; 2 – Characteristic features of allergies such as itching and sneezing are more likely to be present; and 3 – Allergies are more frequently associated to recurrent and chronic conditions and seem to be related in the predisposition to bacterial forms of RS[90].

In each paranasal sinus afflicted by ARS either from a viral or bacterial origin there is a specific combination of symptoms and possible complications. Infection of the maxillary sinus is the most frequent among all sinuses, and is the one that trigger pain more frequently. The pain has a pressure quality related to the affected antrum, less often to the forehead and upper teeth, and responsive to percussion over the cheek and sometimes the related teeth [81].

When the ethmoid sinus is affected it causes pain at the root of the nose or behind the eye. Tenderness over the inner canthus of the eye is characteristic and can spread laterally into the orbit or radiate to the temporal region. It often does not occur in isolation, but combined with maxillary and frontal sinusitis [81].

An infectious spread into the sphenoid sinus is less common. It may, however, trigger pain in different regions such as occipital skull area, retro-orbital and the vertex. Infection of the frontal sinus is rare, likely related to its vertical orientation and drainage through the nasofrontal duct. In frontal sinusitis, forehead and upper orbital rim pain may occur, but it is often seldom [81].

1.5.2.4.3 Acute viral rhinosinusitis (VRS)

Most cases of ARS are due to a viral agent as a consequence of a common cold and in general rhinoviruses are the most frequent pathogens involved in that disease [82, 86]. Viruses are believed to create the proper environment to subsequent

bacterial colonization and are present in nearly half of all patients with ARS. Other respiratory viruses that can cause ARS are influenza types A and B; parainfluenza types I, II and III; respiratory syncytial virus; coronaviruses, herpes simplex; adenovirus; human metapneumovirus; and enteroviruses[82].

A study conducted by Makela et al [91] with 200 patients with early symptoms and signs of the common cold determined a viral etiology in 69% of the sample and in approximately 50% of the studied subjects rhinoviruses were detected. Bacterial infections were rarely detected on that study.

Rhinoviruses are not present in the nasal flora; as a result its inoculation in a non-immune person triggers an infection and inflammatory response in the upper respiratory tract [82]. This infection often progress to the sinuses; Puhakka et al [92] determined in a study evaluating radiographs of 98 subjects with symptoms of the common cold that 64.3% of that sample developed sinus abnormalities (mucosal thickening, total opacity, air-fluid level, or cyst/polyp); where 14.2% of patients showed sinus findings on day 1, 38.8% on day 7, and 11.3% on day 21.

Gwaltney et al [93] evaluated the correlation between CT scans findings and reported symptoms of 31 subjects suffering with the common cold. Nasal and head congestion was reported by 71% of patients. The CT scans taken for that group showed abnormalities of one or more sinuses in all cases. Whereas only 56% of the patients from the group that did not complain of nasal and head

congestion showed pathological findings related to the paranasal sinuses in their CT images.

The symptomatology related to VRS or the common cold generally involve a combination of the following signs and symptoms: sneezing, rhinorrhea, nasal congestion, hyposmia/anosmia, facial pressure, post nasal drip, sore throat, cough, ear fullness, fever and myalgia. It is important to remember that a change in the color of the nasal discharge is not a specific sign to differentiate a viral from a bacterial infection, although it is mostly linked to a bacterial source [94].

The course of VRS is often self-limiting; it is expected to last for less than 10 days, with marked improvement of the symptoms during the course of the disease [84]. The differentiation of VRS and ABRS using illness pattern and duration is preferred, since the signs and symptoms of ARS in patients with mild to moderate clinical presentations are poor predictors of the presence of bacteria [95]. Therefore the treatment of VRS should focus mainly on symptoms control, avoiding the use of antibiotic therapy as first line of treatment and consequently minimizing the possibility of bacterial resistance [84].

There is no approved treatment for the common cold by the U.S. Food and Drug Administration (FDA) except for ipratropium bromide (Atrovent® - anti-cholinergic medication) nasal spray for rhinorrhea reduction. The efficacy of over-the-counter antihistamines has not been supported by double-blind placebo-

controlled trials [96]. Symptomatic relief during VRS is often achieved with use of a nasal decongestant (eg. xylometazoline - Otrivin®), analgesic medication (eg. acetaminophen), and most effectively with time [81].

The presence of concomitant bacterial infection in the common cold does not seem to affect the course of symptoms and the effectiveness of the treatment. For instance a study by Puhakka [92] involving 199 subjects suffering with the common cold had clinical cure of those patients in three weeks after the onset of the symptoms regardless of the presence of concomitant presence of bacterial infection.

A systematic review carried-out by Rosenfeld et al [97] critically evaluated 13 trials pertaining the clinical outcomes of antimicrobial therapy in the natural history of ARS. This study concluded that over 70% of patients with ARS are improved after 7 days, with or without a course of antibiotics. And approximately 7 patients must be treated to achieve one additional positive outcome at 7 to 12 days above and beyond spontaneous resolution. Those results corroborate with the idea that the choice of antibiotics use should be carefully made because it is quite often unnecessary in the early stages of ARS, not changing the course of the disease.

1.5.2.4.4 Acute bacterial rhinosinusitis

Acute bacterial rhinosinusitis (ABRS) is an infectious condition that affects the upper respiratory tract and is frequently preceded by a viral infection. It is estimated that approximately 0.5% to 2% of rhinosinusitis triggered by a viral microorganism would progress to a bacterial infection [94, 98]. Other factors that may trigger inflammation of the underlined mucosa of nose and paranasal sinuses such as allergy, trauma or dental infection can also potentially create a proper environment for ABRS [94].

The distinction of ABRS and VRS can be particularly difficult make. The probability that ARS is from a main bacterial source increases in patients with symptoms of the common cold that unexpectedly becomes worse after several days of improvement, or it maintains its severity for more than 7-10 days [84, 96].

The epidemiology of ABRS is an important fact to be addressed considering that the differentiation of VRS and ABRS is particularly difficult to make, and the decision of therapy with antibiotics should be chosen with caution since it would not be efficient on a strictly viral infection and could create antimicrobial resistance [76, 99].

The most frequent symptom of ABRS is purulent nasal discharge, although it is recognized it can be a poor predictor. Facial pain or pressure combined with

congestion is also common. The most specific symptom is upper teeth pain, however shows a very low frequency of approximately 10% [95, 96]. That pain is usually referred and dull aching or throbbing, felt in several teeth and often associated with pressure below the eye [81]. Other symptoms involved in ABRS include sneezing, rhinorrhea, nasal congestion, hyposmia/anosmia, post nasal drip, sore throat, cough, ear fullness, fever and myalgia; that are also encountered in VRS or the common cold [94].

The most common bacterial microorganisms involved in ARS include *Streptococcus pneumoniae, Haemophilus influenzae,* followed by *Moraxella catarrhalis, and Streptococcus pyogenes*. *Staphylococcus aureus* and the oropharyngeal anaerobes occur in a smaller frequency and acute inflammation is usually of less severity [82].

S. pneumoniae and *H. influenza* remain the most common bacteria involved in ABRS since the first studies on that regard, and are estimated to account for more than 75% of the bacterial isolates [76]. These organisms have been demonstrating β-lactamase production creating remarkable resistance to anti-microbial therapy over the past 5 years. It is estimated that nearly 50% of *S. pneumoniae* bacteria are resistant to penicillin and also frequently to other classes of antibiotics such as macrolides and sulfamethoxazole [100].

The objective of therapeutics in patients suffering with ABRS is to re-establish the sinuses drainage by reducing inflammation and consequently unblocking the passages through the ostiomeatal complex. Eradicating the bacterial source of the infection it is an important goal during the acute phase; witch may prevent complications and progression to a chronic form of the disease [88].

Despite the evidence of bacterial resistance, amoxicillin remains the initial drug of choice for ABRS. The rationale for the use of amoxicillin as first-line therapy relates to its safety, efficacy, low cost and narrow microbiologic spectrum [84]. Amoxicillin is capable of achieving a high concentration in the sinus fluid when recommended doses are used. In case of intermediate resistance of *S. pneumoniae* the alteration in penicillin-binding proteins appear to be potentially overcome by increasing the dose of that drug [100].

In cases of penicillin allergy, folate inhibitors (trimetroprim-sulfamethoxazole) are cost effective alternative to amoxicillin. Cephalosporin or the macrolide class are also other options to be considered in penicillin-allergic patients [84, 100].

An important part of ABRS treatment includes providing adequate drainage and eradication of local infection. The adequate drainage of the involved sinuses can often be accomplished with the use of topical vasoconstrictors and systemic decongestants. Performing that therapy may also enhance the effectiveness of the antibiotic therapy [96]. The use saline nasal irrigation is another effective option as

this type of therapy is effective in rinsing away predisposing agents such as pollen, mold, and dust. It is also effective in increasing mucociliary flow rates and providing brief vasoconstrictive effects [100]. Saline irrigation may also provide a lavage of secretions minimizing the risk of crust formation near the sinus ostia [101].

It is always very important to be cautious when deciding to initiate anti-microbial therapy. The diagnosis of a bacterial infection involved in RS in its earlier stages is difficult to make. This diagnosis has frequently been made too soon leading to increasing resistance among respiratory tract pathogens. For that reason clinicians should have a very good judgment when combining signs and symptoms (poorer predictors) and the disease pattern and duration (more reliable predictors) in the drawing of ABRS diagnosis and further treatment decisions [94].

1.5.2.4.5 Chronic Rhinosinusitis

Inflammation of the mucosa of the nose and the paranasal sinuses that last for twelve weeks or more is considered as a chronic form of rhinosinusitis (CRS) [76, 82]. CRS is a multifactorial condition where several factors such as microorganisms, immunologic variables, genetics and anatomical abnormalities may contribute to the pathophysiology of that disease [83].

The symptoms often encountered in patients suffering with CRS include at least 2 of the following: anterior and/or posterior mucopurulent drainage, nasal

obstruction, facial pressure/fullness, hyposmia/anosmia. Endoscopy evidences presence of inflammation of the nasal mucosa and in selected cases also presence of nasal polyps. CT scanning of the paranasal sinuses of patients with CRS indicates mucosal disease [82].

The symptoms involved in CRS can be quite debilitating, considerably affecting the quality of life of the affected individuals. A study of Gliklich and Metson [102] involving 158 patients with CRS assessed the disease burden of that condition compared to other major chronic illnesses. Results showed substantially worse scores for bodily pains and social functioning in patients with CRS when compared with similarly derived data for angina pectoris, congestive heart failure, chronic obstructive pulmonary disease, and chronic back pain.

A recent consensus convened by the Sinus and Allergy Health Partnership discussed the subclassification of CRS into chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP). It was agreed upon that categorization based on the concept that different pathogenic processes are involved in those two conditions, including differences in inflammatory cellular infiltrate, cytokine and mediators profiles, and immune responses to *Staphylococcus aureus* enterotoxins (SAEs) [76].

Another subset under the umbrella of CRS is allergic fungal rhinosinusitis (AFRS). This condition stands for an allergic and immunologic response to the

presence of fungal colonization within the nasal cavities with consequent production of eosinophilic mucin containing non-invasive hyphae. The typical symptoms of AFRS include the presence of underlying nasal polyps in the majority of cases. The marked correlation between nasal polyps and AFRS was distinctive enough to subclassify CRSwNP into 2 subgroups, one of patients suffering with classic AFRS and other represented by tall he other patients with CRSwNP without a fungal etiologic component [76, 103].

1.5.2.4.6 CRSsNP X CRSwNP

As discussed previously, the Task Force convened by the Sinus and Allergy Health Partneship recommended a subclassification of CRS into polypoid and non-polypoid forms [76]. Similar symptoms are found in CRSsNP and CRSwNP, including mucupurulent nasal drainage, nasal obstruction and facial pain/pressure/fullness and decreased sense of smell. The most distinctive feature is obviously the presence of nasal polyps (NP), its diagnosis require intra-nasal examination with the use of a nasal endoscope. In both situations CT images shows evidence of mucosal thickening within one or more paranasal sinuses. CT imaging is often required to support clinical judgment in CRS [82].

Other possible way of sub-classifying CRS is based on the presence or absence of mucosal infiltration with eosinophils. The underlying principle for the marked importance given to eosinophilic inflamation in CRS relies on the belief that it

plays a central role in the pathogenesis of that condition, especially in the pathophysiology of NPs. Whereas when eosinophils are not present the pathogenesis of CRS appears to be more related with impair local or systemic immunity, mucociliary clearance, or sinus ventilation [76].

CRSsNP is rarely eosinophilic, while CRSwNP occurs in the presence of EG2+ (activated) eosinophils in more than 80% of the cases. In selected cases it is found NPs that have predominance of neutrophils, when typically there is no stromal edema or goblet cell hyperplasia, as found in the presence of eosinophilic inflammation. In those cases the NP overlying epithelium presents squamous metaplasia, and it is frequently diagnosed as an antral choanal polyp [104].

Nasal polyposis is estimated to affect approximately 1-4% of the general population, mostly male adults. NPs appear as pathologic round, smooth, semi-translucent edematous masses that arise from the nasal mucosa, typically along the middle meatus. They can also be encountered within the paranasal sinuses, when are most often related to the ethmoid sinus [105, 106].

NP is a multifactorial illness associated not only with CRS but also with asthma and other respiratory conditions such as cystic fibrosis, primary ciliary dyskinesia and aspirin-associated respiratory disease [106]. This last condition, also known as aspirin hypersensitivity and Samter's triad, represents one of the most refractory eosinophilic subgroups in CRS [104].

Inflammation is believed to be the central focus in NPs formation. Activation of the epithelial cells by different irritant factors (eg. bacteria, virus, allergens, altered amino acid metabolism, etc) leads to release of inflammatory mediators. In consequence it increases the expression of adhesion molecules on the endothelial cells of the blood vessels, resulting in leakage of plasma through widened endothelial junctions and initiating the formation of NPs. Concomitantly, there is increased production of inflammatory cell infiltrate, especially eosinophils, which can further enhance and maintain the inflammatory process by contributing to stromal fibrosis, epithelial damage, increased interstitial edema, and increased extra-cellular matrix protein production [106].

