JYRI MYLLER

Middle Meatal Antrostomy in Endoscopic Sinus Surgery

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ACADEMIC DISSERTATION
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To my family and friends

ABSTRACT

Background: Chronic rhinosinusitis (CRS) is an inflammation of the nose and paranasal sinuses lasting more than 12 weeks. It is diagnosed by typical symptoms and/or a computed tomography (CT) scan and/or endoscopic changes. In a recent study the prevalence of CRS in the European population was found to be 10.9%.

After failure of maximal conservative therapy, endoscopic sinus surgery (ESS) aims to restore normal sinus function and ventilation through the natural ostia. Traditionally, in maxillary sinus surgery, ESS was initiated with the removal of the uncinate process combined with middle meatal antrostomy. Anterior ethmoidal cells were also often opened. The minimally invasive technique of maxillary sinus surgery concentrates only on the uncinate process. Since the introduction of this technique, there have been controversial opinions on the advantages of simple uncinectomy over maxillary sinus antrostomy.

Subjects and methods: The study group comprised 30 patients (20 women and 10 men) aged between 22 and 66 years, with a mean age of 47 years. They all suffered from chronic maxillary rhinosinusitis with associated mucosal thickening or sinus opacification in the CT scan. There was no difference in the symptoms between each side of the nose, and the preoperative CT scans showed identical moderate findings on both sides. A nasal endoscopy was performed to exclude patients with visible polyposis from the study.

The study group underwent ESS under local anaesthesia. Uncinectomy alone was performed on one side. In addition, a middle meatal antrostomy was performed on the contralateral side to duplicate the size of the natural ostium. Ethmoidal bulla was resected bilaterally in 25 patients. Part of the patients in the study group received conservative therapy (intranasal corticosteroid and/or oral antihistamine) both pre- and postoperatively.

Nasal endoscopy, a CT scan and measurements of mucociliary clearance (MCC) were performed preoperatively and nine months postoperatively. Maxillary sinus mucosa biopsy specimens were taken for histopathological and immunohistochemical evaluations intraoperatively and 9 months postoperatively from this study group. Patient questionnaires were completed at 1 month preoperatively, and at 1, 3, 9 and 68 months postoperatively. Maxillary sinus specimens were also obtained from an additional subject group that consisted of healthy controls and CRS patients with or without nasal polyposis.

Results: We were able to demonstrate that the percentage of vessels expressing endothelial sulphated sialyl-Lewis^X epitopes (L-selectin ligands) in maxillary sinus biopsies taken intraoperatively increased during CRS compared with uninflamed control tissue. In addition, the expression level of these epitopes and the number of mucosal eosinophils correlated with the inflammation, and they decreased nine months postoperatively compared with intraoperative samples, especially in patients with intranasal corticosteroid treatment. The postoperative reduction of these L-selectin ligands was independent of the operation technique.

There was a statistically significant correlation between the postoperative number of mucosal eosinophils and the symptom score, which was also independent of the surgical technique. A statistically significant postoperative decrease of mucosal eosinophils, as well as the correlation of the intraoperative eosinophils with the postoperative symptom score, was found only on the antrostomy side.

Surgery did not significantly improve the mucociliary function of the maxillary sinus mucosa; it remained poor even nine months postoperatively. There was no statistical difference between the operative techniques.

Comparison of the preoperative and postoperative CT scans revealed that a significant reduction in the radiological Lund-Mackay (LM) score was achieved on both sides, regardless of the procedure performed. The postoperative area of the ostium remained significantly larger on the antrostomy side compared with the uncinectomy side.

Comparison of long-term subjective outcomes revealed a significant reduction of symptoms on both sides. There were no significant differences between the uncinectomy with additional antrostomy and the uncinectomy-only sides in terms of satisfaction with the operation, facial pain, nasal obstruction, or discharge values. Additional middle meatal antrostomy seemed to be slightly superior in terms of the need for revision operations. However, this difference was statistically insignificant.

The number of prescribed antibiotic courses for acute exacerbations began to increase between the nine- and, on average, 68-month period postoperatively. It seemed that patients with asthma and/or job exposure to irritants might experience less satisfaction with the uncinectomy-only side, whereas patients without these risk factors experienced similar satisfaction after both procedures. This observation did not however reach statistical difference.

Conclusion: Endoscopic sinus surgery (ESS) has a positive impact on subjective outcomes, radiological Lund-Mackay scores, sinus mucosa L-selectin ligands and eosinophils regardless of the type of the operation performed. Mucociliary clearance remains poor even after nine months of ESS, indicating poor recovery of the ciliary function. There were no statistically significant differences between the types of operation. However, there is a slight tendency for better results with ostium-enlarging surgery.

LYHENNELMÄ

Tausta: Pitkäaikaisessa sivuontelotulehduksessa nenän ja sivuonteloiden oireet kestävät yli kolme kuukautta häviämättä välillä täysin. Diagnoosi perustuu esitietoihin, oireisiin ja/tai tietokonekerroskuvauksessa tehtyihin löydöksiin ja/tai nenän tähystyslöydöksiin. Vastikään julkaistun tutkimuksen mukaan pitkäaikaisen sivuontelotulehduksen esiintyvyys Euroopassa on 10,9 %.

Pitkäaikaisessa sivuontelotulehduksessa suositellaan endoskooppiavusteista sivuontelokirurgiaa (ESS), mikäli konservatiivisella hoidolla ei saavuteta riittävää lievitystä oireisiin. Kirurgian tarkoituksena on palauttaa sivuontelon normaali toiminta ja ilmastointi luonnollisen aukon eli ostiumin kautta. Perinteisessä poskionteloiden ESS-kirurgiassa poistetaan processus uncinatus ja lisäksi laajennetaan poskiontelon ostiumia eli tehdään ns. keskikäytäväantrostomia. Toimenpiteeseen kuuluu usein myös etummaisten seulalokeroiden avaus. Uudemmassa mini-invasiivisessa tekniikassa poistetaan pelkkä uncinatus ja ostiumiin ja/tai seulalokeroihin ei kajota. Näiden kahden eri leikkausmenetelmän välisistä mahdollisista eroista, hyödyista ja haittavaikutuksista ei edelleenkään ole täyttä selvyyttä.

Menetelmät: Tutkimukseen osallistui 30 potilasta, 20 naista ja 10 miestä. Potilaista nuorin oli 22-vuotias ja vanhin 66-vuotias. Potilaiden keski-ikä oli 47 vuotta.

Tutkimusryhmän potilailla todettiin molemminpuoliset pitkäaikaisen sivuontelotulehduksen oireet. Ennen leikkausta otetussa tietokonekerroskuvauksessa sivuonteloissa havaittiin vaikeusasteeltaan kohtalaiseksi luokiteltavaa limakalvoturvotusta ja/tai varjostuneisuutta. Nenän tähystyksellä tutkimuksesta poissuljettiin potilaat, joilla esiintyi nenäpolyyppeja.

ESS-kirurgia tehtiin kaikille tutkimuspotilaille paikallispuudutuksessa. Toiselle puolelle tehtiin satunnaistetusti ja potilaalle sokkoutetusti pelkkä processus uncinatuksen poisto, toisella puolella uncinatuksen poiston lisäksi laajennettiin luonnollista ostiumia siten, että sen läpimitta kaksinkertaistui. 25 potilaalla etummainen seulalokero avattiin molemmin puolin toimenpiteen yhteydessä. Osa tutkimusryhmän potilaista käytti konservatiivisia hoitomenetelmiä (kortisoninenäsumutetta ja/tai antihistamiinia) sekä ennen leikkausta, että leikkauksen jälkeen.

Nenän tähystys, tietokonekerroskuvaus ja limakalvon värekarvamittaukset tehtiin ennen leikkausta ja 9 kk:a leikkauksen jälkeen. Poskionteloiden limakalvolta otettiin näytteitä histopatologisia ja immunohistokemiallisia tutkimuksia varten. Potilaat täyttivät kyselylomakkeet kuukausi ennen leikkausta, sekä 1 kk:n, 3 kk:n 9 kk:n ja 68 kk:n kohdalla leikkauksen jälkeen Limakalvonäytteitä otettiin myös toiselta tutkimusryhmältä. Ryhmä koostui terveistä kontrollipotilaista ja pitkäaikaista sivuontelotulehdusta sairastavista potilaista, joista osalla oli myös nenäpolyyppeja.

Tulokset: Pystyimme osoittamaan, että terveeseen poskiontelon limakalvoon verrattuna pitkäaikaisessa sivuontelotulehduksessa verisuonten seinämässä esiintyvän ja valkosolujen L-selektiiniin sitoutuvien sulfatoitujen Lewis x sokerirakenteiden suhteellinen määrä lisääntyi merkitsevästi. Lisäksi osoitimme, että näiden epitooppien ja limakalvon eosinofiilisten tulehdussolujen esiintyvyys oli verrannollinen tulehduksen vaikeusasteeseen. Potilailla, joilla oli käytössä paikallinen nenäkortikosteroidihoito, L-selektiinin ligandien määrä ja limakalvon eosinofiilisolujen määrä väheni postoperatiivisesti 9 kk:n kohdalla verrattuna perioperatiiviseen tilanteeseen. Postoperatiivinen L-selektiinin ligandien vähentyminen oli riippumaton leikkaustekniikasta.

Oirearvioinnin ja postoperatiivisen poskiontelon limakalvon eosinofiilien välillä oli vastaavuussuhde, tämäkin oli riippumaton leikkaustekniikasta. Sekä tilastollisesti merkitsevä postoperatiivisen limakalvon eosinofiilien väheneminen, että perioperatiivisen eosinofiilien ja oirekuvan verrannollisuus pystyttiin osoittamaan ainoastaan tehdyn keskikäytäväantrostomian puolella.

ESS-leikkaus ei parantanut poskiontelon mukosiliaaripuhdistumaa vaan se pysyi huonona myös 9 kk:n seurantatutkimuksessa. Leikkausmenetelmien välillä ei myöskään ollut tilastollisesti merkitsevää eroa.

Ennen leikkausta ja 9 kk:a leikkauksen jälkeen tehtyjen tietokonekerroskuvausten perusteella pystyttiin sivuonteloissa osoittamaan molemmilla puolilla selkeä vähentyminen tutkimuksessa käytetyssä kuvantamispohjaisessa Lund-Mackay pisteytyksessä. Tämä vähentyminen oli riippumaton leikkaustekniikasta. Pelkkään uncinatuksen poistoon verrattuna ostiumin koko säilyi merkitsevästi suurempana keskikäytäväantrostomiapuolella.

Pitkäaikaisseurannassa saavutettiin merkitsevä oirekuvan vähentyminen molemmilla leikkaustekniikoilla. Leikkaustekniikoiden välillä emme havainneet eroa tyytyväisyydessä leikkauksen tulokseen, kasvokipuun, nenäntukkoisuuteen tai limaisuuteen liittyen. Pitkäaikaisseurannassa keskikäytäväantrostomia osoittautui hieman paremmaksi verrattaessa tarvetta uusintaleikkaukseen.

Pitkäaikaisen sivuontelotulehduksen akuuttien pahenemisjaksojen määrä alkoi lisääntyä 9kk:a leikkauksen jälkeen. Potilaat, joilla oli astma ja/tai altistuminen työperäisille hengitysilmaärsykkeille olivat tyytyväisempiä keskikäytäväantrostomiaan, kuin pelkkään uncinektomiaan. Löydös ei kuitenkaan ollut tilastollisesti merkitsevä. Potilaat, joilla tällaisia riskitekijöitä ei ollut, olivat yhtä tyytyväisiä molemmilla menetelmillä tehtyihin leikkauksiin.

Yhteenveto: Endoskooppiavusteisella sivuontelokirurgialla (ESS) saavutetaan positiivinen vaikutus potilaan oirekuvaan, kuvantamispohjaiseen Lund-Mackay pisteytykseen, poskiontelon limakalvon L-selektiini ligandeihin ja eosinofiileihin riippumatta leikkaustekniikasta. Mukosiliaaripuhdistuma jäi huonoksi 9 kk seurantatutkimuksessakin, mikä osoitti värekarvatoiminnan huonoa paranemista. Vaikka tutkimustulokset osoittivat lievää etua tehdystä keskikäytäväantrostomiasta, eri leikkausmenetelmillä saatujen tulosten välillä ei yleisesti ottaen ollut suuria tilastollisesti merkitseviä eroja.

CONTENTS

ABBREVIATIONS

AECRS	Acute exacerbation of chronic rhinosinusitis
AR	Allergic rhinitis
ASA	Acetylsalicylic acid
CBF	Ciliary beat frequency
CRS	Chronic rhinosinusitis
CSS	Chronic sinusitis survey
CT	Computed tomography
EPOS 2012	European position paper on rhinosinusitis and nasal polyps 2012
ESS	Endoscopic sinus surgery
FESS	Functional endoscopic sinus surgery
HECA-452	Monoclonal antibody recognizing α-2,3 sialylation and α-1,3 fucosylation of lactosamine
LM	Lund-Mackay
MCC	Mucociliary clearance
MECA-79	Monoclonal antibody recognizing extended sulphated core-1 lactosamine structures
MTT	Mucociliary transit time
NERD	Nonsteroidal anti-inflammatory drug exacerbated respiratory disease
NSAID	Nonsteroidal anti-inflammatory drug
NP	Nasal polyps
PCD	Primary ciliary dyskinesia
QOL	Quality of life
SF-36	Short form (36) health survey
SNOT-20	Sino-nasal outcome test-20
SNOT-22	Sino-nasal outcome test-22
RSOM-31	Rhinosinusitis outcome measure-31
TEM	Transmission electron microscopy
VAS	Visual analogue scale

LIST OF ORIGINAL CONTRIBUTIONS I–V

This thesis is based on the following publications, which are referred to in the text, and in some additional data, by their Roman numerals (I–V).

I Toppila-Salmi SK, Myller JP, Torkkeli TV, Muhonen JV, Renkonen JA, Rautiainen ME, Renkonen RL (2005): "Endothelial l-selectin ligands in sinus mucosa during chronic maxillary rhinosinusitis". Am J Respir Crit Care Med 15; 171 (12): 1350–1357.

II Myller J, Toppila-Salmi S, Torkkeli T, Heikkinen J, Rautiainen M (2006): "Effect of endoscopic sinus surgery on antral mucociliary clearance". Rhinology 44 (3): 193–196.

III Myller JP, Toppila-Salmi SK, Toppila EM, Torkkeli TV, Numminen JE, Renkonen RL, Rautiainen ME (2009): "Mucosal eosinophils and l-selectin ligands are associated with invasive and noninvasive sinus surgery outcomes". Am J Rhinol Allergy 23 (1): 21–27.

IV Myller J, Dastidar P, Torkkeli T, Rautiainen M, Toppila-Salmi S (2011): "Computed tomography findings after endoscopic sinus surgery with preserving or enlarging maxillary sinus ostium surgery". Rhinology 49 (4): 438–444.

V Myller J, Luukkainen A, Huhtala H, Torkkeli T, Rautiainen M, Toppila-Salmi S (2013): "Satisfaction with maxillary sinus surgery might be influenced by risk factors". Allergy Rhinol 4 (1): e6–e12.

The publishers of the original articles have kindly granted permission to reprint the papers.

1 INTRODUCTION

Chronic rhinosinusitis (CRS) with or without nasal polyposis is an inflammatory disease of the nose and paranasal sinuses that is present for at least 12 weeks without complete resolution. It is characterized by the presence of distinctive symptoms (e.g., nasal blockage, nasal discharge, facial pain and/or reduced sense of smell) and either endoscopic signs or computed tomography (CT) changes characteristic of the disease. CRS has a negative impact on quality of life and can substantially impair daily functioning (Fokkens et al. 2012).

Rhinosinusitis in its many forms constitutes one of the most common conditions encountered in modern medicine. A United States-based survey estimated that if CRS is defined as having sinus complaints for more than three months in the year before the interview, 13.5% of the total population is affected by CRS without nasal polyposis, ranking it second in prevalence among all chronic conditions (Collins 1997). A recent study found CRS prevalence in Europe to be 10.9% (Hastan et al. 2012). Although the mortality of the disease is low, the morbidity is high. CRS patients demonstrate worse quality-of-life scores for physical pain and social functioning than those suffering from chronic pulmonary obstructive disease, congestive heart failure, or angina (Gliklich and Metson 1995). CRS contributes to a significant amount of health care expenditure due to direct costs arising from physician visits and medical therapies (Murphy et al. 2002), and indirect costs related to loss of productivity and absence from work are also notable (Ray et al. 1999).

In Finland, topical glucocorticoids are important treatment modalities in patients with CRS with or without nasal polyposis. Traditionally, systemic glucocorticoids have been frequently prescribed to patients suffering from CRS with nasal polyposis (Hytönen et al. 2011). The clinical efficacy of glucocorticoids may depend in part on their ability to reduce airway eosinophil infiltration by preventing their increased viability and activation (Xaubet et al. 1994, Mullol et al. 1997) or by indirectly reducing the secretion of chemotactic cytokines by nasal mucosa and polyp epithelial cells (Mullol et al. 2000, Xaubet et al. 2001). Antibiotics, including both short-term courses and long-term treatment regimens, are frequently prescribed in the treatment of patients suffering from CRS. Data supporting the short-term (fewer than 14 days) use of antibiotics is limited and lacking, since randomized, placebo-controlled trials do not exist. Studies suggest that long-term (8–12-

week) macrolide antibiotic treatments are effective in treating patients incurable by surgery or glucocorticoids (Hashiba and Baba 1996, Wallwork 2006), yet Videler et al. (2011) could not show a positive effect of long-term azithromycin treatment in a randomized, double-blinded, controlled trial. No evidence-based data is currently available to support the use of oral antihistamines or oral antifungals in the treatment of CRS with nasal polyps.

Endoscopic sinus surgery (ESS), comprising a set of minimally invasive techniques, is now a well-established strategy in the treatment of patients with CRS refractory to maximum medical therapy. The goal of ESS is to restore normal sinus function and ventilation by opening the affected sinus air cells and sinus ostia under direct visualization (Stammberger 1990). Since the number of affected sinuses and the degree of inflammation determines the extent of surgery, there is no standardized set of surgical steps or manoeuvers.

In the early part of the 20th century, Siebenmann et al. (1912) advocated a middle meatal antrostomy because of the ease of the approach. However, there was concern about the possibility of permanent damage to the primary vascular, lymphatic and neurological communications if the ostium was traumatized (Proetz 1941). Based on his experimental study, Hilding (1941) recommended that an antrostomy should be as far from the natural ostium as possible. As a result, the concept of middle meatal antrostomy fell out of favour.

Kennedy (1987) reintroduced endoscopic middle meatal antrostomy in sinus surgery in 1987. Since then, there has been an ongoing debate over whether maxillary sinus antrostomy should be performed or not, and, if it is performed, what the optimal size of the antrostomy should be. Currently, despite much debate, the role of antrostomy remains unclear, as does the optimal maxillary antrostomy size.

2 REVIEW OF THE LITERATURE

2.1 Normal paranasal sinus anatomy and pathophysiology

The paranasal sinuses constitute a collection of air-filled spaces within the anterior skull. They are named after the skull bones in which they are located (frontal, ethmoidal, maxillary and sphenoidal sinuses). Normal sinuses are air-filled spaces lined by a thin layer of respiratory mucosa.

The sinonasal mucosa is lined by pseudostratified columnar epithelium. The epithelium has a variable number of ciliated cells (~75%), goblet cells (~20%), and basal cells (~5%), which are located on an acellular basement membrane (DePoortere et al. 2011) This epithelial lining protects the upper airway system from inhaled pathogens and debris. The epithelium is covered with a mucus that consists of two layers: the lower sol layer and the upper mucus layer. Using ciliary pathways, ciliary beats transport the upper, more viscous mucous film in the sinuses towards the natural ostium (Messerklinger 1966). Through these small apertures, the sinuses communicate with the nasal cavity (Baroody 2007).

There are different but still complementary theories concerning the function and importance of the paranasal sinuses. Theories that have no objective support or evidence include resonance for speech, providing protection to the skull, reducing the weight of the skull, providing thermal insulation to the brain, providing a supply of conditioned air to diffuse with inhaled air, assistance of olfaction, and secreting mucus to keep the nose moist (Wagenmann and Naclerio 1992).

The ostiomeatal complex has a fundamental role in the pathogenesis of CRS. It is a functional unit comprising the maxillary sinus ostium, the anterior ethmoidal cells and their ostia, the ethmoidal infundibulum, the hiatus semilunaris and the middle meatus. Under physiological circumstances, this complex allows sinus ventilation and mucosal clearance. Maintaining ostial patency is crucial, since it affects mucus composition and mucus secretion. An open ostium allows mucociliary clearance to remove particulate matter and bacteria from healthy sinuses (Kennedy 1987). Problems occur if the orifice is too small for the amount of mucus produced or becomes blocked by the thickened mucous membrane, if mucus production is increased or the consistency and properties of mucus change, or if the ciliary function is impaired. Stasis of secretions results and bacterial or inflammatory product export ceases causing exacerbating inflammation. Due to a

decreased aeration in the sinus, ciliary function may be further decreased and result in the development of CRS (Fokkens et al. 2012).

2.2 Definition, epidemiology and microbiology of chronic rhinosinusitis

2.2.1 Definition

The most recent report, the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012), offers three definitions for CRS: one to be used clinically, one to be used in epidemiological studies/general practice, and one more detailed definition for research purposes (Fokkens et al. 2012).

For clinical purposes, the definition of CRS includes nasal polyps. It is defined as an inflammatory disease of the nose and paranasal sinuses persisting for at least 12 weeks without complete resolution, and is characterized by the presence of at least two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) and/or facial pain/pressure and/or reduction or loss of smell. Diagnosis should also include either endoscopic signs (i.e. nasal polyps and/or mucopurulent discharge primarily from the middle meatus and/or oedema/mucosal obstruction primarily in middle meatus) and/or CT changes characteristic of the disease (i.e. mucosal changes within the ostiomeatal complex and/or sinuses). The severity of the disease can be divided into mild, moderate or severe, based on a total severity visual analogue scale (VAS) (Fokkens et al. 2012).