The bacterial organisms reported as being related to CRS include *S. aureus,* coagulase-negative staphylococcus (CNS) and gram-negative anaerobics. That differs from the microbiology encountered in ABRS, with *S. pneumoniae, H. influenza, and M.catarrhalis* as the main bacterial agents involved [96]. The bacteria most often encountered in CRS is CNS, however it appears equally presented in healthy patients. In contrast gram-negatives are rarely found in non-CRS individuals, these microorganims are believed to be either causative or secondarily infect the sinonasal mucosa due to underlying defects in host defense such as impaired clearance or NPs [104].

The microbiology of CRS can be quite diverse in the literature, with conflicting findings and overlaps between microoganisms present in patients without CRS [96]. Niederfuhr and colleagues [107] conducted a comparative microbiologic investigation among CRSsNP, CRSwNP patients and a control group. That study found no significant differences in the bacteriological findings between the CRS groups and controls. Although it was a study with a small population (31 patients with CRSwNP, 13 with CRSsNP and 21 control patients), it supports positively the theory that bacterial colonization is a controversial matter in CRS.

Nasal polyps usually occur bilaterally, when unilateral lesions are encountered within the nasal cavity its important to rule out nasal masses of other histological origins. This careful distinction should be made on the basis of symptoms, nasal endoscopy and computed tomography [108]. A unilateral polyp may represent an inverting papilloma, neoplasm, antral choanal polyp, AFRS or encephalocele [104].

Tritt et al [108] carried out a retrospective analysis of 299 patients with clinical diagnosis of NP. This study comprised 255 patients with bilateral NPs and 44 with unilateral. From the unilateral group further functional endoscopic surgery and pathologic analysis confirmed the diagnosis of CRSwNP for 39% of patients, AFRS for 34%, inverting papilloma was found in 16%, squamous cell carcinoma in 4.5%, and mucocele, esthesioneuroblastoma and HPV-type papilloma in 2.2%. Although neoplasic processes were found in a minority of the cases the clinician should be vigilant and involve those conditions in the differential diagnosis.

When unilateral polyps are encountered further imaging and biopsy is strongly advised [104].

The histopathology of CRS was investigated in a study carried-out by Polzehl et al[109]. The authors were able to find substantial histopathological differences in the ethmoid mucosa of patients with CRSsNP and early stages of CRSwNP. There was more pronounced cell infiltration and stromal edema in the NP group, there was also higher eosinophil and plasma cell counts in the ethmoid mucosa studied. These substantial histological differences between CRSsNP and the early stages of CRSwNP support the concept that those conditions are two distinct entities rather than different stages of one single disease. Those results also support the belief that the presence of NP may also be interpreted as a higher stage of inflammation.

The symptom profile observed in patients with CRS could be quite similar to those found in its acute form. The most important symptoms for differential diagnosis involve headache, facial pain, nasal obstruction, and discharge. What seems to differ in CRS is the intensity of these specific symptoms that usually appear quite mildly in comparison with ARS. In some cases a patient with CRS may only demonstrate one single symptom or the patient may not notice any symptom at all; which can be especially true in cases of concurrent asthma [76].

Headaches sometimes are the only complaint presented by the patient. However that specific symptom alone typically does not lead to a diagnosis of RS without the presence of other usual signs and symptoms. There are several other causes for headaches affecting the anterior face that should also be ruled out, such as migraines, tension, cluster and rebound headaches and temporomandibular joint dysfunction. Nevertheless, all those conditions may occur with concomitant RS, when that condition often affects the overall pain profile negatively [76].

Bhattacharyya[85] studied the symptoms differences between CRS with and without nasal polyposis. He evaluated 462 patients suffering with CRS – 286 with CRSsNP, 131 with primary CRSwNP and 45 with recurrent CRSwNP. It was found that patients with non-polypoid disease demonstrated statistically significant more facial symptoms such as facial pressure, congestion and headaches compared with NP patients. Conversely, patients with recurrent polypoid disease appeared with more nasal symptoms such as nasal obstruction, rhinorrhea and dysosmia. Interestingly, that same study found that, although a distinct symptom phenotype was found in the polypoid and non-polipoid groups, the rates of medication utilization (topical nasal steroids, nonsedating antihistamines and antibiotics), missed workdays and physician visits are similar between those two subsets. Those findings challenge the intuitive concept that CRSwNP carries a bigger disease burden compared to CRSsNP.

Due to the complexity of the pathophysiology of CRS its management remains still quite empirical and based on expert opinions. Currently, the treatment of CRS is basically focused on reducing inflammation of the underlying sinonasal mucosa, controlling infection and re-establishing the normal air passage through the nasal and sinus mucosa. Comorbities such as asthma should be taken into consideration, since it may affect the prognosis [110].

The presence of NPs should be taken as a very important feature, given that the clinical evolution of CRS with or without polyposis seems to largely differ. An accurate differentiation between CRSsNP and CRSwNP leads to a more precise and focused treatment, which may also lead to an increase in the success rate of the medicinal and surgical treatment. And finally, a careful and regular evaluation of treatment efficacy and revision should be warranted [110, 111].

In face of its complex nature, the treatment of CRS requires intensive medical therapy, frequently combining use of antibiotics, oral steroids, nasal irrigations and intranasal steroids. Subramanian and colleagues treated 40 CRS patients with that treatment regimen and assessed its effectiveness after 8 weeks and beyond. That study found that intensive medical treatment resulted in symptomatic and radiographic improvement in 90% of patients. This improvement was sustained beyond 8 weeks by 65% of the studied sample. A history of NPs or previous endoscopic sinus surgery was associated with earlier relapse, whereas presence of

atopy, asthma and obstruction of the osteomeatal unit did not seem to lead to an earlier recurrence of signs and symptoms of CRS [112].

The use of antibiotics in CRS is still quite empirical and thus open for debate, with an extensive variability in treatment practice. To date, no antibiotic has acquired an approval by the US Food and Drug Administration (FDA) to be used in CRS patients. A literature review carried-out by Bhattacharyya [113], regarding anti-microbial therapy in CRS, claims that there is a significant need for prospective, randomized, placebo-controlled trials assessing that matter.

The controversy around antibiotics usage in CRS is based on the assumption that the bacteriology found in CRS differs from that found in ARS, combined to the uncertainty of whether the bacterial presence in chronic forms of RS is causal or commensal. What is currently accepted to be a reasonable theory is that CRS with neutrophilia (generally CRSsNP) is more likely to receive a larger influence from an infectious component compared to CRS with eosinophilia (majority of CRSwNP), that appear to have a minimal influence of bacterial infection on its pathogenesis [104].

The antimicrobial therapy in CRS is an important discussion in view of the increased likelihood of resistant microorganisms and polymicrobial infection, including bacteria of higher virulence such as gram-negative enteric rods and anaerobes. In order to avoid resistance it would be ideal to provide a culture-

guided therapy, unfortunately that is often not possible in a clinical setting, primarily for technical reasons [96].

Factors such as choice of agent, dose and duration of the therapy may affect the effectiveness of the antibiotic in treating CRS [113]. Common choices for antimicrobial therapy in CRS include Amocillin-clavulanate, followed by second and third generation cephalosporins, newer generation macrolides, respiratory fluoroquinolones, and clindamycin for highly resistant *S. Pneumoniae*. The initial therapy consists in an antibiotic course for 2-3 weeks, although there is considerable variability in recommendations. In case of recurrence with resistant organisms and polymicrobial infection consider 3-4 weeks of therapy, ideally culture-guided [96].

Bhattacharyya and Kepnes [114] carried out a study to evaluate the anti-microbial resistance among individuals suffering with CRS that had bacterial cultures as part of their treatment. They evaluated serial cultures from 90 subjects over a 7-year period; each subject had 2 or more cultures drawn in different time frames. The results revealed no significant trend toward increasing bacterial resistance within individual patients. There was no significant increase in gram-positive or gram-negative resistance, and no shift toward gram-negative organisms. These results support the idea that the risk of developing antimicrobial resistance can be minimized by a culture-guided therapy.

The class of macrolide antibiotics has been showing growing evidence of not only anti-microbial capabilities, but also as an effective anti-inflammatory agent. A low dose, long-term macrolide course seems to down-regulated pro-inflammatory cytokines such as interleukin-8, with consequent attenuation of neutrophilic inflammation. Clinically it demonstrates as less facial pain, headache and post-nasal drip, fewer exarcerbations of sinusitis, and ultimately a better quality of life. The treatment should be directed to non-atopic patients with bilateral disease. The macrolide resistance should be monitored as for any other antibiotic, although to date that issue has been of major concern in CRS treatment[115].

Although not as convenient as its systemic counterpart, topical antimicrobials delivered by nebulization or irrigation is another option in the treatment of CRS. The topical delivery of antibiotics appears very appealing considering that high concentrations of the drug will directly reach the sinonasal cavities, with potentially minor systemic involvement and consequently diminish of adverse reactions [113].

A systematic review compiled by Lim et al [116] evaluated 14 studies, seven controlled trials and five double-blinded randomized trials, regarding topical antimicrobials in the management of CRS. The systematic evaluation of those studies enabled the authors to infer that both stable and acute exacerbations of CRS appear to benefit from topical antibiotics, however it should not be first-line of treatment. The authors allege based on their review that topical antibiotic

therapy should rather be attempted when the patient is refractory to traditional topical steroids and oral antibiotics.

To date there is only one drug approved by the FDA for the treatment CRS, probably due to the multifactorial and complex pathophysiology of this condition. The FDA current approved recommendation involves the use of a nasal steroid spray for the treatment of nasal polyps [104].

Joe and colleagues [117] conducted a systematic review about the use of intranasal steroids in the treatment of CRS. They selected 6 randomized, double blinded, and placebo controlled trials for meta-analysis, where the outcome measured was change in polyp size from baseline compared between the treatment and control groups. Those studies either used the corticoid mometasone or budesonide. The results found enabled the conclusion that intranasal steroids are a beneficial treatment of CRSwNP since it effectively decreased polyp size in the evaluated studies. The effectiveness of that medication modality could not be determined in CRSsNP, since no articles in this group met their criteria. Further studies on that matter should be warranted.

Nasal saline irrigation is another therapy often used to treat the symptoms of CRS. It can be delivered by bottle, spray, pump or nebuliser. There are no recognized side effects to this treatment, other than minor nasal burning, irritation and nausea.

Considerable patient effort is required for its usage, since the dose recommendation ranges from once a day to more than four times a day [118].

A systematic review published at the *Cochrane Database of Systematic Reviews* by Harvey et al (2007) evaluated the recent published research on the effectiveness and safety of that type of therapy in CRS treatment. Eight trials satisfied the inclusion criteria. The authors were able to conclude from this review that the effectiveness of saline irrigation is likely to be modest, but its low cost and good tolerability makes it an appealing option to be considered in the treatment of CRS [118].

A study conducted by Heatley et al [119] also found interesting results in favor of adjunct treatment with saline irrigation in CRS. 82 patients were treated with saline during 4 weeks with no true placebo control group. At the end, among other questions, the patients were enquired about their medication intake habits during the study period. The results showed that this adjunct therapy decreased the medication usage during the study therapy in 33-42% of the participants.

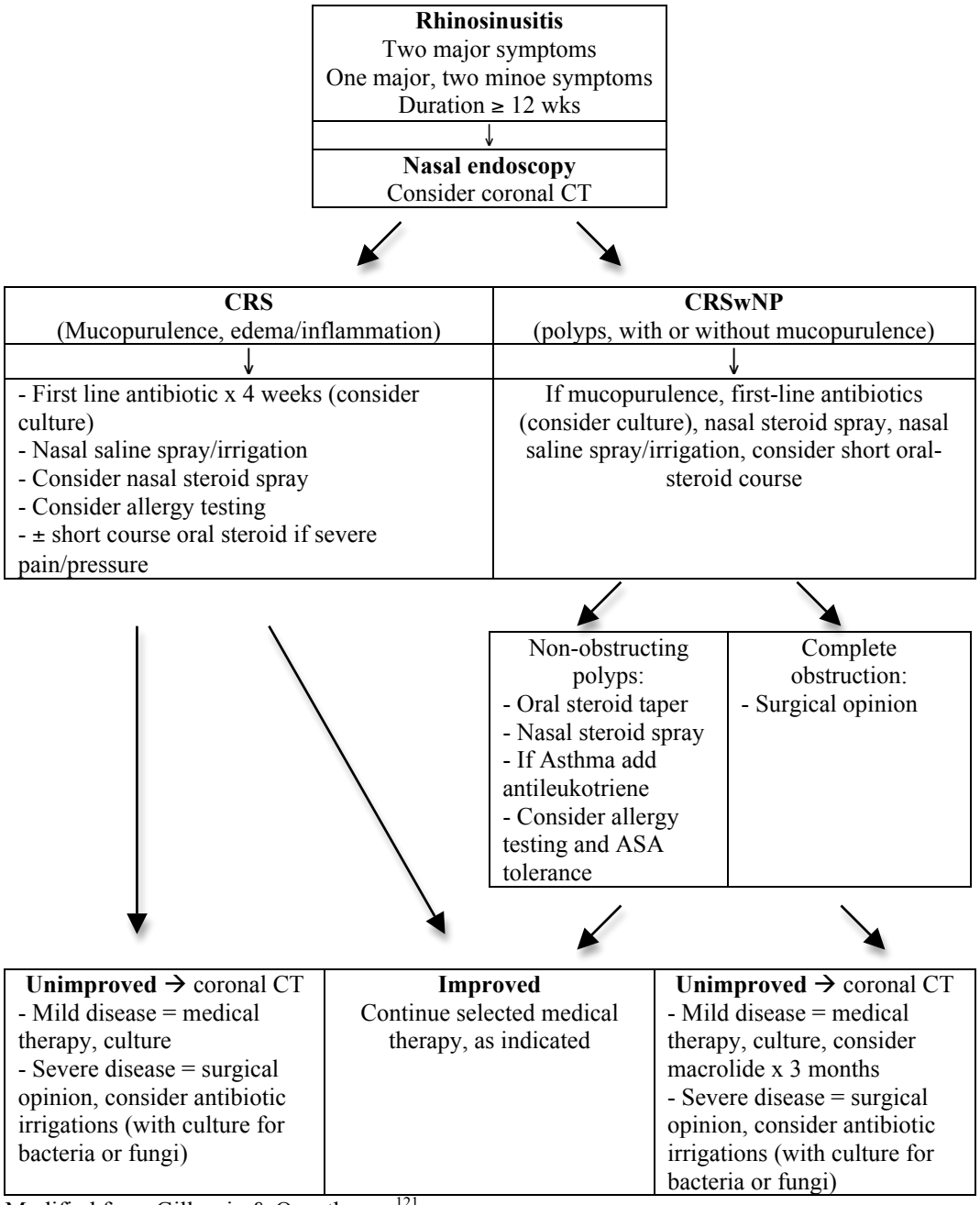
The efficacy of saline irrigation in reducing FESS post-operative signs has also been assessed. Freeman et al treated 22 patients with saline irrigation of one side of the nasal cavity, three times per day during 3 weeks. It was found that this type of management might have an anti-inflammatory effect because it reduced nasal discharge and improved edema during the healing phase following FESS [120].

Oral corticosteroid is another treatment option in CRSwNP, in combination with its intranasal topical forms are considered as the mainstay of NPs treatment [121]. Corticosteroids minimize the expression of inflammatory mediators, which not only impacts inflammatory cells such as lymphocytes and eosinophils but also epithelial and fibroblast cells. Systemic treatment with corticosteroids appears to be quite effective, however higher doses and long-term use may bring serious side effects that mainly include immunosuppression, impaired healing and peptic ulcer, among others. For that reason its prescription by the clinician should be done with very good judgement [104].

The effectiveness of oral and topical corticosteroid treatment in NPs with a three-year follow-up period was assessed in a retrospective medical record review conducted by Bonfils and colleagues [122]. The 100 patients evaluated in this study received treatment with a protocol of short-term oral prednisolone and daily intranasal spray of beclomethasone. That dual steroid therapy was effective in 85% of the patients, where solely 15% had to undergo further surgery because conservative treatment failed. The mean clinical severity index was also reduced, by 77.7%. The authors concluded through those results that a combined steroid therapy appears to be considerably efficacious, therefore a primary medical management of nasal polyps with that medication regimen should be warrant before referral to surgery.

Figure 1.1 summarizes the pharmacologic treatment of CRS through a comprehensive flow chart provided by literature review from Gillespie and Osguthorpe (2004) [121].

Figure 1.1 Summary of CRS pharmacologic treatment



Modified from Gillepsie & Osguthorpe [121]

Functional Endoscopic sinus surgery (FESS) should only be considered once conservative medical treatment has been proved unsatisfactory [122]. However, in some specific situations where severe and complicated consequences of CRS are seen surgery may be a priority. A literature review by Anand and colleagues [80] provided a list of absolute and relative indications for FESS recommended by the Task Force on Rhinosinusitis (table 1.4). It was recommended that a surgery indication should be made after a comprehensive diagnostic process considering clinical and radiological variables.

Table 1.4 Absolute and relative indications to FESS

Absolute indications	**Relative indications**
Bilateral extensive and massive obstructive nasal polyposis with complications	Congenital variations in the anatomy of the nasal cavity and paranasal sinuses
Complications of adult rhinosinusitis	Connective tissue disorders (Wegener's granulomatosis and sarcoidosis)
Chronic adult rhinosinusitis with mucocele or mucopyocele formation	Diabetes mellitus
Invasive or allergic fungal adult rhinosinusitis	Immunodeficient conditions (chemotherapy, immunodeficiency virus infection, and organ transplantation
Diagnosis of a tumor of the nasal cavity or paranasal sinuses	Cystic fibrosis
Cerebral fluid rhinorrhea	Congenital syndromes with involvement of sinus infections (Marfan syndrome)
-	Mucociliary dysfunction
-	AFRS
-	Reactive airway disease

Modified from Anand, Osguthorpe and Rice [80]

A study conducted by Ling and Kountakis [123] evaluated 158 patients that underwent FESS. The authors aimed to evaluate what would be the main symptoms complaints of those patients, as well as determine the rate of symptom

improvement in a 1-year interval. The top four symptoms reported pre-operatively in terms of prevalence and severity were post-nasal drip, nasal obstruction, facial congestion, and facial pain/pressure. One year post-surgery the severity of their symptoms decreased considerably, where the majority improved by at least 80%. Improvement in facial pain/pressure, facial congestion, nasal obstruction and headache were highly correlated.

Those findings corroborate with the results found by Damm et al [124] in study assessing the impact of FESS on symptoms and quality of life (QOL) in CRS. 279 patients were evaluated through questionnaires pre-operatively, and then followed up in 12.4 to 67.9 months. The results found airway obstruction and post-nasal drip as the leading pre-operative complaints, followed by dry mucosa in the upper airway, hyposmia and headache. Post-operatively those symptoms improved by 63.1% to 84%. CRS influenced QOL negatively in 94%. There was a significant correlation of low QOL scores with the presence and severity of nasal obstruction, post-nasal drip and headache. QOL scores were improved after surgery in 85% of the patients.

1.5.2.4.7 Allergic Fungal Rhinosinusitis

Morpeth et al [125] conducted a literature review regarding the classification of fungal RS. Based on their references the authors were able to subdivided fungal RS into four primary categories (table 1.5), two invasive (acute and chronic) and

two non-invasive (fungus ball and AFRS). The distinction of invasive forms of fungal RS is critical because this condition typically presents as a fulminant disease that often leads to mortality [76].

Table 1.5 Classification of fungal RS

Category	Immune Status	Role of Fungus	Tissue Invasion	Sinuses Affected	Course	Current Treatment
Acute fulminant	Compromised	Pathogen	Yes	One	Acute	Radical debriment, systemic antifungals
Chronic Indolent	Competent nonatopic	Pathogen	Yes	Variable	Chronic	Complete excision, systemic antifungals
Fungus ball	Competent nonatopic	Saprophyte	No	One	Chronic	Debriment, aeration
AFRS	Competent nonatopic	Allergen	No	Multiple	Chronic	Debriment, aeration, steroids

Modified from Morpeth et al (1996) [125]

Based on the consensus reached recently by the Sinus and Allergy Health Partnership AFRS is accepted as a distinct subset of CRS [76]. This condition presents a positive evidence of fungal allergy to the fungus colonizing their allergic mucin, being the most common form of fungal RS [76, 125]. The fungi commonly involved in AFRS are the *Bipolaris* species, *Curvularia* species, *Aspergillus* species, *Dreschlera* species, *Alternaria* species, *Mucor* species, *Candida* species, *Sporothrix schenckii,* and *Pseudallescheria boydii* [76, 101].

Demographics and socioeconomics appear to affect the incidence of AFRS. A study carried out by Wise and colleagues [126] found a higher incidence of AFRS in African Americans and individuals with low socioeconomic status. Another study

by Ghegan, Lee and Schlosser [127] also found a higher incidence of AFRS in African Americans, mostly males. That study also found a higher incidence of intracranial and intraorbital extension of AFRS on that ethnical group.

Bony erosion with intracranial and intraorbital extension of AFRS is one important complication of AFRS. It is more frequent in AFRS than in any other type of inflammatory sinusitis combined [126]. Although AFRS may give rise to severe symptoms like bony erosion that may lead to acute visual loss, gross facial dysmorphia or complete nasal obstruction, its clinical presentation is usually subtle [76].

The characteristics commonly found in patients with AFRS include: gross production of mucin, nasal polyposis and allergy to cultured fungi. That allergy seems to be a IgE-mediated mechanism that leads to local eosinophilic chemotaxis, inflammation and tissue injury [76]. The highly viscid fluid mucin encoutered in AFRS is considered its pathognomonic sign; it contains non-invasive fungal hyphae, sheets of eosinophils, and Charcot-Leyden crystals [128].

The symptomatology of AFRS is similar to that found in other types of CRS. For a complete diagnosis one or more of the following should be present: anterior and/or posterior drainage, nasal obstruction, decreased sense of smell, facial pain/pressure [82]. The prognosis of the disease is often good in the short-term;

recurrences should be an expected matter since AFRS is found to be a chronic condition [129].

The treatment of AFRS is mainly focused on FESS in order to provide proper sinonasal ventilation and removal of allergic fungal mucin followed by post-operative immunomodulation with corticosteroids [128]. A study by Landsberg et al [130] found pre-operatory 10-day treatment with corticosteroids to be also effective in the management of AFRS. That drug was successful in controlling the disease and providing a subsequent surgery with a minimally invasive approach. This study also found corticosteroids to be more effective in patients suffering with AFRS than those with non-fungal CRSwNP.

1.5.2.4.8 Computed tomography of sinonasal structures

The surgical treatment of disturbances affecting the nose and paranasal sinuses using an endoscopic technology brought a greater interest to the anatomy and physiology of those structures [17]. RS is an affliction that can be mostly diagnosed clinically, based on symptoms and signs including diagnostic nasal and sinus endoscopy. Current thinking and practice contends that the diagnosis should be made on objective measures such as the aforementioned endoscopic techinique. However; in selected cases where there are complications or recurrence of the disease, a radiological approach gives valuable information that may dramatically change the course of the treatment [76].

Plain radiographs are definitely a less costly imaging option, however images from this older technology enable very little information to draw diagnostic considerations in respect to the sinuses and surrounding structures. The sinonasal anatomy does not appear very clearly in plain films, failing in providing a guide of the paranasal sinus perimeter and extent of inflammatory disease [76]. The appearance of the inferior third of the frontal sinus and the anterior and posterior ethmoid is poor, which is especially true when there is inflammatory disease present creating extra shadowing to the detailed structures of the ostiomeatal chanells [16]. Also, based on the poor resolution of anatomical structures, this modality does not work as a proper assessment of anatomy for aptients undergoing FESS [76].

Besides the cost advantage, plain films carry a less radiation exposure, are easier to perform and happen to be a portable examination. The general practitioner may still order this modality in cases of diagnostic doubt. A positive film for sinusitis may be valuable as a confirmation tool, on the other hand in case the film is negative sinusitis should no be completely refuted. It is recommended nasal endoscopy and CT for further search the source of a puzzling symptomatology [131].

Due to the surgical requirement of a proper anatomical guide, plain radiographs were virtually abandoned to cross-sectional imaging modalities [16]. Computed tomography (CT) imaging appears as an excellent toll to assist the surgeon as a map of the sinonasal anatomical areas [17] and also appears as an objective evidence

for diagnosis and staging of CRS, although it should not be considered in isolation for that purpose [132]. The Task Force for Rhinosinusitis lists two major roles for the use of that technology in RS: 1- to define the anatomy of the sinuses before FESS and 2 - as an aid tool to the diagnoses and treatment or recurrent and/or chronic CRS. This task force actually puts CT scan in the category of an absolute pre-surgical requirement [76].

Magnetic resonance imaging (MRI) is not employed as a routine technique, although it seems a good option, as it would spare the patient from ionizing radiation. CT scanning is primarily chosen because the main goal of radiographic imaging in RS is providing an anatomical mapping of the bony structures for subsequent FESS. Since bone and air are seen as signal voids on MRI scans, this type of imaging doe not provide a reliable source for surgical planning. On the other hand it has a great potential for evaluating complications of RS, such as intraorbital and intracranial pathologies, in those cases MRI imaging enables well depicted [131]. Furthermore MRI is a more expensive and lengthier procedure, and it is not as readily available as CT [76].

Yousem [131] describes a CT technique for uncomplicated sinusitis referred by an ENT specialist. It involves 5mm contiguous coronal sections through the anterior frontal sinuses, 3mm contiguous sections through the ostiomeatal complex, and 5mm thick sections through the sphenoid sinus. The plane used is perpendicular to the hard palate with 120 KvP, 100mA, and 2 second scanning. There is also

specific changes in the study for FESS purposes, in order to enhance the bony anatomy facilitating the visualization for the surgeon. It is used a bone algorithm techinique with very wide window widths (3000 to 4000) and high windows levels (300 to 400), which allows the evaluation of the subtle mucosa thickening while preventing obscuration of the thin bony septae. The disadvantage of this technique is that it diminishes the considerations that can be made to adjacent structures, including brain, meninges, orbits and facial tissues. With the advent of newer generation CT scanners and faster computer processing, the concept of screening or thick/thin/thick cut protocol proposed by Yousem is no longer germane. Most scans nowadays are acquired in the axial plane with 1mm thickness which is easily reformatted to coronal or even sagittal orientations as needed by the radiologist or surgeon. These thin-cut axial scans are also optimized for use in intra-operative surgical navigation.

Several methods were delineated in order to quantify CRS disease severity on CT scan, the CRS staging systems. A literature review compiled by Lund and Kennedy [133] discussed the most recognized staging systems. Those authors discussed the fact that attempts to stage sinonasal disease is never perfect, considering interpretation matters such as the natural absence of the frontal sinus, or difficulties in differentiating between opacification resulting from inspissated mucus and mucosal inflammation. The Lund-Mackay staging system is a simple method, being easy to apply and reproduce, and therefore a trusted tool for validation of outcomes in large clinical studies. It has been actually recommended

by the Task Force for Rhinosinusitis as the system of choice for further outcome research.

The Lund-Mackay system evaluates all groups of sinuses and differentiates the ethmoid sinus in anterior and posterior. The scoring varies from 0 to 24. Each sinus group is graded as 0 for no abnormality, 1 for partial opacification and 2 for total opacification. The ostiomeatal complex is also assessed with a simpler scoring of 0 when not obstructed, or 1 when obstruction is present [133].

Ashraf and Bhattacharyya [134] brought up the fact that incidental abnormalities in sinus CT may bring a Lund-Mackay score greater than zero, which not necessarily reflects a disease state. They conducted a study that ultimately demonstrated that the general population shows some CT evidence of sinusitis and that Lund-Mackay score of 3 or less should be seen as low probability for sinus disease.

That is an important point to be aware when evaluating sinus CT scans, considering that this type of imaging has a high sensitivity in detecting sinus abnormalities. Typically when a diagnostic test exhibits a high sensitivity the chances of false positives have a tendency of increasing. For that reason CT scans are considered to have only moderate specificity in diagnosing CRS, in other words it may give ambiguous information that can only be clarified with appropriate clinical correlation [132]. On the other hand, Jones [17] states in his review of literature in CT of the paranasal sinuses that patients with positive clinical

findings for RS that present negative CT findings should be investigated for an alternative diagnosis.