For epidemiological/general practice use, CRS with or without polyps is defined as the presence of two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) and/or facial pain/pressure and/or reduction or loss of smell for more than 12 weeks. The definition is based on symptomatology without ENT examination or radiology, with validation by telephone or interview. Questions on allergic symptoms (i.e. sneezing, watery rhinorrhoea, nasal itching, and itchy, watery eyes) should be included (Fokkens et al. 2012).

For research purposes, the clinical definition of CRS is used. CRS is the major finding, and CRS with nasal polyposis is a subgroup of this entity. A differentiation between CRS without nasal polyposis and CRS with nasal polyposis should be made with an outpatient nasal endoscopy. Patients with bilateral nasal polyps in the middle meatus are considered to have CRS with nasal polyposis, whereas patients without bilateral nasal polyps in the middle meatus are considered to have CRS without nasal polyposis (Fokkens et al. 2012).

An acute exacerbation of chronic rhinosinusitis (AECRS) is defined as a sudden worsening of symptoms in a patient already diagnosed with CRS, with return to baseline symptoms after treatment (Lanza and Kennedy 1997).

2.2.2 Epidemiology

The lack of common agreement on the definition of chronic rhinosinusitis with or without nasal polyposis is reflected in epidemiological data, since the incidence of CRS depends on the diagnostic criteria used. The heterogeneity of the disorder and the diagnostic imprecision used in publications has made an accurate estimate of the prevalence on CRS speculative (Fokkens et al. 2012).

In a survey on the prevalence of chronic conditions, it was estimated that CRS, defined as having "sinus trouble" for more than 12 weeks in the year before interview, affects 15.5% of the total population of the United States (Collins 1997). The high prevalence of CRS was confirmed in another survey suggesting that 16% of the adult US population has CRS (Blackwell et al. 2002).

Recently, Hastan et al. (2012) studied the prevalence of CRS in Europe and found it to be 10.9%. In this multicentre study, a postal questionnaire was sent and information obtained from 57,128 responders living in 12 countries. CRS was more common in smokers than in non-smokers, and showed marked geographical variation.

2.2.3 Microbiology

The role of bacteria in the pathogenesis of CRS remains unclear and unestablished (Slavin 2006). The most common bacteria isolated from the middle meatus and sinuses are *Staphylococcus aureus*, a coagulase-negative staphylococcus species (*Staphylococcus epidermidis* and *Staphylococcus saprophyticus*), and *Streptococcus pneumonie* (Araujo et al. 2003). The fact that both anaerobic and aerobic species can be recovered from both the diseased and the non-diseased contralateral side of patients with chronic rhinosinusitis casts doubt on the aetiological role of bacteria in CRS (Bhattacharyya 2005).

There is no evidence of the role of persistent viral infection in the pathogenesis of CRS. However, there is limited information indicating that patients with CRS might have an increased incidence of rhinovirus infection and some suggestion that they might have an exaggerated response to viral infection (Jang et al. 2006, Hamilos 2014).

Varieties of fungus have been cultured from the mucin of human sinuses, the most common being *Aspergillus*, *Penicillium*, *Cladosporium*, *Candida*, *Aureobasidium* and *Altenaria* (Ponikau et al. 1999). It has been suggested that an exaggerated immune response to fungi is crucial in the pathogenesis of CRS (Ponikau et al. 1999). Kern et al. (2007) have postulated that eosinophils in the nasal mucosa attack and destroy the fungi by releasing a toxic substance called major basic protein (MBP) from the granules in eosinophils. The release of the toxic MBP not only destroys the fungi, but also produces collateral damage, injuring the sinonasal mucosal lining tissue, thus making the mucosa susceptible to secondary bacterial infection. Treatment with topical antifungal agents has proven to be ineffective, however (Ebbens et al. 2006, Liang et al. 2008).

2.3 Associated diseases and predisposing factors

2.3.1 Asthma

Recent evidence suggests that allergic inflammation in the upper (e.g., rhinitis) and lower airways (e.g., asthma) usually coexist and should be seen as a continuum of inflammation. The arguments and consequences of these observations are summarized in the latest "Allergic Rhinitis and its Impact on Asthma" (ARIA) document (Pawankar et al. 2008). CRS and asthma are frequently associated in the same patients, especially in those suffering CRS with nasal polyposis, although the nature of this interrelationship is poorly understood (Rugina et al. 2002).

2.3.2 Allergy

Review articles on rhinosinusitis have suggested that atopy is a predisposing factor for the development of CRS (Kaliner 1994, Krause 2003). Fokkens et al. (2012) postulate that mucosal swelling in the region of the ostiomeatal complex may comprise sinus ventilation, leading to mucus retention and infection.

Several studies report more prevalent markers of atopy in populations with CRS (Settipane and Chafee 1977, Shapiro et al. 1991, Emanuel and Shah 2000). In a study of 200 CRS patients undergoing sinus surgery, the prevalence of a positive skin prick test was 84%, of which, 60% of patients had significant allergic sensitivity and majority of all patients (52%) had multiple sensitivities (Emanuel and Shah 2000).

Since no increase in the incidence of rhinosinusitis is observed in pollen-sensitized patients during the pollen season (Karlsson and Holmberg 1994), the role of atopy in CRS without nasal polyposis remains unclear. Similarly, Settipane and Chafee (1977) demonstrated that only 1.5% of allergic rhinitis patients have nasal polyps in their nose and paranasal sinuses compared to 4.7% of subjects without allergic rhinitis. This questions the role of atopy in CRS with nasal polyps.

2.3.3 NSAID-exacerbated respiratory disease (NERD)

Nonsteroidal anti-inflammatory drugs (NSAIDs) may induce a hypersensitivity reaction that can vary in timing, organ involvement, and severity. NSAID-exacerbated respiratory disease (NERD) is a condition in which aspirin or other NSAIDs manifest primarily as bronchial obstruction, dyspnoea, and nasal congestion/rhinorrhoea in patients with an underlying chronic airway respiratory disease (asthma/rhinosinusitis/nasal polyps) (Kowalski et al. 2013). Previously used synonyms are Aspirin-Exacerbated Respiratory Disease (AERD), Aspirin triad and Samter's syndrome. Kowalski et al. found the prevalence

of NERD to be 0.6–5%, and estimated that it is underdiagnosed due to its variable clinical picture and the fact that asthma patients are usually advised to avoid NSAIDs. Spector et al. (1979) have shown that up to 96% of NERD patients have radiographic changes affecting paranasal sinuses. Interestingly, a recent Finnish population-based study showed that the prevalence of nasal polyps in ASA-sensitive asthma patients was only 27% (Luukkainen et al. 2013). Others have shown that the prevalence of nasal polyps in ASA-sensitive asthmatic patients may be as high as 60–70%, whereas the prevalence of nasal polyps in ASA-tolerant asthmatics is only 10% (Settipane and Chafee 1977). In contrast to NSAID-tolerant patients, patients with NERD tend to have more severe asthma symptoms, a recurrence of nasal polyps, chronic otitis media, and a progression of airway inflammation.

2.3.4 Mucociliary impairment

Mucociliary clearance is an essential component of the human respiratory system. Its function is to remove both normal and pathological secretions from the sinuses and airways. The mucociliary system is also the primary defence mechanism against inhaled particulate matter (Cohen 2006). The paranasal sinuses are almost completely dependent on the activity of cilia for removal of mucus, whereas in the lower airways, deficient mucociliary clearance (MCC) can be compensated for by coughing (van der Baan 2000). MCC is dependent on normal cilia function and mucus composition. When the epithelium, cilia or mucus do not function correctly, the respiratory secretions stagnate and ultimately harbour infection, resulting in inflammation. In time, this becomes a chronic inflammatory state with or without active infection (Antunes et al. 2009).

Primary ciliary dyskinesia (PCD), or immotile cilia syndrome, is an inherited disorder resulting in abnormal ciliary morphology and dysfunctional cilia that manifests as severely impaired MCC (Pedersen and Mygind 1976). These patients typically present with chronic airway and recurrent middle ear infections. Impairment of organ lateralization (such as situs inversus), infertility, hydrocephalus, sensorineural hearing loss, and renal failure may also result from severe cilia abnormality on a systemic level. The prevalence of PCD in Finland is 0.13/10,000, which is a fifth of the prevalence in other Nordic countries. This might indicate that PDC is underdiagnosed in Finland (Korppi et al. 2011). PCD may be suspected in children with recurrent episodes of otitis, rhinosinusitis, pneumonia, and bronchiectasis. Children with clinical findings of PCD, radiographic findings (bronchiectasis, bronchial wall thickening), or heterotaxy should be screened with saccharin test, radioaerosol test or nasal nitric oxide (NO) test. Diagnostic testing includes electron microscopy analysis of ciliary structure, ciliary beat pattern and frequency analysis, and genetic testing (Popatia et al. 2014). Early diagnosis is important in order to start intensive follow-ups and rehabilitation to avoid complications, such as bronchiectasis and the need for lung transplantation.

There is overwhelming evidence in the literature that MCC is decreased in patients with CRS, as demonstrated by the use of saccharin transit time and radionuclide tracer clearance studies (Cohen 2006). It is still uncertain whether the decrease of MCC in these patients is due to the cilia, mucus, or both. There is also controversy over whether ESS will restore MCC in sinonasal mucosa even in the long-term. Moriyama's study (1996) indicates complete recovery of MCC six months after endoscopic sinus surgery, but there is also evidence that MCC does not significantly improve even six months postoperatively, and that there are still many histological findings similar to those seen preoperatively (Toskala and Rautiainen 2005).

Diminished ciliary function (i.e. secondary ciliary dyskinesia) can also result from the exposure to various environmental pathogens. Common bacterial pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas* produce specific toxins to impair ciliary motion and co-ordination (Ferguson et al. 1988). Virus infections may alter cilia ultrastructure and function for up to three weeks (Boon 2013). Viruses responsible for common upper respiratory infections can also change the viscosity of mucus, thus altering MCC (Jones 2001).

2.3.5 Cystic fibrosis

Cystic fibrosis is one of the most common autosomal recessive disorders in the Caucasian population. It is caused by a single gene mutation resulting in defective electrolyte transport and, consequently, abnormal mucus secretion (Accurso 2007). The defect is in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7. Mutations cause blockage of ion and water transport into and out of cells leading to a production of abnormally thick, viscous mucus. As a result, cilia are unable to transport mucus, leading to CRS and other upper airway malfunctions.

2.3.6 Environmental factors

It is known that airway exposure to occupational agents can give rise to occupational airway disease (Bousquet et al. 2001). Occupational rhinitis is defined as an inflammation of the nasal mucosa due to causes attributable to a particular work environment. Symptoms of runny nose, nasal obstruction, itch, sneezing, and nose bleeds linked to spesific exposures at work are suggestive for occupational rhinitis (Moscato et al. 2008). Additional complaints of facial pressure, postnasal drip, and smell reduction are suggestive for progression toward rhinosinusitis (Hox et al. 2014).

The term occupational rhinosinusitis has been proposed only recently (Hox et al. 2012). There is very limited data on the impact of occupational agents on sinus disease (Hox et al. 2014). In a retrospective study of 890 patients who had undergone one or more ESS

procedures, occupational exposure to inhaled agents at work represented a risk factor for the occurence of rhinosinusitis and its recurrence after surgery (Hox et al. 2012). In a Korean study the relationship between CRS and occupation was also studied. It was found, that there were significantly increased prevalence ratios of CRS in plant and machinery operators and assemblers, elementary occupations, crafts and related trade workers, and the unemployed compared with clerical workers (Koh et al. 2009). Still, the convincing aetiological role of pollutants and toxins in CRS remains unclear.

Cigarette smoking has been associated with a higher prevalence in CRS (Tomassen et al. 2011). It has also been demonstrated that smoking is associated with having CRS in all parts of Europe (Hastan et al. 2012).

2.4 Diagnosis and objective measurements of CRS

2.4.1 Symptoms

Symptoms in CRS patients with or without nasal polyposis are principally the same, although the symptom pattern and intensity may vary. These symptoms include nasal blockage, congestion or stuffiness, nasal discharge (anterior and/or posterior), facial pain and/or facial pressure and/or reduced sense of smell. In addition, patients may report distinct symptoms (sore throat, dysphonia and cough) and general symptoms (drowsiness, malaise and fever) (Fokkens et al. 2012). The degree of symptoms can be estimated using various grading tools, of which the Visual Analogue Scale (VAS) is the most commonly used (Wewers and Lowe 1990).

2.4.2 Endoscopy

Since anterior rhinoscopy alone is inadequate to diagnose CRS, nasal endoscopy is advised in patients suspected of suffering from CRS with or without nasal polyposis. Rigid endoscopy can be performed without the decongestion of nasal mucosa, but decongestion is usually necessary to visualize the area of the ostiomeatal complex. Semi-quantitative scores for polyps, oedema, discharge, crusting and post-operative scarring can be obtained, which may be useful at intervals following therapeutic interventions (Lund and Kennedy 1995).

2.4.3 Imaging

Plain sinus X-rays are considered to be insensitive and of limited use in CRS due to the large number of false positive/negative results (Iinuma et al. 1994). Ultrasound has also been criticized for low sensitivity and specificity, and it is not recommended for the imaging of chronic rhinosinusitis (Fokkens et al. 2012). Computed tomography (CT) is the imaging modality of choice for confirming the extent of pathology in any of the paranasal sinuses

and for assessing the relevant, bony, sinonasal anatomy preoperatively. Given the fact that it carries a certain dose of radiation, it should not be considered as the first step in the diagnosis of CRS unless there are unilateral signs or symptoms, or other sinister signs. Interest in CT has therefore recently focused on improving resolution whilst reducing the dose of radiation (Hodez et al. 2011). Cone beam computed tomography (CBCT) devices – with their relatively low cost, ease of storage, and low-dose radiation exposure – have become an indispensable tool in the diagnosis and treatment of CRS (Leung et al. 2011). Magnetic resonance imaging (MRI), although providing a superior visualization of soft tissue compared to CT, is not considered to be a primary imaging modality in CRS (Fokkens et al. 2012), but it can be used in combination with CT when diagnosing soft tissue tumours or for imaging perineural invasion and orbital or intracranial spread of paranasal disease (Eggesbø 2006).

2.4.4 Lund-Mackay staging

A number of staging systems based of CT scanning have been described, but the Lund-Mackay system is most commonly used (Fokkens et al. 2012). It is based on a simple numeric score (0 to 2), driven from the CT scan, in which every sinus group is assigned a numeric grade depending on the extent of the disease (Lund and Mackay 1993).

Table 1. Lund-Mackay staging system.

Paranasal sinuses	Right	Left
Maxillary 0, 1, 2		
Anterior ethmoid 0, 1, 2		
Posterior ethmoid 0, 1, 2		
Sphenoid 0, 1, 2		
Frontal 0, 1, 2		
Ostiomeatal complex 0* or 2*		
Total points to each side		

0 = no abnormalities; 1 = partial opacification; 2 = total opacification
0* = not occluded; 2* = occluded

Although CT and endoscopic scores correlate well, the correlation between CT changes and symptom scores has generally shown to be poor and not a good indicator of outcomes (Holbrook et al. 2005). In addition, incidental abnormalities are found on scanning in up to a fifth of the normal population (Fokens et al. 2012).

For ethical reasons, European Position Paper on Rhinosinusitis and Nasal Polyps 2012 considers CT staging or scoring only as an inclusion criterion for studies, not as an outcome assessment.

2.4.5 Mucociliary function

Mucociliary function can be examined by measuring ciliary beat frequency (CBF), mucociliary transit time (MTT) or mucociliary clearance (MCC). A morphological investigation on a single cilium level is performed with transmission electron microscopy (TEM). CBF and waveform analysis can also be performed using phase contrast microscopy (Pfifferi et al. 2001).

The use of saccharin, dye or radioactive particles to measure nasal MTT has been available for decades (Andersen et al. 1974, Puchelle et al. 1981). In their study, Andersen et al. placed a saccharin particle on the nasal respiratory mucosa, and the reporting of the sweet taste after transportation toward the nasopharynx was the indicator of the mucociliary transport time (MTT). Normal values for MTT are considered to be from 12 to 15 minutes, but great inter- and even intra-individual variability (sides, time) exist. Values exceeding 30 minutes are considered pathological. In another study, minute amounts of radioactively labelled technetium were used to record the velocity of the mucociliary transport rate in the nasal cavity (Kärjä et al. 1982). Normal values were considered to be 7 mm per minute; less than 3 mm per minute was considered abnormal. These methods allow the recognition of early alterations of sinonasal homeostasis, although they cannot distinguish differences between primary or secondary causes of ciliary dysfunction (Fokkens et al. 2012).

In the radionuclide measurement of MCC, the decrease of the radioactivity of the tracer per unit is measured from the area involved. The results are reported in percentages or in minutes needed for halving of radioactivity (T½) (Dal et al. 1997).

The majority of the studies on the mucociliary function in the sinonasal cavity have been conducted on the nasal mucosa. Studies investigating MTT in the maxillary sinus mucosa are limited because placing a saccharin particle in the maxillary sinus requires the surgical opening of the ostium, thus making it difficult to compare different treatment modalities in CRS (Asai et al. 2000). It is possible to determine the MCC both pre- and postoperatively using a radioisotope, but the methods used are invasive and require great effort (Dal et al. 1997, Toskala and Rautiainen 2005).

2.4.6 Rhinomanometry and acoustic rhinometry

The measurement of nasal airway resistance by assessing nasal flow at constant pressure (rhinomanometry) is of limited usefulness in CRS, although it can be of use in stating that improvement in nasal congestion is the result of a reduction in inflammation in the middle meatal area rather than mechanical obstruction (Lund and Scadding 1994).

Acoustic rhinometry is an objective method enabling measurements between the cross-sectional area of the nasal cavity and the distance into the nasal cavity. The method is based on the analysis of sound reflection from the nasal cavity taking into account the properties of incident sound submitted to the nasal cavity, along with associated reflected

sound waves (Hilberg et al. 1989). Changes resulting from medication or surgery can thus be demonstrated (Pirilä and Tikanto 2001, Numminen et al. 2003, Ragab et al. 2004).

2.4.7 Adhesion molecules and mucosal eosinophils

In chronic rhinosinusitis, the mucosal lining is characterized by basement membrane thickening, goblet cell hyperplasia, and subepithelial oedema, as well as mononuclear and eosinophilic cell infiltration (Fokkens et al. 2012). The infiltration of leukocytes to the sites of inflammation is accomplished by selectins, integrins and the immunoglobulin superfamily. Being broadly distributed on most leukocytes, L-selectin and its endothelial glycosylated ligands initiate leukocyte infiltration into inflamed tissues (van Zante and Rosen 2003). Under normal conditions, properly glycosylated L-selectin ligands are not expressed on the endothelia of tissues other than lymphatic tissues (Turunen et al. 1995). However, during inflammatory conditions such as asthma and CRS, the induction of sulphated sialyl-LewisX ligands on the postcapillary microvascular endothelium occurs (Toppila et al. 2000, Toppila-Salmi et al. 2005).

Eosinophilia has been widely reported as a marker of inflammation in CRS tissue. Histological studies have demonstrated that the inflammation typically involves the accumulation of activated eosinophils in the sinus mucosa and submucosa (Harlin et al. 1988). The mechanism by which eosinophilic inflammation damages the epithelium and contributes to CRS and to recurrent acute exacerbations have not been fully elucidated, but it has been linked to the production of inflammatory mediators and subsequent tissue damage within the sinonasal mucosa (Harlin et al.1988, Ghaffar et al. 1998). The degree of peripheral eosinophilia has also been found to predict extensive CRS (Newman et al. 1994). Other data also suggests that high tissue and peripheral eosinophilia may be predictive of failure, with revision endoscopic sinus surgery needed (Matsuwaki et al. 2008).

2.4.8 Disease-specific health status instruments and quality-of-life questionnaires

Patients' self-assessments of CRS severity and improvement following ESS have proven to be the best measures, since models that predict symptom outcomes using objective measures such as computed tomography (CT) or endoscopic scores have remained unreliable (Chester 2009). Various disease-specific health status instruments are currently available. Of these, the Chronic Sinusitis Survey (CSS), Sinonasal Outcome Test-20 (SNOT-20), and Rhinosinusitis Disability Index (RSDI) are most widely used (Chester et al. 2009, Benninger and Senior 1997).

The need for new kinds of questionnaires became apparent because attention was given only to the patient's symptoms, not the patient's quality of life. Generic health status instruments, of which the Medical Outcomes Study Short Form 36 (SF-36) is the most

widely used, thus enable us to compare the quality of life of a patient suffering from CRS with other patient groups (Ware et al. 1995). It is well validated and has been used to assess the quality of life of CRS patients (Ragab et al. 2004).

2.5 General considerations

2.5.1 Treatment principles

Treatment of chronic rhinosinusitis consists of conservative therapy and invasive methods. The choice between the different treatment modalities depends on the patient and on the severity and duration of the disease.

The conservative treatment of chronic rhinosinusitis is based on self-care. In Finland, the recommended initial conservative treatment consists of a nasal steroid spray or drops, regular nasal rinsing with an iso- or hypertonic saline solution, and humidifying nasal drops or sprays (Hytönen et al. 2013). Antihistamines and allergen avoidance in allergic patients are recommended (Fokkens et al. 2012).

Short-term antibiotics (fewer than 14 days) may be helpful in acute exacerbations of CRS (Fokkens et al. 2012). Long-term macrolide antibiotic treatment (up to three months) may be recommended for patients with unsuccessful initial therapy or with moderate to severe symptoms, although the domestic treatment guideline does not include long-term antibiotic treatment for CRS (Hytönen et al. 2013).

For patients suffering from CRS and nasal polyposis, systemic corticosteroid treatment is recommended in moderate or severe cases. However, the duration of the treatment is limited to two weeks and its frequency to a maximum of three times per year (Fokkens et al. 2012).

Invasive methods are considered if the result of conservative treatment is unsatisfactory.