Several authors have researched the matter of incidental sinonasal findings in CT scans in non-RS populations over the years with mixed results. Havas et al [135] evaluated 666 patients with conditions such as head injuries or seizures, sinonasal incidental findings were found in 42.5% of the sample. Bolger et al [136] assessed thirty-six CT scans of asymptomatic patients and found sinus incidental abnormalities in 41.7% of that sample. Flinn et al [137] evaluated non-sinus related CT scans of 100 patients and found incidental sinus opacification in 26% of the patients. Jones et al [138] assessed 100 CT scans from patients with intra-orbital disease and found incidental sinus mucosal thickening in 17% of the studied subjects. A study by Cha et al [12] searched for incidental findings in CBCT scans ordered for dental purposes and detected airway findings (including sinusitis, retention cysts, polyps, deviated nasal septum and/or large turbinates) in 18.2% of the subjects. Wittkopf et al [139] evaluated 50 CT scans of patients with no sinus symptoms and found incidental sinus abnormalities in 3% of the sample.

The study by Wittkopf et al [139] makes a large discussion about this mixed results in the literature regarding incidental sinonasal findings. The authors claim that the studies with a high rate of incidental findings do not make a distinction of those findings. For example, findings of different clinical importance such as mucosal thickening (more important) and mucus retention cysts (unimportant) are seen at

the same level. That may explain the high rate of false-positive findings on sinus CT of patients who do not meet the diagnostic criteria for sinusitis.

Concha Bullosa (CB) is an often occurring incidental finding related to sinonasal structures. It occurs when the middle turbinate, also known as concha, becomes pneumatized [16]. Prevalence studies regarding the presence of CB in symptomatic groups show large variability, ranging from 22% to 73% [138, 140-146]. The prevalence of CB in asymptomatic groups has been estimated to be of 15.9% by Calhoun et al [147], and 23% by Jones et al [138].

Another important incidental finding is the presence of septal deviation (SD), this abnormality has the potential to lead to unilateral nasal obstruction, which disturbs the patient's normal breathing pattern and may require surgical correction [73]. Prevalence studies in RS populations found septal deviation ranging between 36% [141] to 65% [144]. In asymptomatic groups the prevalence of SD was estimated to be of 19.5 % by Calhoun et al [147], and 24% by Jones et al [138]. A study conducted by Bolger et al [136] found septal deviation in 18.8% of a sample of both symptomatic (n =166) and asymptomatic patients (n = 36).

The presence of mucus retention cysts (RC) deserves a discussion since they often appear in CT scans of the paranasal sinuses. Those cysts usually occur in the maxillary sinus and are usually asymptomatic. However, they may become clinically important if causing obstruction of the sinus outflow tract, when occur

with concomitant CRS, or when the diagnosis is in doubt. A study by Bhattacharyya [148] challenged that line of thinking with his results that determined that RC of the maxillary sinus do not represent obstructive pathology, and are not associated with potentially obstructive sinus variation.

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CHAPTER 2

RESEARCH PROJECT

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2.1 INTRODUCTION

Orofacial pain is prevalent within the general population [1-3]. Diagnosis of orofacial pain is challenging as a result of the numerous anatomical structures involved and psychological importance of this region [4]. The diagnostic capabilities for orofacial pain has recently been expanded with the introduction of Cone Beam Computed Tomography (CBCT)[5]. This technology has been primarily used in dentistry for imaging related to dental implants, maxillofacial surgery, orthodontics and temporomandibular disorders (TMD)[6]. Significant advantages of this technology have included lower costs [7], lower radiation exposure [8-10], and more importantly, equivalent image quality to conventional CT [7, 10-15].

When CBCT scans are acquired for TMD the field of the scan also acquires images of surrounding head and neck structures, which may reveal additional

medical/dental findings that are unrelated to the scans primary diagnostic purpose, resulting in other diagnostic possibilities [16].

A recent study of prevalence of incidental findings with CBCT taken for dental purposes has found incidental findings related to the sinonasal structures in 18.8% of 300 scans [16]. Studies in non-dental asymptomatic populations have shown prevalences ranging from 3% to 42.5% [16-21].

To date there are no studies that have assessed the prevalence and/or clinical significance of incidental sinonasal findings when CBCT scans taken for TMD purposes. This assessment may be of clinical value especially considering that pathologies of the sinonasal structures may be related to facial pain complaints, such as TMD. It may also improve diagnostic evaluation and therefore more accurate treatment planning and/or referral strategies for orofacial pain patients.

This retrospective study aimed to assess the prevalence and potential clinical significance of incidental sinonasal findings on CBCT taken for temporomandibular joint diagnostic purposes. The primary objectives were:

1) Evaluating the prevalence of incidental sinonasal findings in CBCT scans requested for temporomandibular joint diagnostic purposes;
2) Evaluating the potential clinical significance of the incidental sinus findings identified in CBCT scans taken for a TMD population.

The secondary objective of this retrospective study was:

To determine the prevalence of specific sinonasal findings based on their level of clinical significance.

2.2 METHODS AND MATERIALS

The University of Alberta Human Ethics Research Board approved (issue #7263) the study protocol (Appendix 1). The project analyzed CBCT images from 500 consecutive scans taken with the original purpose of TMD diagnosis.

CBCT images were obtained at Edmonton Diagnostic Imaging (EDI) Inc., a private radiology clinic in the city of Edmonton, Alberta, Canada. The sample size was similar to that used by a previous similar study by Cha et al [16]. Since this is a prevalence study it was aimed to include a large sample size in order to represent more effectively the targeted population of patients suffering with TMD, a common condition in the general population [1-3]. The current study included five hundred consecutive scans obtained between years 2005 and 2006. Our sample consisted of males and females over 18 years of age.

CBCT scans were obtained with the Newtom QR 9000® (Quantitative Radiology, Verona, Italy) volume scanner. The slice thickness for primary reconstruction was standardized at 0.3mm and the highest image resolution by this scanner was used (40-second scan: effective radiation dose of 0.17 mSv). The device was operated

at the 110 kV (peak) and mA settings fixed based on the individual subjects body weight. The field of reconstruction enabled visualization of the TMJ, nose, maxillary, ethmoid and sphenoid sinuses. The frontal sinus was not within the scope of visualization for the majority of the scans and not considered in this study. In addition, scans that had a restricted field of view, limiting considerations about nasal structures, maxillary, ethmoid and sphenoid sinuses were not used.

Specific structures were evaluated within each sinus and nasal cavity (table 2.1). The evaluation of the abnormal paranasal and nasal structures included parameters to assess clinical significance. Some of these points were selected based on previous study by Cha et al [16] and combined with other variables based on the clinical expertise of an otolaryngology specialist involved in the study (Erin Wright - EW) (table 2.1).

Table 2.1: Sinonasal findings evaluation

	0 = absent 1 = present	Code for statistical evaluations
NASAL RELATED		
1. Significantly deviated nasal septum		Nasal1
2. Severe and bilateral turbinate hypertrophy		Nasal2
3. Concha bullosa		Nasal3
4. Nasal Polyp		Nasal4
MAXILLARY SINUS		
1. Mucosal Thickening < 3mm		Max1
2. Mucosal Thickening >3mm		Max2
3. Localized mucosal thickening		Max3
4. Diffuse mucosal thickening		Max4
5. Retention Cyst/Polyp		Max5
6. Ostial obstruction		Max6
7. Air/fluid level		Max7
ETHMOID SINUS		
1. Mucosal Thickening		Eth
SPHENOID SINUS		

1. Mucosal Thickening < 3mm		Sph1
2. Mucosal Thickening >3mm		Sph2
3. Localized mucosal thickening		Sph3
4. Diffuse mucosal thickening		Sph4
5. Retention Cyst/Polyp		Sph5
6. Air/fluid level		Sph6
CLINICALLY SIGNIFICANT		ClinSig

Modified from Cha et al [16]

For the nasal structures if none of the parameters listed in table 2.1 were found the images were considered normal. The sinuses were considered normal if fully aerated and the absence of soft-tissue pathology identified.

Visualization of the scans was via NEWTOM® software (KRNNT version 2.04, Italy). The primary orientation used for visualization and evaluation was the coronal plane. Each coronal slice was 1mm thick and 150mm wide. Scrolling through the axial plane was performed in search of positive findings not detected on the main plane.

The primary examiner (Ines Guedes - IG) carried out the evaluation of the CBCT scans subsequent to calibration with EW. The calibration process included understanding and viewing normal radiographic anatomy of the nose and paranasal sinuses, followed by study of abnormal radiographic findings of the same anatomical structures. Thereafter; the incidental sinonasal findings listed in table 2.1 were categorized in accordance to their clinical significance based on EW clinical experience and expertise as a board-certified otolaryngologist (table 2.2).

Table 2.2: Clinical importance of incidental sinonasal findings

Important	Possibly important	Unimportant
Significantly deviated nasal septum	Concha bullosa	Mucosal thickening < 3mm
Severe and bilateral turbinate hypertrophy	Mucosal Thickening > 3mm	Retention cyst/polyp
Nasal Polyp	Diffuse mucosal thickening	-
Maxillary sinus ostial obstruction	Localized mucosal thickening	-
Air/Fluid Level	-	-
Mucosal thickening at the ethmoid sinus	-	-

The term "clinical importance" used in table 2.2 relates to imaging signs of abnormality found in advanced imaging that may positively correlate with symptoms. When a certain disease is been radiographically studied and signs of another condition is incidentally detected a few questions need to be answered: 1 - would these findings correlate with clinical symptoms? ; 2 - if it does correlate with symptoms, would these symptoms impact the symptomatology of the disease that was originally being studied? ; 3 - would it require a referral to another specialty?

Rhinosinusitis is the main condition that may be unveiled by incidental sinonasal findings. Table 2.2 lists several sinus and nasal abnormalities that may be detected through CT imaging. The literature has extensively research many of those in correlation with clinical symptoms, and it has been established that a few typically do not correlate with clinical symptoms. Mucosal thickening smaller that 3mm is

part of the normal clearance of the sinuses; and retention cysts have been disproved as a source of obstruction of the sinus outflow tract [22]. Therefore these two variables were defined as "unimportant" by the categorization proposed on table 2.2.

Mucosal thickening greater than 3mm either diffuse or localized depends on further obstruction of the maxillary ostium to be considered a relevant factor for the presence of symptomatology. Concha bullosa is the pneumatization of the middle turbinate. It has the potential of diminishing the airway passage by narrowing the space between the lateral nasal wall and the septum predisposing to obstruction of the osteomeatal complex (OMC) and subsequent sinus infection, but it only has this potential when the pneumatization is very large [23]. Due to the weak potential to create symptoms these variables were defined as "possibly important" in table 2.2.

The following variables were categorized as "clinically important":

- "Significantly deviated nasal septum": it has the potential to lead to unilateral nasal obstruction, which disturbs the patient's normal breathing pattern and may require surgical correction [23]. In addition, contact points between the nasal septum and lateral nasal wall may serve as a trigger point for headaches akin to Sluder's Neuralgia [24];
- "Severe and bilateral turbinate hypertrophy": it is an inflammation of the nasal turbinates due to non-allergic rhinitis, allergic rhinitis, or rhinitis

medicamentosa. It creates an engorgement of the turbinates increasing upper airway resistance, and consequently symptoms of nasal obstruction. Medical and/or surgical treatment may be required for its management [23];

- "Nasal polyps": pathologic round, smooth, semi-translucent edematous masses that arise from the nasal mucosa, typically along the middle meatus. It is associated with CRS, asthma and other respiratory conditions [25, 26]. Symptomatology includes anterior and/or posterior mucopulurent drainage, nasal obstruction, and decreased sense of smell [27];
- "Maxillary sinus ostial obstruction": This is a critical area in close relation to the ostiomeatal complex (OMC). The OMC is seen as a functional unit; it is from that passage that secretions from the anterior ethmoid, frontal and maxillary sinus are drained [28]. Obstruction of that area relates to the pathogenesis of both acute (ARS) and chronic (CRS) rhinosinusitis. Symptomatology may include facial pain (located mainly on the forehead, cheeks, between the eyes, temples and occipital skull area) [29], as well as anterior and/or posterior mucopulurent drainage, and nasal obstruction [27]. Those symptoms are typically more pronounced in acute forms of RS [27].
- "Air-fluid level": it may occur in acute forms of RS [30]. Symptoms may include anterior and/or posterior mucopulurent drainage, nasal obstruction, and facial pain/pressure/fullness [27].
- "Mucosal thickening of the ethmoid sinus": this sinus is in close anatomic relation to the OMC [23], therefore; it is safe to say that mucosal thickening in

the ethmoid sinus likely leads to OMC blockage, with potential of leading to the symptomatology described for “maxillary sinus ostial obstruction”.

2.2.1 Inter and Intra-rater reliability

Inter and intra-rater reliability tests were performed between IG and EW. The reliability study consisted of evaluating 30 CBCT scans selected by an administrative support staff at EDI. In order to prevent the scans chosen from all being unremarkable for sinonasal findings, the support staff was instructed to randomly choose 20 scans that had previous oral and maxillofacial radiologist report of no sinonasal abnormalities and 10 scans with a report of sinonasal findings.

To determine the extent of which test results from a given subject were stable over time when administered by the same rater [31], an intra-rater study was carried-out for both the primary examiner (IG) and the otolaryngology specialist (EW), based on the assumption that even specialists may have different test scores over time. To establish whether EW and IG could obtain comparable measurements when assessing a given subject [31], an inter-rater study was also performed.

Each examiner scored the same thirty scans independently and blindly three times using the same methodology as established previously. The evaluations were performed with at least a 2-week interval between each other. The second scoring

was chosen to perform the statistical analysis for inter-rater reliability, in which the examiners are probably less biased on the repeatability of their scoring.

Following the inter-rater and intra-rater reliability studies the data was inputted by a dental research assistant (Rae Varughese - RV) into an Excel® file for statistical analysis. The data analysis was performed using the SPSS statistical package system version 17.0 (Chicago, IL). Since scoring was dichotomous (0 = absent and 1 = present) the reliability was measured using 2X2 tables (all 2X2 tables are obtained in appendix 2) and Kappa statistics (κ) as outlined in table 2.3 and table 2.4.

Table 2.3: 2X2 table – Summary of binary ratings by two raters

	Examiner 2 (EW)		
Examiner 1 (IG)	1 = present	0 = absent	Row totals
1 = present	a	b	r_1 = a + b
0 = absent	c	d	r_2 = c + d
Column totals	c_1 = a + c	c_2 = b + d	n = a + b + c + d

Table 2.4: Formulas for calculation of Kappa (κ) statistics

Kappa statistics	$\kappa = \frac{(Po - Pe)}{(1 - Pe)} = \frac{2(ad - bc)}{c_1 r_2 + r_1 c_2}$
Observed probability of concordance between the raters	$Po = \frac{a + d}{n}$
Expected probability of concordance between the two raters	$Pe = \frac{r_1 c_1 + r_2 c_2}{n^2}$

The interpretation of Kappa statistics is made based on the following: Kappa scores $\geq$ 0.75 demonstrate excellent reproducibility; scores < 0.75 but > than 0.40 demonstrate good reproducibility; scores < than 0.40 demonstrate marginal reproducibility.