2.5.2 Economic aspects

Chronic rhinosinusitis can impose a major direct economic cost on both the patient and society. These direct costs include expenses related to medication used and visits to the physician. In a US-based study, the direct costs treating a CRS patient have been estimated to be USD 2,609 per year – 6% more than on the average adult (Murphy et al. 2002). In 1996, there were 26.7 million visits to physicians, hospital offices and emergency departments for rhinosinusitis, at a total cost of USD 5.8 billion (Ray et al. 1999).

The total cost of CRS to society is even higher due to the indirect costs of the disease. Since 85% of patients with CRS are of working age, indirect costs such as missed workdays and reduced productivity increase the economic burden of disease (Blackwell et al. 2002). Despite the fact that the economic loss due to absenteeism or decreased productivity cannot

be easily quantified, rhinosinusitis has been named one of the top ten most costly health conditions to employers in the United States (Goetzel et al. 2003).

2.6 Endoscopic Sinus Surgery (ESS)

2.6.1 History of sinus surgery

The first descriptions of maxillary sinus surgery date back to the 17th century, when the maxillary sinus was accessed through the alveolar margin. Nathaniel Highmore, an English surgeon and anatomist, described in 1651 a method to open the "antrum Highmori" (as the maxillary sinus was referred to those days) through the maxillary alveolus after having first removed a tooth (Lund 2002). In the 18th century, a French surgeon, Louis Lamoier, presented a method of opening the maxillary sinus without the need for tooth extraction. According to him, the maxillary sinus could be opened through the space between molar tuberosity and the third molar tooth (Tange 1991).

John Hunter and Anselme-Louis-Bernard-Berchillet Jourdain, who independently introduced a method of entering the maxillary sinus via the middle meatus (Tange 1991), published the first studies of intranasal surgery on the maxillary sinus in the late 18th century. The lack of proper visualization of the middle meatus created significant problems for this approach, and this technique was largely abandoned after haemorrhagic problems and the realization of potential damage to the orbit (Lund 2002). During the 19th century, surgical treatment of maxillary sinusitis was usually introduced through an oroantral fistula after the removal of a tooth; the passage through middle meatus was forgotten (Tange 1991).

Development of modern rhinology began in the early 1880s when a trocar for the puncturing the maxillary antrum via the inferior meatus was independently introduced by Johan von Mikulicz-Radecki in 1886 and Herman Krause in 1887 (Tange 1991). At the end of the 19th century, three authors – George Walter Caldwell, Robert Henry Scanes Spicer and Henry Paul Luc – independently described the method of enlarged canine fossa opening, complete removal of sinus mucosa, and an intranasal antrostomy in the inferior meatus (Tange 1991). This idea of "radical sinus surgery", which was later called the Caldwell-Luc operation, was by far the most common surgical treatment modality for chronic maxillary disease at the beginning of the 20th century. However, its popularity began to diminish due to the complications associated with the procedure, the introduction of antibiotics, and the evolution of endonasal sinus surgery (Matheny and Duncavage 2003).

An inferior meatal antrostomy has also been used without addressing the maxillary sinus mucosa. Mikuliz first described the method in 1887 (Yanagisawa and Joe 1997). It has since been used in treating maxillary sinus infections (Lund 1988). In this method, the purpose of inferior antrostomy is to create a route for passive drainage and the mechanical

cleaning of the infected maxillary sinus (Al-Belasy 2004). Inferior antrostomy has been criticized for low patency rates, the risk of injury to the nasolacrimal duct or canine teeth, and more importantly, for creating a deviation from the normal sinus function (Yanisagawa and Joe 1997, Lund 1988, Al-Belasy 2004).

Development of endoscopic sinus surgery and the characterization of mucociliary clearance towards the natural maxillary sinus ostium have decreased the popularity of inferior meatal antrostomy in recent decades (Yanagisawa and Joe 1997).

2.6.2 Evolution of ESS

Historically, the introduction of nasal endoscopy is credited to Alfred Hirschmann, who in 1901 attempted an endoscopic examination of the sinonasal cavity using a modified cystoscope (Jacobs 1997). The following year, M. Reichert performed the first endoscopic sinus surgery using an endoscope to manipulate the maxillary sinuses through the oroantral fistulae (Pownell et al. 1997). Maltz promoted the use of endoscope for diagnostic evaluation of the sinonasal cavity in 1925; he also coined the term sinuscopy at the same time (Cohen and Kennedy 2005).

Professor Harold Hopkins invented the rod endoscope in the 1950s, and it was brought into clinical practise in 1961. During the 1970s, many rhinosurgeons reported the use of these endoscopes in endonasal and intrasinus surgical interventions, the foremost of them being Professor Walter Messerklinger from Graz, Austria (Stammberger 1994).

In his experimental work, Professor Messerklinger was able to show that the osteomeatal complex in the middle meatus is the key structure in the pathogenesis of maxillary, ethmoidal, and frontal sinusitis (Messeklinger 1978). Based on his findings, he introduced the concept of functional endoscopic sinus surgery (FESS). The aim of FESS is to resect the inflammatory and anatomical structures that interfere with the physiological mucociliary function and thus predispose to mucosal inflammation. This principle of limited surgical resection presented a profound change in the former practise of radical sinus surgery aimed at the total removal of the inflamed maxillary sinus mucosa.

The combined influence of the invention of the rod endoscope, Professor Messerklinger's concept of the osteometal area as the key structure for the pathogenesis of rhinosinusitis, and the development and the availability of computed tomography launched the evolution of endoscopic sinus surgery (Govindaraj et al. 2010). The principles of FESS were first published in 1985 and the first courses were held in the same year. Soon after that, FESS largely replaced radical sinus surgery and spread worldwide (Stammberger 1994).

Following the Hopkins rod, the next major technical step forwards was the evolution of instrumentation. Early endoscopic sinonasal surgery was often performed using grasping forceps, with limited regard for local mucosal preservation (Govindaraj et al. 2010). Areas of exposed bone resulted in scarring, chronic inflammation and occasionally in mucocele formation. Subsequent remucosalization in these areas possessed decreased ciliary density

and function, and was occasionally associated with chronic inflammation and pain (Kennedy et al. 2001). For this reason, through-cutting instruments were adapted.

The microdebrider, originally developed for orthopaedic procedures, followed the through-cutting instrumentation. It was introduced for endonasal surgery by Setliff and Parsons in 1996. The use of disposable blades enabled maintenance of a consistently sharp cutting interface, thus minimizing the risk of mucosal stripping. Another major advantage of the microdebrider is its concurrent suction, allowing visualization even in the presence of significant bleeding. On the other hand, the use of microdebriders resulted in markedly more rapid and severe complications when the orbit or intracranial cavity were entered (Hackman and Ferguson 2005).

Suction-irrigating drills provided another significant advance in instrumentation. In chronic rhinosinusitis, drills allow the removal of bone when it is considered necessary. More importantly, they have improved the ability to remove intranasal tumours, since it is important to remove underlying bone in tumours in order to ensure an appropriate tumour resection margin.

Visualization has always been a major issue in endoscopic sinus surgery. Traditionally, endoscopes with a diameter of 4 mm have been used during standard procedures. In paediatric cases, endoscopes with a diameter of 2.7 mm are available. The standard endoscope length is 18 cm and it has angles of 0°, 30°, 45°, and 70°. There are also endoscopes with a variable direction of view.The image is dependent on the quality of the endoscope, the light source, the cable connected to the endoscope, the camera and the monitor used. Recent technical improvements in all of these fields have provided a better and more precise view of the operating area.

The development of CT imaging improved the understanding of chronic rhinosinusitis and provided a major initial impetus to develop the concept of endoscopic sinus surgery. The subsequent advent of high-resolution CT imaging further facilitated accurate assessment of disease severity, and it provides anatomical detail to enable pre-operative surgical planning and preparation. Interactive imaging, developed in the late 1980s, has improved surgical planning as well as intra-operative decision-making; although there is no strong evidence that it reduces the incidence of complications. Nevertheless, computer interactive imaging is helpful with regard to orientation during extensive and revision surgical procedures.

Balloon sinuplasty, developed in 2002, is a novel method in endoscopic sinus surgery (Lanza and Kennedy 2006). The sinus ostium is entered in an atraumatic fashion via a catheter-based system, and the ostia are dilated while minimizing the injury to surrounding tissue. Currently, the indications for balloon sinuplasty remain unclear and long-term studies will be necessary before recommendations on the use of technique can be made (Govindaraj et al. 2010).

2.6.3 Indications and contraindications for ESS

The main indications for ESS include acute recurrent or chronic maxillary, frontal or sphenoidal sinusitis that is unresponsive to conservative treatment (Kennedy 1985). Other indications include nasal polyposis, cerebrospinal fluid leaks, benign and malignant tumours of the nasal cavity and the sinuses, olfactory disturbances, pituitary tumours, skull base tumours, orbital or optic nerve decompression, and infection of the orbit (Davidson and Stearns 1994).

Contraindications proposed for ESS include the presence of acute infectious intracranial complication or incomplete access to the pathology with the endoscopic approach (Gleeson et al. 2008).

2.6.4 Surgical technique in ESS

In the surgical treatment of chronic maxillary rhinosinusitis, the main aim is to restore normal mucociliary clearance of the diseased sinus or sinuses. In ESS, this is accomplished by opening the sinus ostium and clearing it of swollen and/or diseased mucosa and/or removing obstructing or diseased structures in the anterior ethmoidal region. The diseased mucosa of the maxillary sinus itself is not removed, because it should heal after the proper function of the osteomeatal complex has been restored. The extent of endoscopic sinus surgery is always dependent on the extent of the disease, and a step-by-step approach is recommended (Kennedy 1985, Stammberger and Posawetz 1990).

2.6.5 Anaesthesia in ESS

Selection of the anaesthetic method is based on the type and extent of the surgery performed, and on patient-related factors. Primary endoscopic sinus surgery limited to the ostiomeatal complex can be performed under local anaesthesia with or without intravenous sedation on most adult patients. Surgery that is more extensive may require the use of general anaesthesia (Kennedy 1985, Danielsson et al. 2003).

2.6.6 Postoperative debridement, treatment and recovery after ESS

During the early years of ESS, frequent postoperative debridement was considered mandatory. It was believed to facilitate the healing of nasal and sinus mucosa, prevent postoperative infections and hinder scar formation (Kennedy 1985). However, there is little data concerning postoperative mucosal healing and the efficacy of postoperative debridement and its optimal timing after ESS (Thaler 2002). This has led to variable postoperative care schemes.

Postoperative treatment after ESS usually includes different packing and spacer materials left in the middle meatus (Chandra et al. 2005), nasal douches, and the use of topical and systemic medication, such as steroids and antibiotics (Delgaudio and Wise 2006, Bhattacharrya et al. 2004). All of these treatments are used in different combinations and intensities, but the evidence of efficacy is limited.

Scientific data concerning patient recovery to normal daily activities after ESS is limited. In a retrospective postal questionnaire survey, patients have been shown to have recovered two weeks after ESS. Postoperative pain and infection were reported as the most important reasons for a delayed return to normal daily activities (Chidambaram et al. 2001).

2.6.7 Complications after ESS

Complications after ESS are related to the variability of the region's anatomy and the proximity of the brain and orbits. Major complications occur in approximately 1% of cases. These complications include bleeding from ethmoidal, sphenopalatine or carotid artery, orbital haematoma, anosmia, diplopia, injury to the optic nerve, damage to the nasolacrimal duct, cerebrospinal fluid leak, pneumocephalus, encephalocele, brain abscess, meningitis, intracranial bleeding, direct brain trauma, toxic shock syndrome and death. Minor complications occur in 5–6% of cases, and include minor bleeding, local infection, orbital emphysema, eyelid ecchymosis, atrophic rhinitis and temporary dysfunction of the olfactory and infraorbital nerves. (Fokkens et al. 2012.)

2.6.8 Outcomes of ESS

As with all surgery, it is often impossible to organize randomized controlled trials (RCT) in endoscopic sinus surgery. The Cochrane Collaboration (Khalil and Nunez 2009) reassessed and revised 2,323 studies concerning surgery on CRS. Using strict methodological quality inclusion criteria, only three of them fulfilled the criteria of RCTs, with only two having an acceptable sample size (Hartog et al. 1997, Ragab et al. 2004). The Cochrane Collaboration (2009) stated that "ESS has not been demonstrated to confer additional benefit to that obtained by medical treatment with or without antral irrigation in relieving the symptoms of chronic rhinosinusitis". However, in EPOS 2012, it was stated that there was simply insufficient evidence in these studies for any comment about the value of ESS compared to medical treatment (Fokkens et al. 2012).

Large prospective studies and case series have shown that ESS is an effective and safe procedure for the management of patients with CRS who have failed medical treatment (Hopkins et al. 2006). Chester et al. (2009) screened 289 studies, and eventually included 21, using symptom severity scores to analyse at least three CRS symptoms (facial pressure, nasal obstruction, postnasal discharge, hyposmia or headache). All symptoms improved

compared with their preoperative scores. Nasal obstruction improved the most. Facial pain and postnasal discharge demonstrated moderate improvements, while hyposmia and headache improved the least.

Both generic (SF-36) and disease specific (SNOT20, SNOT22, RSOM31) quality-of-life (QOL) outcome measures have shown improvement after surgery on CRS (Croy et al. 2010, Hopkins et al. 2006, Deal and Kountakis 2004, Hopkins et al. 2009). Croy et al. showed that SF-36 scores which were significantly decreased before surgery improved and came very close to normal levels four months after surgery. In disease specific QOL measurements, improvement in after surgery was more pronounced in patients with nasal polyps compared to those patients with CRS without polyps.

2.6.9 Controversies in maxillary sinus surgery and ESS

Since ESS is not a standardized procedure, the extent of surgery in ESS may vary from simple partial uncinectomy to radical sphenoethmoidectomy. Surgery on the frontal sinuses or nasal turbinates may also be performed.

In a prospective trial of 65 patients with CRS with/without nasal polyposis, Kuehnemund et al. (2002) studied the difference between uncinectomy and a sphenoectomy with a wide opening to the frontal recess. Outcome parameters included symptom scores, rhinoscopy scores and nasal saccharin transport time. There were no relevant differences after periods of 3, 6 and 12 months. In a retrospective study, Jankowski et al. (2006) compared a case series of 37 ESS-treated patients with extensive nasal polyps with a historic group of patients with a similar disease extent treated with sphenoethmoidectomy and middle turbinate resection. Nasal symptoms, the number of patients with revision surgery, and nasal endoscopy scores were assessed five years after surgery. The radical surgical procedure showed better symptom scores, fewer recurrences and better endoscopic scores at the follow-up visit. In both of these studies, however, the recall rate was low and differed between the investigated groups.

The role of middle meatal antrostomy has also been a topic of discussion since the introduction of minimally invasive techniques in ESS (Catalano 2006). Only a few controlled studies have compared the effects of antrostomy and simple uncinectomy in CRS. In a prospective study comparing small (less than 6 mm) to large (more than 16 mm) antrostomies, no statistically significant correlation between the degree of improvement of the main rhinosinusitis symptoms was found (Albu and Tomescu 2004). In a prospective study of patients with CRS with additional polyps comparing uncinectomy and additional middle meatal antrostomy, it was found that that a large middle meatal antrostomy had a better patency rate than an undisturbed maxillary sinus ostium only in the early phase of evaluation (three months postoperatively). From the six months to the final evaluation (one year), there was no statistically significant difference between the surgical techniques, recurrent polyposis being the main reason for re-occlusion of the ostium. CT findings were not evaluated in this study (Wadwongtham and Aeumjaturapat 2003). While there is some

evidence that more extensive surgery may be associated with better objective outcomes, the consensus is to tailor the extent of surgery to the extent of disease (Fokkens et al. 2012).

2.6.10 Revision sinus surgery

Approximately 20% of patients with CRS with/without polyps respond unsatisfactorily to ESS with concomitant medical therapy, and they eventually require revision surgery (Hopkins et al. 2009). Extensive polyps, bronchial asthma, ASA-intolerance, cystic fibrosis, a computed tomography stage and previous surgery are predictors of an unsatisfactory surgical result (Deal and Kountakis 2004, Marks and Shamsa 1997, McMains and Kountakis 2005). Success rates of revision ESS have been reported to range between 50% and 70% (Kennedy 1992, King et al. 1994). Complication rates of ESS revision surgery are substantially higher compared with initial surgery, ranging from approximately 1% up to 7% (Chu et al. 1997).

3 AIMS OF THE STUDIES

The aim of the studies was to evaluate two different techniques in endoscopic sinus surgery (ESS): uncinectomy with additional maxillary sinus antrostomy and uncinectomy without additional maxillary sinus antrostomy. The studies were concluded as prospective randomized clinical trials in patients with chronic maxillary rhinosinusitis (CRS) without nasal polyposis.

Special attention was given:

1. To evaluate the presence of L-selectin ligands in maxillary sinus mucosa in CRS;
2. To compare mucociliary clearance (MCC) in maxillary sinuses after simple uncinectomy and uncinectomy with additional maxillary sinus antrostomy;
3. To evaluate the pre- and postoperative expression of L-selectin ligands and mucosal eosinophils in maxillary sinus mucosa;
4. To compare preoperative and postoperative CT findings by Lund-Mackay scores after simple uncinectomy and uncinectomy with additional maxillary sinus antrostomy;
5. To compare subjective symptoms and sequelae, both during the early postoperative period, and nine months and five years postoperatively.

4 MATERIALS AND METHODS

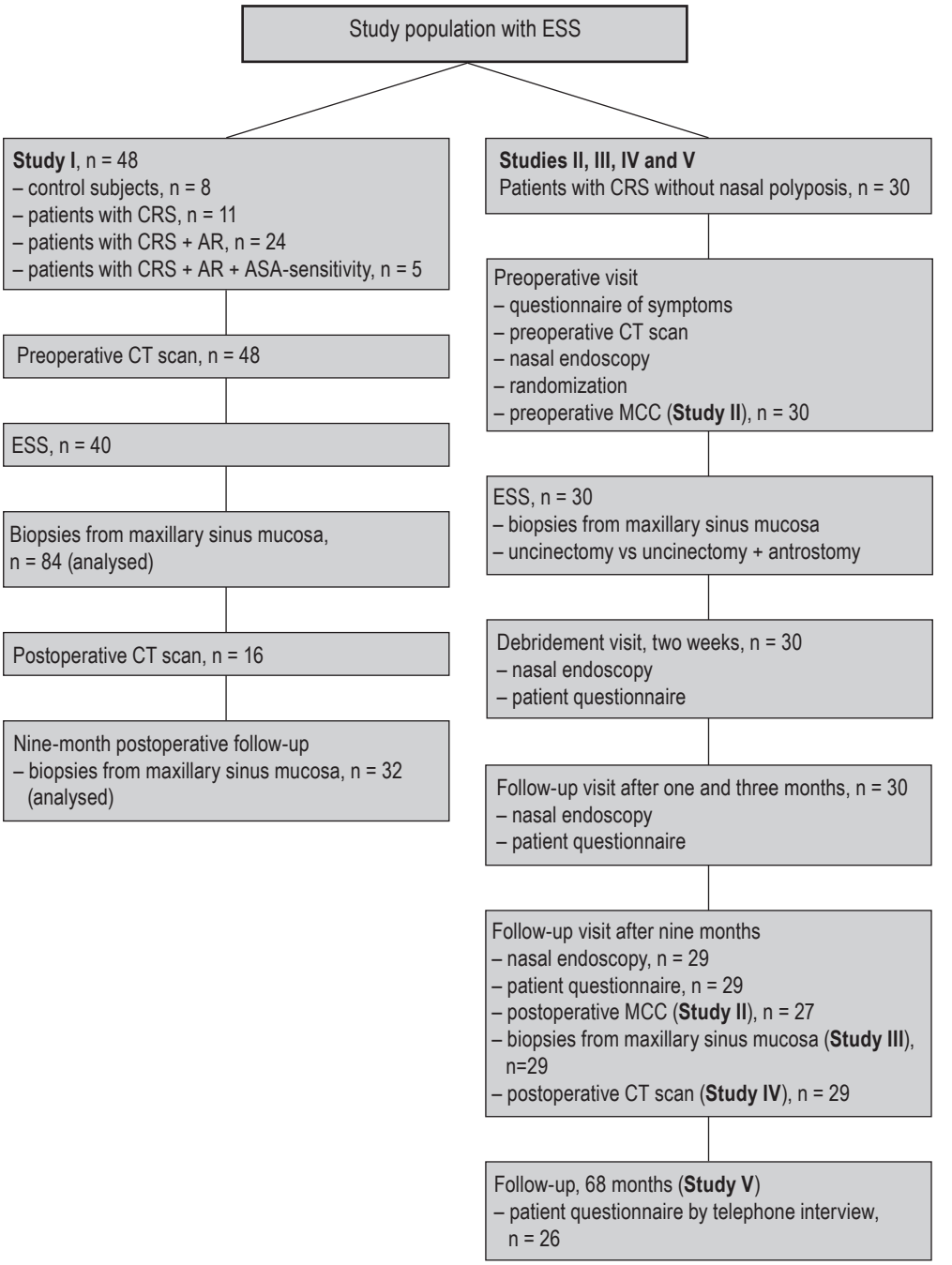

Figure 1. Flowchart of the studies

4.1 Patients

The candidates for inclusion in the studies were patients with chronic rhinosinusitis.

Inclusion criteria in studies II–V were: moderate to severe sinus-related symptoms lasting at least 12 weeks despite maximal medical treatment (intranasal corticosteroid and/or antihistamine), e.g., at least two major factors (facial pain, nasal obstruction, nasal discharge, hyposmia, and anosmia), or at least one major or two minor factors (fever, halitosis, fatigue, dental pain, cough, and ear ache); endoscopic findings (mucosal thickening, purulent discharge); and total Lund-Mackay sinus computed tomography scores of at least 6/24 but no more than 18/24. Exclusion criteria were: an age under 18 years; oral corticosteroid treatment during the two months prior to surgery; previous nasal surgery; a history or physical examination suggestive of severe nasal septal deviation (that causes only unilateral nasal obstruction and/or requires septoplasty before performing ESS); unilateral sinusitis; nasal polyposis grade I or more (Hadley's clinical scoring system); aspirin sensitivity, chronic bronchitis, cystic fibrosis, tumour or disease with severe impact on general immunity; mild sinus-related symptoms; and the following computed tomography findings: severe chronic pansinusitis (total opacification in posterior ethmoidal and/or sphenoidal and/or frontal sinuses and/or total obstruction of the frontal recess) and a Lund-Mackay score less than 6/24 or more than 18/24.