In the current study there was a higher tendency of scoring 0 (absent), due to dealing with a non-rhinosinusitis (RS) population, in which more cases of incidental sinonasal findings were absent than cases where those variables were present. This shift towards scoring 0 (absent) creates an imbalance in the 2 X 2 tables. Kappa statistics is affected by the low prevalence of the disease studied [32], when that imbalance occurs the calculated Kappa suggests more disagreement between the raters than what actually happened [33]. For these reasons, in addition to Kappa, the index of average positive agreement ($P_{present}$), negative agreement (P_{absent}), and overall agreement ($P_{overall}$), was calculated based on the equations listed on table 2.5 [32, 33].

Table 2.5 Calculation of index of average positive agreement ($P_{present}$), negative agreement (P_{absent}), and overall agreement ($P_{overall}$)

$P_{present}$	$\frac{2a}{2a + b + c}$
P_{absent}	$\frac{2d}{2d + b + c}$
$P_{overall}$	$\frac{a + d}{n}$

The calculations listed in table 2.5 enable the determination of sufficient inter and intra-rater reliability when the Kappa cannot be satisfactorily obtained. Since with the estimation of agreement proportion we are dealing with a calculation of the average of the positive (presence) and negative (absence) responses [33] we can infer that a perfect proportion of agreement would be equal to 1.

Once the reliability of the primary examiner was established 500 consecutive scans were analyzed for sinonasal findings as per table 2.1. No more than 30 scans were evaluated per day in order to avoid examiner fatigue. After each scan was scored a final decision of potential clinical significance was made based on the previous calibration provided by EW (table 2.2). In order to make a clinical significance assumption based on radiographic findings, we determined that only when variables established as important (table 2.2) appeared in the scan, alone or in combination the scan would be scored as clinically significant. The decision of including only the important variables was made with the intention of diminishing the chances of unsuitably scoring a scan as clinically significant. When variables established as possibly important and unimportant (table 2.2) appeared in the scan, alone or in combination within or between these two groups that scan was scored as not clinically significant.

After the evaluation of 500 scans the data was inputted into an Excel® file by a dental research assistant (RG). The data analysis was performed using the SPSS statistical package system version 17.0 (Chicago, IL).

2.3 RESULTS

2.3.1 Intra-reliability

The intra-reliability was assessed for IG is shown in table 2.6.

Table 2.6 Results for Kappa, P yes, P no and P all for IG

T1 = 1st evaluation	T2 = 2nd evaluation		T3 = 3rd evaluation	
Kappa > 0.75 → excelent reproducibility				
	Kappa	P yes	P no	P all
1. Max1T1 X Max1T3	1.000	1.000	1.000	1.000
2. Max2T1XMax2T3	1.000	1.000	1.000	1.000
3. Max3T1 X Max3T3	1.000	1.000	1.000	1.000
4. Max4T1 X Max4T3	1.000	1.000	1.000	1.000
5. Max5T1 X Max5T2	1.000	1.000	1.000	1.000
6. Max5T1 X Max5T3	1.000	1.000	1.000	1.000
7. Max5T2 X Max5T3	1.000	1.000	1.000	1.000
8. Max6T1 X Max6T2	1.000	1.000	1.000	1.000
9. Max6T1 X Max6T3	1.000	1.000	1.000	1.000
10. Max6T2 X Max6T3	1.000	1.000	1.000	1.000
11. EthT1 X EthT2	1.000	1.000	1.000	1.000
12. Sph2T1 X Sph2T2	1.000	1.000	1.000	1.000
13. Sph2T1 X Sph2T3	1.000	1.000	1.000	1.000
14. Sph2T2 X Sph2T3	1.000	1.000	1.000	1.000
15. Sph4T1 X Sph4T2	1.000	1.000	1.000	1.000
16. Sph4T1 X Sph4T3	1.000	1.000	1.000	1.000
17. Sph4T2 X Sph4T3	1.000	1.000	1.000	1.000
18. Sph5T1 X Sph5T2	1.000	1.000	1.000	1.000
19. Sph5T1 X Sph5T3	1.000	1.000	1.000	1.000
20. Sph5T2 X Sph5T3	1.000	1.000	1.000	1.000
21. ClinSigT1 X ClinSigT2	1.000	1.000	1.000	1.000
22. ClinSigT1 X ClinSigT3	1.000	1.000	1.000	1.000
23. ClinSigT2 X ClinSigT3	1.000	1.000	1.000	1.000
24. Max3T1 X Max3T2	.911	.930	.970	.960
25. Max3T2 X Max3T3	.911	.930	.970	.960
26. Max4T1 X Max4T2	.870	.880	.980	.960
27. Max4T2 X Max4T3	.870	.880	.980	.960
28. Nasal3T2 X Nasal3T3	.862	.910	.940	.930
29. Nasal3T1 X Nasal3T3	.856	.900	.940	.930
30. Nasal1T2 X Nasal1T3	.814	.850	.950	.930
31. Max2T2 X Max2T3	.842	.880	.950	.930
32. Max2T2 X Max2T3	.842	.880	.950	.930
33. EthT1 X EthT3	.783	.800	.980	.960
34. EthT1 X EthT2	.783	.800	.980	.960
35. Nasal1T1 X Nasal1T2	.757	.820	.930	.900
0.40 < kappa < 0.75 → good reproducibility				

	Kappa	P yes	P no	P all
1. Nasal3T1 X Nasal3T2	.724	.830	.910	.860
2. Nasal2T1 X Nasal2T3	.672	.720	.930	.900
3. Nasal2T2 X Nasal2T3	.634	.660	.960	.930
4. Max1T1 X Max1T2	.634	.660	.960	.930
5. Max1T2 X Max1T3	.634	.660	.960	.930
6. Nasal1T1 X Nasal1T3	.595	.700	.880	.830
0 < kappa < 0.4 → marginal reproducibility				
	Kappa	P yes	P no	P all
1. Nasal2T1 X Nasal2T2	.380	.440	.900	.830
Kappa is undefined (κ = 0/0)				
	Kappa	P yes	P no	P all
1. Nasal4T1 X Nasal4T2	-	.000	1.000	1.000
2. Nasal4T1 X Nasal4T3	-	.000	1.000	1.000
3. Nasal4T2 X Nasal4T3	-	.000	1.000	1.000
4. Max7T1 X Max7T2	-	.000	1.000	1.000
5. Max7T1 X Max7T3	-	.000	1.000	1.000
6. Max7T2 X Max7T3	-	.000	1.000	1.000
7. Sph3T1 X Sph3T2	-	.000	1.000	1.000
8. Sph3T1 X Sph3T3	-	.000	1.000	1.000
9. Sph3T2 X Sph3T3	-	.000	1.000	1.000
10. Sph6T1 X Sph6T2	-	.000	1.000	1.000
11. Sph6T1 X Sph6T3	-	.000	1.000	1.000
12. Sph6T2 X Sph6T3	-	.000	1.000	1.000

The majority of the evaluations demonstrate excellent to good reproducibility of IG. Note that in a few cases the variables studied (table 2.1) were scored as absent in all scans in the 2 evaluation times selected. Although there was no intra-rater disagreement in these cases, the Kappa value was undefined (0/0) and the $P_{present}$ index equal to zero. In these situations the scores of $P_{overall}$ and P_{absent} of 1.000 can be used to determine sufficient intra-rater agreement.

A marginal reproducibility is seen for the variable “severe and bilateral turbinate hypertrophy” (Nasal 2) during T1 and T2. This result had in fact a inferior performance, however; it could have also been affected by the large imbalance towards the absence of the variable studied, as it is seen a reasonably high overall

agreement ($P_{overall}$) and a much smaller value of Kappa. The poor reproducibility seen in this case may also be credited to the fact that the nature of this variable may not enable a clear interpretation.

The intra-reliability was assessed for EW and shown in table 2.7.

Table 2.7 Results for Kappa, P yes, P no and P all for EW

T1 = 1st evaluation	T2 = 2nd evaluation		T3 = 3rd evaluation	
Kappa > 0.75 → excelent reproducibility				
	Kappa	P yes	P no	P all
1. Max4T1 X Max4T2	1.000	1.000	1.000	1.000
2. Max4T1 X Max4T3	1.000	1.000	1.000	1.000
3. Max4T2 X Max4T3	1.000	1.000	1.000	1.000
4. Max7T2 X Max7T3	1.000	1.000	1.000	1.000
5. Sph2T1 X Sph2T3	1.000	1.000	1.000	1.000
6. Sph5T2 X Sph5T3	1.000	1.000	1.000	1.000
7. Sph6T2 X Sph6T3	1.000	1.000	1.000	1.000
8. Max2T1 X Max2T2	.902	.923	.978	.966
9. Max5T1 X Max5T2	.831	.875	.954	.933
10. Nasal1T1 X Nasal1T3	.830	.875	.954	.933
11. Max5T1 X Max5T3	.814	.857	.956	.933
12. Nasal3T2 X Nasal3T3	.783	.857	.923	.900
13. EthT1 X EthT3	.760	.800	.960	.933
14. EthT2 X EthT3	.760	.800	.960	.933
0.40 < kappa < 0.75 → good reproducibility				
	Kappa	P yes	P no	P all
1.Max3T2 X Max3T3	.444	.545	.897	.833
2. Max3T1 X Max3T2	.455	.571	.869	.800
3. Nasal2T1 X Nasal2T2	.455	.571	.869	.800
4. Sph4T1 X Sph4T2	.464	.500	.964	.933
5. Nasal2T2 X Nasal2T3	.492	.625	.863	.800
6. EthT1 X EthT2	.520	.600	.920	.866
7. Max2T1 X Max2T3	.535	.600	.920	.866
8. Nasal3T1 X Nasal3T2	.545	.666	.857	.800
9. Max6T2 X Max6T3	.561	.666	.888	.833
10. Max6T1 X Max6T3	.583	.666	.916	.866
11. Nasal2T1 X Nasal2T3	.586	.666	.916	.866
12. ClinSigT1 X ClinSigT2	.595	.705	.883	.833
13. Max2T2 X Max2T3	.615	.666	.941	.900
14. Max5T2 X Max5T3	.661	.750	.909	.866
15. Sph2T1 X Sph2T2	.651	.666	.980	.966
16. Sph2T2 X Sph2T3	.651	.666	.980	.966
17. Sph3T2 X Sph3T3	.651	.666	.980	.966
18. Sph4T1 X Sph4T3	.651	.666	.980	.966

19. Sph4T2 X Sph4T3	.651	.666	.980	.966
20. Nasal1T1 X Nasal1T2	.734	.800	.933	.900
21. Nasal1T2 X Nasal1T3	.734	.800	.933	.900
22. Nasal3T1 X Nasal3T3	.737	.800	.933	.900
23. Max6T1 X Max6T2	.734	.800	.933	.900
0 < kappa < 0.4 → marginal reproducibility				
	Kappa	P yes	P no	P all
1. Max1T2 X Max1T3	.103	.222	.862	.766
2. Max1T1 X Max1T3	.167	.333	.833	.733
3. ClinSigT1 X ClinSigT3	.282	.500	.750	.666
4. Max1T1 X Max1T2	.359	.444	.901	.833
5. ClinSigT2 X ClinSigT3	.372	.608	.756	.700
6. Max3T1 X Max3T3	.386	.533	.844	.766
Kappa = 0				
	Kappa	P yes	P no	P all
1. Max7T1 X Max7T2	.000	.000	.983	.966
2. Max7T1 X Max7T3	.000	.000	.983	.966
3. Sph1T1 X Sph1T2	.000	.000	.947	.900
4. Sph1T2 X Sph1T3	.000	.000	.947	.900
5. Sph3T1 X Sph3T2	.000	.000	.965	.933
6. Sph3T1 X Sph3T3	.000	.000	.983	.966
7. Sph5T1 X Sph5T2	.000	.000	.983	.966
8. Sph5T1 X Sph5T3	.000	.000	.983	.966
9. Sph6T1 X Sph6T2	.000	.000	.983	.966
10.Sph6T1 X Sph6T3	.000	.000	.983	.966
Kappa is undefined ($\kappa = 0/0$)				
	Kappa	P yes	P no	P all
1. Nasal4T1 X Nasal4T2	-	.000	1.000	1.000
2. Nasal4T1 X Nasal4T3	-	.000	1.000	1.000
3. Nasal4T2 X Nasal4T3	-	.000	1.000	1.000
4. Sph1T1 X Sph1T3	-	.000	1.000	1.000

The majority of the evaluations demonstrate excellent to good reproducibility for EW. In some scans Kappa was scored as undefined and as equal to zero. Kappa result equal to zero occurs when the examiner scores "absent" in a large number of scans (≥ 90%) in agreement, however in all the few cases were "present" was scored there was disagreement. When that occur a high $P_{overall}$ and P_{absent} is seen (≥ .900), however Kappa and $P_{present}$ is equal to zero. In these situations the high scores of $P_{overall}$ and P_{absent} can be used to determine sufficient intra-rater agreement.

The low value of Kappa led to a marginal reproducibility interpretation of the evaluation of the variables "maxillary sinus - mucosal thickening < 3mm" (max 1), "maxillary sinus – localized mucosal thickening" (max 3) and "clinical significance" (ClinSig) in the evaluation times listed in table 2.7. As explained in the previous table, this poor performance may have been impacted by the large imbalance towards the absence of the variable studied. Another factor to be accounted is the gap between the evaluation T1 and T2 by E.W of approximately 2 months.

The reproducibility of the variable "maxillary sinus - mucosal thickening < 3mm" (max 1) demonstrates an especially poorer performance when compared to the remaining. In addition to the reasons mentioned above, the poor reproducibility seen in this case may also be credited to the fact that the nature of this variable may not enable a clear interpretation by the examiner.

2.3.2 Inter-reliability

The assessment of the inter-reliability between IG and EW during their second evaluation time (T2) was assessed as follows in table 2.8.

Table 2.8 Results for Kappa, P yes, P no and P all for inter-reliability assessment between IG and EW at T2.