The material in Studies I–V consisted of patients examined at the Departments of Otorhinolaryngology at Tampere University Hospital and Mikkeli Central Hospital. In Studies II–V, the study group comprised 30 patients (20 women and 10 men) who suffered from CRS and met the criteria for surgical intervention. The average age was 47 years (range 22–66 years).

Study I involved 48 patients, consisting of the same 16 patients as in Studies II–V plus 32 patients of whom 8 did not suffer from CRS. There were 30 women and 18 men in this study, with an average age of 47 years (range 19–75 years). 7 of these patients had nasal polyposis.

The clinical otorhinolaryngological examinations, rigid nasal endoscopies, operative care, tissue sampling and the follow-up of the patients took place at the Department of Otorhinolaryngology, Head and Neck Surgery, Tampere University Hospital and at the Department of Otorhinolaryngology, Mikkeli Central Hospital. The HRCT images were performed at the Medical Imaging Centre, Department of Radiology, Tampere University Hospital, and at the Department of Radiology, Mikkeli Central Hospital. Reconstructions of the ostiomeatal complex area from the original HRCT images were made at the Medical Imaging Centre, Department of Radiology, Tampere University Hospital. The measurements of the mucociliary clearance were made at the Departments of Nuclear Medicine at Tampere University Hospital and Mikkeli Central Hospital. Tissue samples of the maxillary sinus mucosa were stained and analysed at the Department of Otorhinolaryngology, Head and Neck Surgery, Tampere University and at the Haartman Institute, Department of Bacteriology and Immunology, University of Helsinki.

Dropouts from the studies: one patient died accidentally prior to the postoperative control. Three additional patients missed the last follow-up (68 months) due to the fact that we were unable to contact them by telephone.

4.2 Methods

4.2.1 Preoperative and postoperative assessment

During the patient's preoperative visit to the polyclinic, a complete medical history was taken, and the diagnostic criteria, the execution of proper conservative treatment, and the presence of exclusion criteria were recorded. All patients underwent complete otorhinolaryngological examination with nasal endoscopy under local anaesthesia.

The patients also completed preoperative study forms during the preoperative visit. A clinical otorhinolaryngological examination and nasal endoscopy was repeated on visits two weeks, one month, three months and nine months postoperatively. The patients completed postoperative study forms at the same postoperative visits (Studies I–IV). Long-term postoperative results (an average of 68 months) were recorded in a conversation with the patient during a telephone call (Study V).

4.2.2 Computed tomography scan and Lund-Mackay staging

High-resolution CT imaging of the nasal airways and paranasal sinuses was performed on a ProSpeed PLUS scanner (General Electric, Milwaukee, WI, USA) equipped with a helical CT tube. The tube had a voltage of 120 kV and tube current of 200mA. The thickness of the coronal slices was 3 mm with no intervening gap, a field of view was 25 cm and matrix size was 512. Imaging was done preoperatively (Studies I–V) and nine months postoperatively (Studies II–V). Analysis of the preoperative and postoperative CT scans and the Lund-Mackay staging of the CT scans were done on one occasion by two blinded authors (Studies I–V).

The ostiomeatal complex was reconstructed with a 1 mm slice thickness. Two blinded authors calculated the anterioposterior (AP) and the cephalocaudal (CC) dimensions of the ostium on one occasion using the distance measurement data from the postoperative CT scan database. The maxillary sinus ostium was considered to be an ellipse with AP and CC dimensions as the major and minor axis respectively. Thus, the postoperative ostium size was determined to be $0.25\pi APCC$ (Study IV).

4.2.3 Surgical methods

Endoscopic sinus surgery was performed under local anaesthesia. Cotton applicators soaked in a solution of cocaine hydrochloride combined with lidocaine 10 mg/ml with 5 µg/ml adrenaline were applied for 30–40 minutes before the operation under the middle and lower turbinates and in the roof of the nose cavity to block the sphenopalatine and ethmoidal nerves. At the beginning of the operation, 1 ml of lidocaine 10 mg/ml with 5 µg/ml adrenaline was injected submucosally into the medial infundibular wall. Intravenous sedation (midazolam 1–2 mg and/or fentanyl 0.05–0.1 mg were given at the beginning of surgery and repeated thereafter when needed.

The operation was performed using the endoscopic sinus surgery technique, using rigid 4 mm endoscopes (Karl-Storz, Tuttingen, Germany) with deflection angles of 0° and 30°. The maxillary sinus ostium was first identified using an ostium seeker. The uncinate process was then identified and medialized, and the lower two-thirds was removed using backbiting forceps. If mucosa blocked the maxillary sinus ostium on the uncinectomy-only side, as little as possible was carefully removed from it without disturbing the bony ostium. Otherwise, the bony ostium was left intact. On the additional middle meatal antrostomy side, the diameter of the ostium was duplicated in the posterior direction with cutting forceps. The ethmoidal bulla was opened on both sides on 25 of the 30 patients. The posterior ethmoidal cells, sphenoidal sinuses and frontal sinuses were left undisturbed. Biopsies from both maxillary sinuses were taken using sinus giraffe forceps for microscopic evaluation.

Haemostasis was achieved with nasal packing (Merocel® Medtronic Xomed Surgical Products, Jacksonville, USA) under the middle turbinate. The packing was removed on the following day by the surgeon or patient him/herself.

The operations were performed by the ENT resident surgeon (the author) and the ENT surgeon working at the Clinic of Otorhinolaryngology of Tampere University Hospital and Mikkeli Central Hospital during the years 2001–2003.

4.2.4 Mucociliary measurements

MCC measurements were taken preoperatively and nine months postoperatively. Irrigation tubes (SinoJect®, Atos, Hörby, Sweden) were introduced through the inferior meatus into the maxillary sinuses at least 30 minutes before the measurement to avoid any reflectory ciliostasis due to the puncture. The procedure was performed under local anaesthesia, with 4% lidocain c. adrenalin cotton placed in the inferior meatus for 10 minutes. With a thin catheter and a 1 ml syringe, a drop (0.03 ml) of sterile human serum albumin labelled with 99mTc (Venticol, Sorin Biomedica, Saluggia, Italy) was applied through the irrigation tube to the bottom of both maxillary sinuses at the same time. Each patient was seated in front of a gamma camera (Picker SX-300, Elscint 409 ECT, Siemens Ecam) with an all-purpose

parallel-hole collimator (high-resolution in Siemens) connected with a Gamma-11, Elscint or Siemens computer system for processing. Clearance of the tracer in both sinuses was monitored at the same time from an anterior view for 40 minutes. The area of the initial tracer in the sinuses was marked and clearance of tracer from the sinuses, as well as the possible appearance of activity in the pharynx, was measured with gamma imaging at time-points 0, 10, 20, 30 and 40 minutes from the anterior view, with residual activity (percentage from the initial) determined in the sinuses. Two cobalt buttons were fixed on the forehead and one on the upper part of the sternum for the control of errors caused by patients' movements. The radiation activity of the amount of tracer used for both sides totalled 40 μCi; the dose of radiation per patient was 50 μSv.

4.2.5 Tissue samples and Immunohistochemistry

The biopsies of the maxillary sinus mucosa were taken intraoperatively from all subjects, and additionally from the patients with CRS nine months postoperatively under local anaesthesia. The control maxillary sinus biopsies from eight subjects without CRS were obtained during orbital decompression or bimaxillary osteotomy. These patients had never suffered from chronic sinusitis or allergic rhinitis. Intraoperative maxillary sinus biopsies from 10 additional CRS patients with or without nasal polyps were also taken to increase statistical power in evaluating the histological alterations.

Sections of paraffin-embedded tissue samples were stained with hemalaun-eosin for calculating the number of mucosal eosinophils/mm^2. L-selectin ligands were studied immunohistochemically with two monoclonal antibodies (mAbs). MAb HECA-452 recognizes α2,3-sialylation and α1,3-fucosylation of lactosamine, and MAb MECA-79 recognizes an extended sulphated core 1 lactosamine structure. MAb HECA-452 (rat IgM) (2 μg/ml) and mAb MECA-79 (rat IgM) (1 μg/ml) were kindly provided by Professor S. Jalkanen (University of Turku, Turku, Finland). Anti-human CD34, class II (mIgG1) (2 μg/ml; DAKO, Glostrup, Denmark) was used as a positive control for the detection of endothelial cells. MAbs 7C7 (mouse IgM) (1.2 μg/ml) and TIB-146 (rat IgM) (10 μg/ml), both kindly provided by Professor S. Jalkanen, were used as negative controls. For immunohistochemical techniques and microscopic analysis of the specimens, the mean number of mAb HECA-452^+, and mAb MECA-79^+ vessels was divided by the mean number of $CD34^+$ vessels from the whole specimen, yielding the percentage of sialyl-$Lewis^X$- or sulfated lactosamine-reactive vessels.

Disabilities in following the study protocol: Postoperative biopsies were not taken from the seven patients at Mikkeli Central Hospital because of misinterpretation of the study protocol. In addition, one or two pre- or postoperative samples from three patients were non-representative. Altogether, the number of patients with acceptable intra- and postoperative specimens from both sinuses comprised only 16 patients.

4.2.6 Statistics and software

In Study I, data values were expressed as means ± SD, and in Studies II–V as median and interquartile ranges. In Studies I and III, the results were first analysed by the non-parametric Kruskal-Wallis variance by ranks, and then by the non-parametric Mann-Whitney U-test for multiple comparisons in different groups. In Studies I–V, the non-parametric Spearman rank correlation was used to study the correlation between the ranks. In Study I, the Spearman rank-order correlation coefficient (r) was also used to assess bivariate association. In Studies II–V, the non-parametric Wilcoxon rank sum test was used for comparison of matched pairs.

In all studies, a two-tailed p value less than 0.05 was considered significant with all tests.

Patient characteristics and variables were analysed with Statistical Package for Social Sciences (SPSS Base 11.0 Statistical Software package, SPSS Inc., Chicago, IL).

4.2.7 Ethical considerations

The studies were approved by the Research Ethics Committee of Pirkanmaa Hospital District, Tampere, Finland (decision numbers R01070, R01036). The patients were given oral and written information of the trial protocol, and they provided written consent. The principles of good clinical practice were followed in the trials.

5 RESULTS

5.1 Endothelial L-selectin ligands and eosinophils in maxillary sinus mucosa (I, III)

Compared with the control samples, an increased number of mucosal eosinophils and percentages of endothelial sulfated sialyl-Lewis^X epitopes were found in maxillary sinus specimens taken from patients with CRS during the operation. A higher number of mucosal eosinophils was observed from intraoperative specimens obtained from CRS patients with allergic rhinitis (AR) than from CRS patients without allergic rhinitis. The mucosal parameters did not differ significantly between CRS groups with or without nasal polyposis.