	T2 = 2nd evaluation			
Kappa > 0.75 → excelent reproducibility				
	Kappa	P yes	P no	P all
1. Sphe5T2 X 5WT2	1.000	1.000	1.000	1.000
2. Max4T2 X 4WT2	.870	.888	.980	.960

3. Nasal1T2 X Nasal1WT2	.814	.857	.956	.930
4. Max5T2 X 5WT2	.754	.823	.930	.900
0.40 < kappa < 0.75 → good reproducibility				
	Kappa	P yes	P no	P all
1. Sph4T2 X4WT2	.464	.500	.964	.933
2. EthT2 X WT2	.526	.571	.943	.900
3. Max6T2 X 6WT2	.528	.615	.893	.833
4. ClinSigIT2 X WT2	.571	.666	.888	.833
5. Max3T2 X 3WT2	.586	.666	.916	.866
6. Sphen2T2 X 2WT2	.651	.666	.982	.966
7. Nasal3T2 X Nasal3WT2	.658	.800	.857	.833
8. Max2T2 X 2WT2	.667	.750	.909	.866
0 < kappa < 0.4 → marginal reproducibility				
	Kappa	P yes	P no	P all
1. Nasal2T2 X Nasal2WT2	.286	.363	.857	.766
2. Max1T2 X 1WT2	-.087	0.000	.900	.833
Kappa = 0				
	Kappa	P yes	P no	P all
1. Max7T2 X 7WT2	.000	.000	.980	.966
2. Sphen1T2 X 1WT2	.000	.000	.947	.900
3. Sphen3T2 X 3WT2	.000	.000	.965	.933
4. Sphen6T2 X 6WT2	.000	.000	.983	.966
Kappa is undefined ($\kappa = 0/0$)				
1. Nasal4T2 X 4WT2	-	.000	1.000	1.000

The majority of the evaluations demonstrate excellent to good reproducibility of scores between IG and EW. Again note that Kappa was scored as undefined and as equal to zero for the reasons thoroughly explained in the previous tables. In these situations the high scores of $P_{overall}$ and P_{absent} can be used to determine sufficient inter-rater agreement.

The low value of Kappa led to a marginal reproducibility interpretation of the evaluation of the variables “severe and bilateral turbinate hypertrophy” (nasal 2) and “mucosal thickening < 3mm” (max1) between the two raters. Interestingly, poor intra-rater reproducibility was identified for “nasal 2” by IG, and for “max 1” by EW. These marginal results for “nasal 2” may be credited to the fact that

"severe" enables a range of interpretation, with unclear boundaries when the changes are not gross. For "max 1", on the other hand, the poor reproducibility may be related to the difficulty to visualize minimal changes of very few millimeters. With that said, it is possible to argue that these variables do not demonstrate sufficient potential of reproducibility and perhaps should be eliminated from the guidelines proposed in this study.

2.3.3 Main study

The main study consisted in the evaluation of 500 consecutive CBCT scans for sinonasal incidental findings. Scans were taken for TMD diagnosis and the sample consisted of male and female patients over 18 years of age.

From the 500 scans studied 396 (79.2%) were female and 104 (20.8%) male. The mean age was 37.4 years. The mean age of the female and male population was 37.7 years and 35.9 respectively (table 2.9).

Table 2.9: Age and gender

Total = 500 subjects	Female	Male
Gender	396 subjects (79.2%)	104 subjects (20.8%)
Age (total mean = 37.36 years)	37.73 years (18 years – 79 years)	35.94 years (18 years – 70 years)

Sixteen percent (80 scans) of the 500 scans studied were unremarkable, i.e. completely aerated with no findings. Therefore, 84.0% of the sample showed at least one incidental sinonasal finding (table 2.10). The largest number of incidental findings was detected in relation to the maxillary sinus (61.0% - 305/500 scans), followed by the nasal region (59.6% - 298/500 scans), then the sphenoid sinus (14.0% - 70/500 scans) and finally the ethmoid sinus (11.6% - 58/500 scans) (table 2.10).

Table 2.10: Frequency of incidental sinonasal findings

	Absent	Present
At least 1 incidental sinonasal finding	16%	84%
Maxillary Sinus	39%	61%
Nasal Region	40.4%	59.6%
Esphenoid Sinus	86.0%	14%
Ethmoid Sinus	88.4%	11.6%

Based on the clinical importance of the incidental sinonasal findings detected, it was possible to determine the frequency of clinically important, possibly important and unimportant variables as per in table 2.11, 12 and 13. Among the clinically important incidental sinonasal findings the most prevalent variable was a significantly deviated septum, identified on 16% of the 500 scans; followed by ostial obstruction of the maxillary sinuses (15.8%), severe and bilateral turbinate

hypertrophy (14.2%), mucosal thickening of the ethmoid sinus (11.6%), air/fluid level of the maxillary sinus (5.0%), air/fluid level of the sphenoid sinus (1.4%) and finally nasal polyps (0.8%), which appeared as the least frequent (table 2.11) of all variables evaluated in our study.

Table 2.11: Frequency of clinically important variables

	Absent	Present
Significantly deviated nasal septum	84.0%	16.0%
Maxillary Sinus – ostial Obstruction	84.2%	15.8%
Severe and bilateral turbinate hypertrophy	85.8%	14.2%
Ethmoid sinus – mucosal thickening	88.4%	11.6%
Maxillary Sinus – air/fluid level	95.0%	5.0%
Sphenoid Sinus – air/fluid level	98.6%	1.4%
Nasal Polyp	99.2%	0.8%

The assessment of possibly clinically significant incidental sinonasal findings demonstrated the concha bullosa as the most frequent finding (46%), not only in this group but also of all the variables studied in the 3 groups (table 2.12). The variables related to the maxillary sinus also showed frequencies in the higher end in comparison to the remaining findings assessed. Mucosal thickening greater than 3mm located in the maxillary sinus was present in 35.4% of the scans studied, followed by diffuse mucosal thickening of the maxillary sinus (32.2%) and localized mucosal thickening of the maxillary sinus (20.4%) (table 2.12). The

findings encountered in relation to the sphenoid sinus demonstrated lower frequency. Localized mucosal thickening was the most frequent finding with the sphenoid sinus (6.4%), followed by diffuse mucosal thickening (6.2%) and mucosal thickening greater than 3mm (5.8%) (table 2.12).

Table 2.12: Frequency of possibly clinically important variables

	Absent	Present
Concha bullosa	54.0%	46.0%
Maxillary sinus – mucosal thickening > 3mm	64.6%	35.4%
Maxillary sinus – diffuse mucosal thickening	67.8%	32.2%
Maxillary sinus – localized mucosal thickening	79.6%	20.4%
Sphenoid sinus – localized mucosal thickening	93.6%	6.4%
Sphenoid sinus – diffuse mucosal thickening	93.8%	6.2%
Sphenoid sinus – mucosal thickening > 3mm	94.2%	5.8%

The study of the incidental findings of no clinical importance found retention cysts of the maxillary sinus as the most frequent variable of this group (21.8% of the 500 scans), followed by mucosal thickening of the maxillary sinus smaller than 3mm (17.4%), mucosal thickening of the sphenoid sinus smaller than 3mm (6.8%) and retention cysts located in the sphenoid sinus (1.6%) (Table 2.13).

Table 2.13: Frequency of clinically unimportant variables

	Absent	Present
Maxillary Sinus – retention cyst	78.2%	21.8%
Maxillary Sinus – mucosal thickening < 3mm	82.6%	17.4%
Sphenoid sinus – mucosal thickening < 3mm	93.2%	6.8%
Sphenoid sinus – Retention cyst	98.4%	1.6%

During each examination, based on the variables previously established with table 2.2 it was determined whether the evaluated scan was potentially clinically significant for incidental sinonasal findings. It was determined that 24.2% of the total of 500 scans studied presented clinically significant sinonasal findings. It was also possible to infer that in the scans that presented at least one incidental finding (420 scans or 84% of the total studied sample) 28.8% presented findings of potential sinonasal clinical significance.

2.4 Discussion

The matter of incidental sinonasal findings encountered in computed tomography for non-RS purposes has been researched through the years. Previous prevalence estimations of this type of incidental findings in random populations range from 3% [21] to 42.5% [17]. The wide prevalence variability of incidental sinonasal findings in CT scans taken for non-RS purposes encountered in the current literature can be credited to poor categorization for clinical significance potential.

Bhattacharyya and Fried [34] investigated the accuracy of CT scanning in CRS diagnosis, particularly regarding the possible varying degrees of positivity with this type of advanced imaging. They claim that this imaging modality exhibits a high sensitivity, which however increases the chances of false-positives during their interpretation. These authors have found the specificity of CT in diagnosing RS to be of only 46%. For these reasons the authors suggest that CT may add to the diagnostic accuracy of CRS, but only when correlated to clinical findings.

The scans evaluated in the present study belonged to patients that were referred for advanced imaging (CBCT) for TMD diagnosis purposes. That means that the studied sample is made of subjects that may be suffering of pain affecting their facial region since that is one of the main symptoms related to TMD. Therefore, this sample has a common characteristic of a TMD background that is not representative of the general or an asymptomatic population.

Reconstructed images from CBCT technology are of equivalent diagnostic quality when compared with conventional CT [7, 10-15]. A study by Zoumalan et al [35] has suggested that images acquired by CBCT scans provide useful radiological documentation of CRS, adding quality information for diagnosis and treatment of that condition in addition to clinical impressions gained from nasal endoscopy.

In daily TMD clinical practice is possible to note a considerable prevalence of incidental sinonasal findings in CBCT scans that have been ordered for TMD diagnostic purposes. The clinical question was whether the prevalence of those findings would be any different from those found in the general population. It can be judged that there would be a potential of that prevalence being higher, considering that in both TMD and RS a complaint of facial pain may be involved. There is a theoretical possibility that a selected number of patients seeking for TMD treatment due to their facial pain complaints could be actually suffering from RS issues instead or in combination to their TMD problems.

Uncovering clinically significant CBCT sinonasal findings in a TMD population and associating it with clinical complains would warrant an appropriate referral to an otolaryngologist to further query the necessity of management. Providing an appropriate specialist referral enhances the quality of treatment that we offer as health care providers and ultimately enables the patient to have their pain complaints addressed through well-targeted treatment plans.

The present study retrospectively evaluated 500 scans, searching for sinonasal variables as outlined in table 2.1. The comprehensive evaluation of those scans enabled a well discriminated estimation of each finding, which consequently separated clinically important variables from those that were of low or no clinical importance.

It was decided aganist using CRS staging systems such as the Lund-McKay [36]. The current study considers that these systems are designed for outcome assessment in clinical trials, and not exactly to assess diagnostic potential. It lacks a discriminated assessment of items such air/fluid level present within sinonasal cavities, as well as issues related to the nasal structures, including presence of deviated nasal septum, turbinate hypertrophy, concha bullosa (CB) or nasal polyps (NPs). It is critical the assessment of those variables in order to determine the RS diagnostic potential as per the most recent guidelines from the Task Force for Rhinosinusitis (TFR) [37].

The present study consisted of 79.2% of females and 20.8% of male subjects with a mean age of 37.36 years. The mean age of the gender subgroups was proportional (females = 37.73 years and males = 35.94 years). The high female count is consistent with previous TMD epidemiologic studies. LeResche [38] conducted a literature review in the epidemiology of TMD and encountered the prevalence of that disease to be 1.4 to 2.6 times higher in females. The mean age of our sample is also consistent with the literature review compiled by LeResche [38] that concluded that TMD is most prevalent in young and middle-aged adults.

From the population of TMD patients studied, 84% presented at least one incidental sinonasal finding, of clinical significance or not. The remaining 16% presented unremarkable CBCT scans for their sinonasal structures. Those results are much higher when compared with similar previous studies with samples of

asymptomatic adults [16-21]. This increased percentage of incidental findings in the present study may be linked to the following factors: all incidental findings related to the sinonasal structures were accounted in this preliminary assessment, either of clinical significance or not; it was included the evaluation of abnormalities related to the nasal passages, which has not been done in most assessments of incidental findings of the paranasal sinuses; there is a possibility that a percentage of patients seeking TMD treatment due to their facial pain complaints could be actually suffering from RS issues instead or in combination to their TMD problems.

It was found that the sinonasal area most often affected is the maxillary sinus - 61% of the 500 scans studied (table 2.10). Followed by the nasal region (59.6%), sphenoid sinus (14%) and ethmoid sinus (11.6%). These results are in partial agreement with a previous studies with asymptomatic groups [18, 21, 39]. This may be due to the fact that the maxillary sinus is the largest of all sinuses, which allows for improved visualization. Another possibility is that retention cysts, a frequent incidental finding, are most often found in the maxillary sinuses [22].

The frequency of clinically important variables showed the presence of significantly deviated nasal septum as the most prevalent issue, being present in 16% of the subjects studied. Followed by ostial obstruction of the maxillary sinus (15.8%); severe and bilateral turbinate hypertrophy (14.2%); mucosal thickening

related with the ethmoid sinus (11.6%); air fluid level related with the maxillary sinus (5.0%) and the sphenoid sinus (1.4%); and nasal polyps (0.8%).

The percentage of septal deviation detected by the current study was slightly lower than that detected for asymptomatic groups by Calhoun et al (19.5 %) [39], and by Jones et al (24%) [20]. However; it was quite different from other previous studies in RS populations that found septal deviation ranging between 36% [40] to 65% [41]. This difference can be primarily credited to the fact that those studies investigated patients suffering with RS, but it can also relate to the difficulty of standardizing what is considered a significantly deviated nasal septum, since minor and major deviations of the nasal septum may be considered at the same level. In the current study we only selected severe deviation of the nasal septum as clinically significant, in order to diminish the possibility of false-positives.

The obstruction of the maxillary sinus ostium was seen in 15.8% of the studied scans. Since this structure is in close relation to the anterior ethmoid cells and their ostia, the ethmoid infundibulum, the hiatus semilunaris and the middle meatus, its blockage can be extrapolated into the consequent obstruction of the ostiomeatal complex (OMC). The OMC is seen as a functional unit; it is from that passage that secretions from the anterior ethmoid, frontal and maxillary sinus are drained [28]. Considering that is a critical area, Yousem et al [42] estimated the predictive value of CT infundibular opacification for the presence of maxillary RS to be of as high as 78%.

For the reasons described above, ostial obstruction of the maxillary sinus is very possibly the most clinically relevant incidental finding among those listed in table 2.2, because it represents a variable with a significant relationship with the pathogenesis of RS and consequently the presence of clinical symptoms. A CT evaluation conducted by Calhoun et al [39] found OMC disease in 37% of 100 sinus patients and in 8.5% of 82 asymptomatic patients; the prevalence of maxillary sinus ostium obstruction (15.8%) found by the present study was almost twice as high than what was found for this asymptomatic group, however considerably lower than what was detected for the RS group.

Severe and bilateral turbinate hypertrophy was present in 14.2% of the studied sample. This finding positively correlates with inflammation of the underlying mucosa of the nose leading to turbinate enlargement, usually caused by acute rhinosinusitis (ARS), non-allergic rhinitis, and rhinitis medicamentosa. The engorgement of this structure increases upper airway resistance, which triggers symptoms of nasal obstruction [23].

Mucosal thickening related to the ethmoid sinus was found in 11.6% of the studied sample. The ethmoid sinus is considered the central structure of the nose, it has a complex anatomy and it is often called as "the labyrinth" [23, 28]. Mucosal thickening of this sinus frequently occurs in combination with inflammation of other sinuses [29]. Disease within the ethmoid sinus generates a higher clinical

concern likely due to its close relation with the OMC. A CT evaluation conducted by Calhoun et al [39] found ethmoid disease in 34% of 100 sinus patients and in 4.9% of 82 asymptomatic patients; the prevalence of ethmoid sinus mucosal thickening found by the present study was almost twice as high than what was found for this asymptomatic group, however considerably lower than what was detected for the RS group.

The percentage of air/fluid related to the maxillary and sphenoid sinus was of 5.0% and 1.4% respectively. Air/fluid level within sinus cavities is a feature of acute rhinosinusitis and the common cold, where air and fluid can be propeled into the sinuses due to the pressure created by nose blowing [30]. A study conducted by Puhakka et al [43] with patients suffering with common cold also found air/fluid level to be a frequent CT finding.

The least frequent clinically significant sinonasal finding was the presence of NP (0.8%). It is estimated that approximately 1-4% of the general population is affected by chronic rhinosinusitis with nasal polyps (CRSwNP) [26]. NP refers to a multifactorial condition characterized by the presence of edematous masses in the nasal cavity and sinus that usually lead to post-nasal drainage, loss of smell and obstruction of the nasal passages [23].

The lower prevalence found for NPs in the current study is related to nasal endoscopy being the instrument of choice to investigate these structures. CT

technology may not differentiate between non-polyp edema, polyps and secretion. Lobulated abnormal structures seen in the nasal passages may either be mucosal hypertrophy or NPs in CT images and therefore this modality does not allow the appropriate diagnose of NPs [44].

Among the possibly significant variables investigated the presence of concha bullosa (CB) was the most often detected (46%) and interestingly was the most frequent of all the variables evaluated in the current study. CB is considered one of the most common anatomical variation in sinonasal anatomy [45] and more prevalent in RS-symptomatic groups [39].

CB occurs when ethmoid air cells grow larger than normal pneumatizing the middle turbinate, also known as concha [46]. When a large aeration of that area occurs it has a potential of diminishing the airway passage between the lateral nasal wall and the septum leading to nasal obstruction, which may ultimately predispose the obstruction of the OMC and subsequent sinus infection [23]. For that reason, the assessment of CB's clinical significance depends more on its size than merely its presence. Those variations should, however, always be reported because they help in functional endoscopic sinus surgery (FESS) guidance [47].

Prevalence studies regarding the presence of CB in symptomatic groups show large variability, ranging from 22% to 73% [20, 40-42, 48-51]. The prevalence of CB in asymptomatic groups has been estimated to be of 15.9% by Calhoun et al [39], and

23% by Jones et al [20].The percentage detected in the current study falls into the range for symptomatic groups, and considerably higher than previous estimations for asymptomatic groups. This can be credited to the fact that CB has different levels of severity, which may have differed among the above-mentioned studies creating this large prevalence variability.

The prevalence of the other possibly significant variables studied included mucosal thickening of more than 3mm (35%), diffuse (32.2%) and localized (20.4%) mucosal thickening related to the maxillary sinuses. As well as the prevalence of mucosal thickening of more than 3mm (5.8%), diffuse (6.2%) and localized (6.4%) mucosal thickening related to the maxillary sinuses. These variables were considered of possible clinical significance because as long as those findings are not related with clinically significant variables there is a smaller likelihood that the evaluated images would correlate with clinical symptoms of RS. The Task force for Rhinosinusitis [27] lists nasal obstruction and mucupurulent drainage as the most common symptoms expected to be found in all forms of RS, which is consistent with previous studies [52-54]. Based on this information it is possible to infer that when causative factors for nasal obstruction such as septal deviation, OMC obstruction, severe and bilateral turbinate hypertrophy and nasal polyps are not present the chances of a clinically significant scan are unlikely.

The prevalence of clinically unimportant variables included the presence of retention cysts in the maxillary sinus (21.8%) and sphenoid sinus (1.6%); as well

as the presence of mucosal thickening smaller than 3mm within the maxillary sinus (17.4%) and the sphenoid sinus (1.6%). Mucosal thickening smaller than 3mm is considered in our study a result of the normal, physiological mucociliary clearance of the sinuses, thus a finding of no clinical implication.

The presence of retention cysts has been found to be a non-clinically relevant factor in obstruction of the OMC, and therefore should not be taken as suggestive of sinus disease in CT imaging of the maxillary sinuses [22]. In the current study we extrapolated this recommendation to retention cysts found in relation to the sphenoid sinus, since there is a lack of research on this specific sinus structure.

The results acquired by the present study revealed the prevalence of sinonasal clinically relevant findings in a TMD/OFP pain population to be of 24.2%. That implies that almost one in four patients that present to a TMD/OFP pain clinic may potentially require an otolaryngology referral. This is a relevant number given that it is not usual to consider sinonasal variables in relation to a TMD/OFP pain population. It can also be taken into consideration that an otolaryngology referral is an infrequent choice in TMD/OFP practice, where it is more common to involve disciplines such as neurology, psychology and sleep medicine.

The prevalence estimation of clinically relevant variables found by the current study was smaller than those found for asymptomatic patients by Havas et al (42.5%) [17] and Bolger et al (41.7%) [18], however in these studies there was no

clinical significance differentiation of the variables researched. Jones et al [20], conducted a more detailed assessment with focus on involvement of the ethmoid sinus, which may correlate better with the presence of clinical symptoms. They detected incidental sinus findings in 13% of 100 asymptomatic patients; nasal variables were not included in this estimation. This prevalence is nearly half of what was detected by the current study (24.2%), but because the authors did not include nasal variables it is not possible to properly use their estimation for a direct comparison.

Cha et al [16] also conducted a more detailed assessment of airway related incidental findings in a dental population, including evaluation of septal deviation, turbinate hypertrophy, and presence of retention cysts/polyps, however abnormalities in the sinuses were only described as "sinusitis" with no discrimination of amount of mucosal thickening or OMC blockage. The authors detected airway findings in 18.8% of the dental patients studied (n = 500). The categorization of airway findings was described only for the orthodontic subset (n = 252) where relevant clinical abnormalities, such as large turbinate (0.4%) and septal deviation (0.4%) were found in a very small proportion.

Using detailed assessment and well-established guidelines for evaluation of the sinonasal structures, the present study has strengthened previous parameters used to evaluate incidental sinonasal findings in CT scanning ordered for non-RS purposes. As a result, the assessment guidelines proposed by the current

methodology should allow for better prediction of the clinical meaning of CT incidental sinonasal abnormalities by non-sinus specialists for research or clinical purposes.

The assessment guidelines proposed and the prevalence of incidental CBCT sinonasal findings in a TMD population revealed by the present research improve clinical judgment, considering non-TMD related factors that may directly or indirectly affect the patient's facial pain symptoms and overall quality of life. Improved diagnosis leads to a more appropriate treatment planning and hence better care for the patient.

2.5 Conclusion

The following conclusions are based on the results of this retrospective study:

- The prevalence of incidental sinonasal findings in CBCT imaging of the temporomandibular joint detected (84%) was considerably higher than prevalence estimations made by previous random populations studies.
- The prevalence estimation of clinically important incidental findings (24.2%) appears as a relevant number, as this proportion correlates with a group attending a TMD/Orofacial Pain Clinic that potentially requires an otolaryngology referral to further query the necessity of treatment. That is particularly important considering that otolaryngology referral is not typical in a TMD/Orofacial Pain practice.

- The prevalence of clinically significant incidental sinonasal findings found cannot be reasonably compared with previous studies since our parameters of assessment were more stringent than those used in previous similar evaluations.
- The guidelines for assessment of incidental CT findings proposed by the current study need further prospective clinical validation, which may subsequently allow for a more appropriate clinical significance prediction of CT incidental sinonasal abnormalities by non-sinus specialists.

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CHAPTER 3

GENERAL DISCUSSION AND RECOMMENDATIONS

CHAPTER 3

GENERAL DISCUSSION AND RECOMMENDATIONS

3.1 GENERAL OVERVIEW OF THE STUDY AND CLINICAL IMPLICATIONS

Orofacial pain is prevalent health concern among the general population and its diagnosis can be particularly challenging task as a result of the numerous anatomical structures involved. Diagnosis and treatment may overlap many health specialties [1]. The American Association of Orofacial pain recognizes many sources that can be involved in the occurrence of orofacial pain symptoms, including otolaryngology [2].

The diagnosis of inflammatory disease affecting the sinonasal complex (RS) can be difficult. It requires a comprehensive clinical evaluation, including careful search for etiologic factors and underlying conditions, as well as the use of radiographic modalities. [3].

When CBCT scans are acquired for the temporomandibular joints (TMJ) the field of the scan also acquires images of surrounding head and neck structures and in some cases there are additional medical/dental findings that are found and unrelated to the scans primary purpose that may result in other diagnostic possibilities [4]. For that reason incidental sinonasal findings in those images are

particularly challenging, since they often cannot be interpreted in the context of clinical variables [3, 5].

The matter of incidental sinonasal findings encountered in computed tomography for non-RS purposes presents a wide prevalence variability [6,7], probably due to poor categorization for clinical significance potential. It has also been determined that the CT technology exhibits a high sensitivity in the detection of sinonasal abnormalities, which however increases the chances of false-positives during their interpretation. Therefore, CT may add to the diagnostic accuracy of chronic rhinosinusitis (CRS), but only when correlated to clinical findings [8].

Reconstructed images from CBCT technology are of equivalent diagnostic quality when compared with conventional CT [9-15]. It has been suggested that images acquired by CBCT scans provide useful radiological documentation of RS, adding quality information for diagnosis and treatment of that condition in addition to clinical impressions gained from nasal endoscopy [16].

The presence of incidental sinonasal findings in CBCT scans when they have been ordered for TMD diagnostic purposes is not atypical. Whether the prevalence of those findings is any different from those found in the general population was this current study clinical question, taking into consideration there is a potential of that prevalence being higher with both TMD and RS having facial pain as a symptom. In theory, patients seeking TMD treatment for facial pain may

be experiencing RS issues instead or in combination to their TMD problems. Uncovering clinically significant CBCT sinonasal findings in a TMD population and associating it with clinical complains would warrant an appropriate referral to an otolaryngologist to further query the necessity of management.

In this retrospective study we evaluated the prevalence of incidental sinonasal findings in CBCT scans requested for TMJ diagnostic purposes. We also performed an assessment of the potential clinical significance of the incidental sinus findings identified in CBCT scans taken for a TMD population. Our studied sample was made of subjects that may be suffering pain affecting their facial region, since this is one of the symptoms related to TMD. Our study comprehensively evaluated 500 scans, searching for sinonasal variables in a well discriminated fashion, separating clinically important variables from those that were of low or no clinical importance.

Our results uncovered a high prevalence of incidental sinonasal findings in CBCT imaging requested for TMD diagnostic reasons (84%). The prevalence of clinically important subset (24.2%) also appeared as a relevant number, as this proportion correlates with a group attending a TMD/Orofacial Pain Clinic that potentially requires an otolaryngology referral. This is especially important since otolaryngology referral is not typical in a TMD/Orofacial Pain practice. Our study also proposed a valuable set of guidelines in the clinical significance assessment

of incidental CT findings, which enables a future better prediction of the clinical significance of CT incidental sinonasal abnormalities by non-sinus specialists.

3.2 LIMITATIONS AND RECOMMENDATIONS FOR FUTURE STUDIES

Retrospective evaluations can have intrinsic weaknesses and our methodology was limited due to lack of direct correlation between CT findings and patient reported symptoms. For this reason our investigation could not determine the percentage of the clinically significant CT findings detected that would actually correlate with a patient with RS symptomatology.

Future prospective studies are required to assess the clinical significance of incidental sinonasal findings detected on CT or CBCT scanning of either asymptomatic, TMD or other type of symptomatic populations such as chronic tension type headaches or migraines. Research that investigates clinical correlation to potentially clinically significant findings detected radiographically may also be helpful.

The ideal scenario would be starting with a recent database of CT scans taken for the non-RS group of interest and then recruiting those patients to be comprehensively assessed in a RS point of view, including a quality of life questionnaire, physical examination and nasal endoscopy.

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APPENDICES

APPENDIX 1

Health Research Ethics Board

213 Heritage Medical Research Centre
University of Alberta, Edmonton, Alberta T6G 2S2
p.780.492.9724 (Biomedical Panel)
p.780.492.0302 (Health Panel)
p.780.492.0459
p.780.492.0839
f.780.492.7808

ETHICS APPROVAL FORM

Date: **February 6, 2008**

Name of Principal Investigator(s): Dr. Norman Thie

Department: Dentistry

Title: **Incidental sinonasal findings in cone-beam tomography (CBCT) imaging of the temporomandibular joints: prevalence and clinical significance**

The Health Research Ethics Board (Biomedical Panel) has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation. The REB has also reviewed and approved the subject information material and consent form.

Specific Comments:

The Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. The REB Panel determined that the research described in the ethics application is an analysis of scans already completed for which subject consent for access to personally identifiable health information would not be reasonable, feasible or practical. Subject consent therefore is not required for access to the personally identifiable health information described in the ethics application.

J.S. Bamforth, M.D.
Associate Chairman
Health Research Ethics Board (Biomedical Panel)

FEB 1 3 2008
Date of Approval Release

This approval is valid for one year

Issue #7263

UNIVERSITY OF ALBERTA

Capital Health
Edmonton and area

CARITAS HEALTH GROUP

APPENDIX 2

Inter-reliability and Intra-reliability 2 X 2 tables

- Inter-reliability

	Nasal1 WT2		
Nasal 1T2	1	0	total
1	6	1	7
0	1	22	23
total	7	23	30

	Nasal2 WT2		
Nasal 2T2	1	0	total
1	2	0	2
0	7	21	28
total	9	21	30

	Nasal3 WT2		
Nasal 3T2	1	0	total
1	10	3	13
0	2	15	17
total	12	18	30

	Nasal4 WT2		
Nasal 4T2	1	0	total
1	0	0	0
0	0	30	0
total	0	30	30

	Max1 WT2		
Max1 T2	1	0	total
1	0	2	2
0	3	25	28
total	3	27	30

	Max2 WT2		
Max2 T2	1	0	total
1	6	4	10
0	0	20	20
total	6	24	30

	Max3 WT2		
Max3 T2	1	0	total
1	4	3	7
0	1	22	23
total	5	25	30

	Max4 WT2		
Max4 T2	1	0	total
1	4	1	5
0	0	25	25
total	4	26	30

	Max5 WT2		
Max5 T2	1	0	total
1	7	1	8
0	2	20	22
total	9	21	30

	Max6 WT2		
Max6 T2	1	0	total
1	4	0	4
0	5	21	26
total	9	21	30

	Max7 WT2		
Max7 T2	1	0	total
1	0	0	0
0	1	29	30
total	1	29	30

	Eth WT2		
Eth T2	1	0	Total
1	2	0	2
0	3	25	28
total	5	25	30

	Sph1 WT2		
Sph1 T2	1	0	total
1	0	0	0
0	3	27	30
total	3	27	30

	Sph2 WT2		
Sph2 T2	1	0	total
1	1	1	2
0	0	28	28
total	1	29	30

	Sph3 WT2		
Sph3 T2	1	0	total
1	0	0	0
0	2	28	30
total	2	28	30

	Sph4 WT2		
Sph4 T2	1	0	total
1	1	1	2
0	1	27	28
total	2	28	30

	Sph5W T2		
Sph5 T2	1	0	total
1	1	0	0
0	0	29	29
total	1	29	30

	Sph6W T2		
Sph6 T2	1	0	total
1	0	0	0
0	1	29	30
total	1	29	30

	ClSigW T2		
ClSig T2	1	0	total
1	5	0	5
0	5	20	25
total	10	20	30

- Intra-reliability - Examiner 1 (IG)

	Nasal1 T2		
Nasal1 T1	1	0	total
1	7	3	10
0	0	20	20
total	7	23	30

	Nasal1 T3		
Nasal1 T1	1	0	total
1	6	4	10
0	1	19	20
total	7	23	30

	Nasal1 T3		
Nasal1 T2	1	0	total
1	6	1	7
0	1	22	23
total	7	23	30

	Nasal2 T2		
Nasal2 T1	1	0	total
1	2	5	7
0	0	23	23
total	2	28	30

	Nasal2 T3		
Nasal2 T1	1	0	total
1	4	3	7
0	0	23	23
total	4	26	30

	Nasal2 T3		
Nasal2 T2	1	0	total
1	2	0	2
0	2	26	28
total	4	28	30

	Nasal3 T2		
Nasal3 T1	1	0	total
1	10	1	11
0	3	16	19
total	13	17	30

	Nasal3 T3		
Nasal3 T1	1	0	total
1	10	1	11
0	1	18	19
total	11	19	30

	Nasal3 T3		
Nasal3 T2	1	0	total
1	11	2	13
0	0	17	17
total	11	19	30

	Nasal4 T2		
Nasal4 T1	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Nasal4 T3		
Nasal4 T1	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Nasal4 T3		
Nasal4 T2	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Max1 T2		
Max1 T1	1	0	total
1	2	2	4
0	0	26	26
total	2	28	30

	Max1 T3		
Max1 T1	1	0	total
1	4	0	4
0	0	26	26
total	4	26	30

	Max1 T3		
Max1 T2	1	0	total
1	2	0	2
0	2	26	28
total	4	26	30

	Max2 T2		
Max2 T1	1	0	total
1	8	0	8
0	2	20	22
total	10	20	30

	Max2 T3		
Max2 T1	1	0	total
1	8	0	8
0	0	22	22
total	8	22	30

	Max2 T3		
Max2 T2	1	0	total
1	8	2	10
0	0	20	20
total	8	22	30

	Max3 T2		
Max3 T1	1	0	total
1	7	1	8
0	0	22	22
total	7	23	30

	Max3 T3		
Max3 T1	1	0	total
1	8	0	8
0	0	22	22
total	8	22	30

	Max3 T3		
Max3 T2	1	0	total
1	7	0	7
0	1	22	23
total	8	22	30

	Max4 T2		
Max4 T1	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Max4 T3		
Max4 T1	1	0	total
1	4	0	4
0	0	26	26
total	4	26	30

	Max4 T3		
Max4 T2	4	1	total
1	4	1	5
0	0	25	25
total	4	26	30

	Max5 T2		
Max5 T1	1	0	total
1	8	0	8
0	0	22	22
total	8	22	30

	Max5 T3		
Max5 T1	1	0	total
1	8	0	8
0	0	22	22
total	8	22	30

	Max5 T3		
Max5 T2	1	0	total
1	8	0	8
0	0	22	22
total	8	22	30

	Max6 T2		
Max6 T1	1	0	total
1	4	0	4
0	0	26	26
total	4	26	30

	Max6 T3		
Max6 T1	1	0	total
1	4	0	4
0	0	26	26
total	4	26	30

	Max6 T2		
Max6 T1	1	0	total
1	4	0	4
0	0	26	26
total	4	26	30

	Max7 T2		
Max7 T1	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Max7 T3		
Max7 T1	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Max7 T3		
Max7 T2	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Eth T2		
Eth T1	1	0	total
1	2	0	2
0	0	28	28
total	2	28	30

	Eth T3		
Eth T1	1	0	total
1	2	0	2
0	1	27	28
total	3	27	30

	Eth T3		
Eth T2	1	0	total
1	2	0	2
0	1	27	28
total	3	27	30

	Sph1 T2		
Sph1 T1	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Sph1 T3		
Sph1 T1	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Sph1 T3		
Sph1 T2	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Sph2 T2		
Sph2 T1	1	0	total
1	2	0	2
0	0	28	28
total	2	28	30

	Sph2 T3		
Sph2 T1	1	0	total
1	2	0	2
0	0	28	28
total	2	28	30

	Sph2 T3		
Sph2 T2	1	0	total
1	2	0	2
0	0	28	28
total	2	28	30

	Sph3 T2		
Sph3 T1	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Sph3 T3		
Sph3 T1	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Sph3 T3		
Sph3 T2	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Sph4 T2		
Sph4 T1	1	0	total
1	2	0	2
0	0	28	28
total	2	28	30

	Sph4 T3		
Sph4 T1	1	0	total
1	2	0	2
0	0	28	28
total	2	28	30

	Sph4 T3		
Sph4 T2	1	0	total
1	2	0	2
0	0	28	28
total	2	28	30

	Sph5 T2		
Sph5 T1	1	0	total
1	1	0	2
0	0	29	28
total	1	29	30

	Sph5 T3		
Sph5 T1	1	0	total
1	1	0	2
0	0	29	28
total	1	29	30

	Sph5 T3		
Sph5 T2	1	0	total
1	1	0	2
0	0	29	28
total	1	29	30

	Sph6 T2		
Sph6 T1	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Sph6 T3		
Sph6 T1	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Sph6 T3		
Sph6 T2	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	ClSig T2		
ClSig T1	1	0	total
1	5	0	5
0	0	25	25
total	5	25	30

	ClSig T3		
ClSig T1	1	0	total
1	5	0	5
0	0	25	25
total	5	25	30

	ClSig T3		
ClSig T2	1	0	total
1	5	0	5
0	0	25	25
total	5	25	30

- Intra-reliability - Examiner 2 (EW)

	Nasal1 WT2		
Nasal1 WT1	1	0	total
1	6	2	8
0	1	21	22
total	7	23	30

	Nasal1 WT3		
Nasal1 WT1	1	0	total
1	7	1	8
0	1	21	22
total	8	22	30

	Nasal1 WT2		
Nasal1 WT1	1	0	total
1	6	1	7
0	2	21	23
total	8	22	30

	Nasal2 WT2		
Nasal2 WT1	1	0	total
1	4	1	5
0	5	20	25
total	9	21	30

	Nasal2 WT3		
Nasal2 WT1	1	0	total
1	4	1	5
0	3	22	25
total	7	23	30

	Nasal2 WT3		
Nasal2 WT2	1	0	total
1	5	4	9
0	2	19	21
total	7	23	30

	Nasal3 WT2		
Nasal3 WT1	1	0	total
1	6	0	6
0	6	18	24
total	12	18	30

	Nasal3 WT3		
Nasal3 WT1	1	0	total
1	6	0	6
0	3	21	24
total	9	21	30

	Nasal3 WT3		
Nasal3 WT2	1	0	total
1	9	3	12
0	0	18	18
total	9	21	30

	Nasal4 WT2		
Nasal4 WT1	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Nasal4 WT3		
Nasal4 WT1	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Nasal4 WT3		
Nasal4 WT2	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Max1WT2		
Max1 WT1	1	0	total
1	2	4	6
0	1	23	24
total	3	27	30

	Max1WT3		
Max1 WT1	1	0	total
1	2	4	6
0	4	20	24
total	6	24	30

	Max1WT3		
Max1 WT2	1	0	total
1	1	2	3
0	5	22	27
total	6	24	30

	Max2WT2		
Max2 WT1	1	0	total
1	6	1	7
0	0	23	23
total	6	24	30

	Max2WT3		
Max2 WT1	1	0	total
1	3	4	7
0	0	23	23
total	3	27	30

	Max2WT3		
Max2 WT2	1	0	total
1	3	3	6
0	0	24	24
total	3	27	30

	Max3WT2		
Max3 WT1	1	0	total
1	4	5	9
0	1	20	21
total	5	25	30

	Max3WT3		
Max3 WT1	1	0	total
1	4	5	9
0	2	19	21
total	6	24	30

	Max3WT3		
Max3 WT2	1	0	total
1	3	2	5
0	3	22	25
total	6	24	30

	Max4WT2		
Max4 WT1	1	0	total
1	4	0	4
0	0	26	26
total	4	26	30

	Max4WT3		
Max4 WT1	1	0	total
1	4	0	4
0	0	26	26
total	4	26	30

	Max4WT3		
Max4 WT2	1	0	total
1	4	0	4
0	0	26	26
total	4	26	30

	Max5WT2		
Max5WT1	1	0	total
1	7	0	7
0	2	21	23
total	9	21	30

	Max5WT3		
Max5WT1	1	0	total
1	6	1	7
0	1	22	23
total	7	23	30

	Max5WT3		
Max5WT2	1	0	total
1	6	3	9
0	1	20	21
total	7	23	30

	Max6WT2		
Max6WT1	1	0	total
1	6	0	6
0	3	21	24
total	9	21	30

	Max6WT3		
Max6WT1	1	0	total
1	4	2	6
0	2	22	24
total	6	24	30

	Max6WT3		
Max6WT2	1	0	total
1	5	4	9
0	1	20	21
total	6	24	30

	Max7WT2		
Max7WT1	1	0	total
1	0	0	0
0	1	29	30
total	1	29	30

	Max7WT3		
Max7WT1	1	0	total
1	0	0	0
0	1	29	30
total	1	29	30

	Max7WT3		
Max7WT2	1	0	total
1	1	0	1
0	0	29	29
total	1	29	30

	EthWT2		
EthWT1	1	0	total
1	3	2	5
0	2	23	25
total	5	25	30

	EthWT3		
EthWT1	1	0	total
1	4	1	0
0	1	24	25
total	5	25	30

	EthWT2		
EthWT1	1	0	total
1	4	1	5
0	1	24	25
total	5	25	30

	Sph1WT2		
Sph1WT1	1	0	total
1	0	0	0
0	3	27	30
total	3	27	30

	Sph1WT3		
Sph1WT1	1	0	total
1	0	0	0
0	0	30	30
total	0	30	30

	Sph1WT3		
Sph1WT2	1	0	total
1	0	3	3
0	0	27	27
total	0	30	30

	Sph2 WT2		
Sph2 WT1	1	0	total
1	1	1	2
0	0	28	28
total	1	29	30

	Sph2 WT3		
Sph2 WT1	1	0	total
1	2	0	2
0	0	28	28
total	2	28	30

	Sph2 WT3		
Sph2 WT2	1	0	total
1	1	0	1
0	1	28	28
total	2	28	30

	Sph3 WT2		
Sph3 WT1	1	0	total
1	0	0	0
0	2	28	30
total	2	28	30

	Sph3 WT3		
Sph3 WT1	1	0	total
1	0	0	0
0	1	29	30
total	1	29	30

	Sph3 WT3		
Sph3 WT2	1	0	total
1	1	1	2
0	0	28	28
total	1	28	30

	Sph4W T2		
Sph4W T1	1	0	total
1	1	1	2
0	1	27	28
total	2	28	30

	Sph4W T2		
Sph4W T1	1	0	total
1	1	1	2
0	0	28	28
total	1	29	30

	Sph4W T3		
Sph4W T2	1	0	total
1	1	1	2
0	0	28	28
total	1	29	30

	Sph5W T2		
Sph5W T1	1	0	total
1	0	0	0
0	1	29	30
total	1	29	30

	Sph5W T3		
Sph5W T1	1	0	total
1	0	0	0
0	1	29	30
total	1	29	30

	Sph5W T3		
Sph5W T2	1	0	total
1	1	0	1
0	0	29	29
total	1	29	30

	Sph6W T2		
Sph6W T1	1	0	total
1	0	0	0
0	1	29	30
total	1	29	30

	Sph6W T3		
Sph6W T1	1	0	total
1	0	0	0
0	1	29	30
total	1	29	30

	Sph6W T3		
Sph6W T2	1	0	total
1	1	0	0
0	0	29	30
total	1	29	30

	ClSigWT2		
ClSigWT1	1	0	total
1	6	1	7
0	4	19	23
total	10	20	30

	ClSigWT2		
ClSigWT1	1	0	total
1	5	2	7
0	8	15	23
total	13	17	30

	ClSigWT3		
ClSigWT2	1	0	total
1	7	3	10
0	6	14	20
total	13	17	30