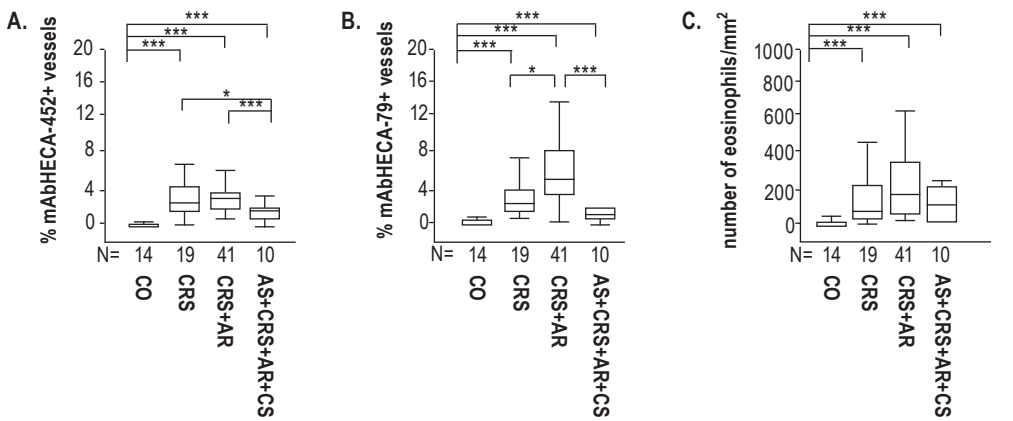

Figure 2. Comparison of the percentages of vessels expressing sulfo sLe^X epitopes (analysed with anti-sLe^X antibody (mAb HECA-452) and anti-sulfated extended core 1 lactosamine antibody (mAb MECA-79)) and of the number of eosinophils in intraoperative maxillary sinus mucosa (AS = aspirin-sensitive patient, CO = normal control subjects, CS = preoperative oral corticosteroid treatment). Only the significant differences are marked (***p < 0.001, *p < 0.05).

When comparing the two sides of each CRS patient before operation, there were no statistically significant differences in the presence of endothelial sulfated sialyl-Lewis^X glycans, mucosal eosinophils, symptom score, or mucociliary clearance values. Therefore, any postoperative difference in the parameters between the sides was considered to be due to the difference between ostium-preserving and enlarging techniques.

When comparing the specimens taken from patients during ESS and nine months postoperatively, the expression level of mAb HECA-452^{+} and mAb MECA-79^{+} vessels had decreased significantly postoperatively with both ostium enlarging or saving techniques. The postoperative decrease of mucosal eosinophils reached significance only on the antrostomy side but not on the side with the uncinectomy only. No statistically significant differences were observed in the presence of tissue eosinophils or percentages of endothelial sulfated sialyl-Lewis^{X} epitopes when comparing the postoperative specimens from each side.

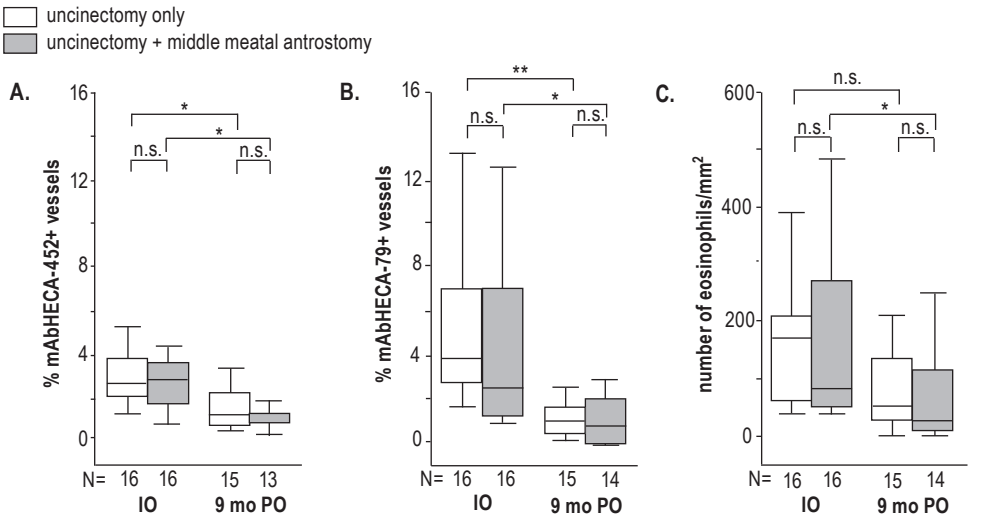

Figure 3. Comparison of the percentages of vessels expressing sulfated sialyl-Lewis^{X} epitopes, and the number of eosinophils in the maxillary sinus mucosa of patients with CRS (IO = intraoperative, 9 mo PO = nine months postoperatively). ** = $p < 0.01$, * = $p < 0.05$, n.s. = no significant difference.

5.2 Mucociliary clearance (II)

Preoperatively, the mean residual activity measured after 40 minutes was 87.2% on the uncinectomy side. On the middle meatal antrostomy side, the mean residual activity after 40 minutes was 94.2%. Preoperatively, there were 13 out of 27 (48.1%) sinuses on the uncinectomy side and 15 (55.5%) sinuses on the middle meatal antrostomy side where no clearance was seen during the 40-minute follow-up time. Residual activity was considered as good (< 50%) in two (7.4%) sinuses on the uncinectomy side and in one (3.7%) sinus on the middle meatal antrostomy side.

Postoperatively, the mean residual activity on the uncinectomy side after 40 minutes was 94.1%. On the middle meatal antrostomy side, the mean residual activity after 40 minutes was 88.4%. Postoperatively there were 14 (51.9%) sinuses on the uncinectomy side and 14 (51.9%) sinuses on the middle meatal antrostomy side where no clearance was seen during

the 40-minute follow-up. Residual clearance was considered good (< 50%) in one (3.7%) sinus on the uncinectomy side (not the same sinus as in preoperative measurements). On the middle meatal antrostomy side, residual clearance was considered good in four (14.8%) sinuses (including one of the same sinuses as in preoperative measurements).

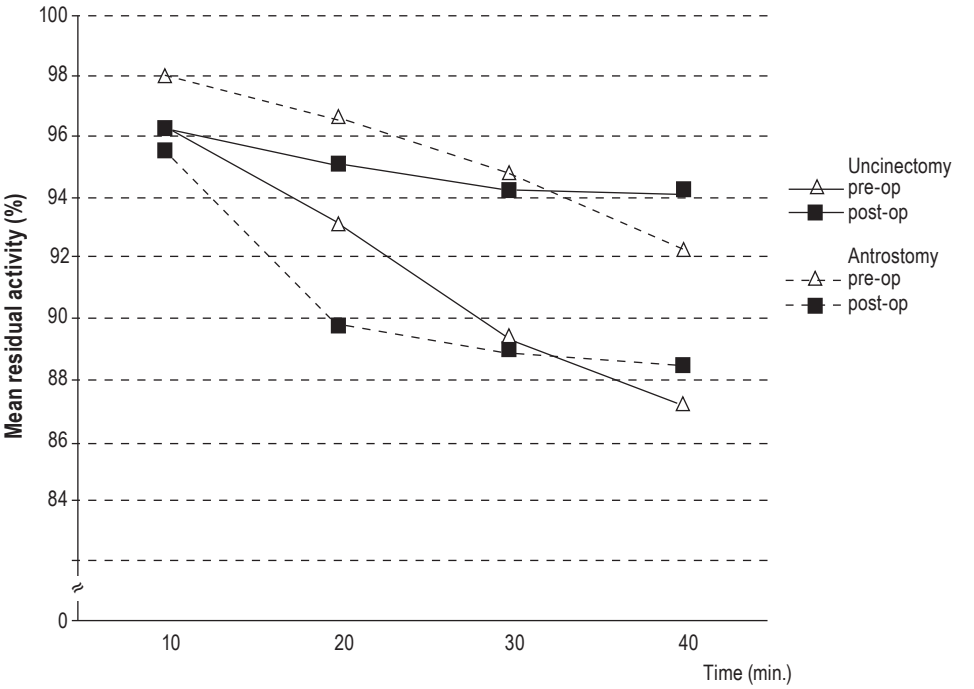

Figure 4. Mean residual mucociliary activity preoperatively and postoperatively in uncinectomy alone (n=27) and in uncinectomy combined with the middle meatal antrostomy (n=27).

5.3 Computed tomography (IV)

Observation of both sides of each CRS patient before operation revealed no statistically significant differences in the Lund-Mackay scores or Lund-Mackay values for maxillary sinus or ostiomeatal opacification. Therefore, any postoperative differences in CT parameters between the sides were considered to be due to the difference between ostium-preserving and enlarging techniques.

Comparison of the Lund-Mackay scores with CT scans taken prior to surgery and nine months postoperatively exposed a statistically significant difference on both the ostium enlarging and preserving sides. However, no statistically significant difference was observed in the postoperative Lund-Mackay scores when comparing both sides.

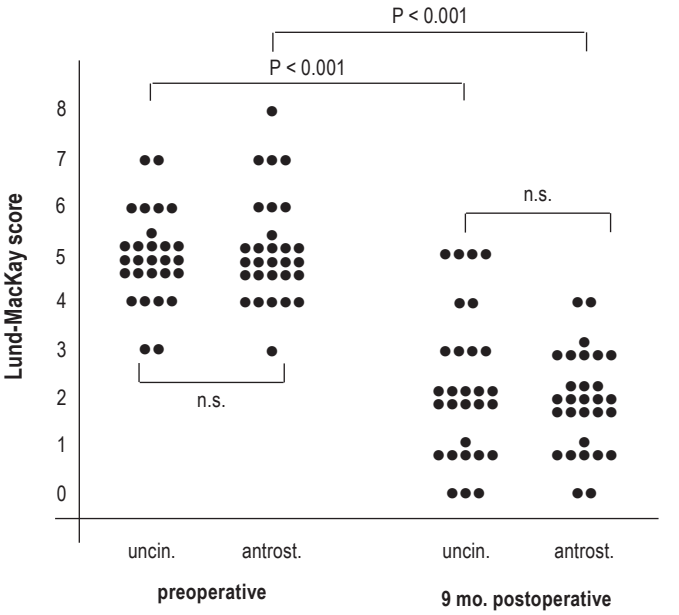

Figure 5. Comparison of unilateral Lund-Mackay (LM) scores from CT scans.

When observing both sides from postoperative CT scans, the anteroposterior (AP) diameter of the antrostomy side was statistically significantly greater than that of the uncinectomy side (the mean values were 0.98 cm and 0.52 cm, respectively). Similarly significant differences were found for the cephalocaudal (CC) diameter in postoperative CT scans (the mean values were 0.75 cm and 0.41 cm, respectively). Moreover, the ostium area was also significantly greater on the antrostomy side in calculations from postoperative CT scans (the mean values were 0.70 cm^2 and 0.23 cm^2, respectively).

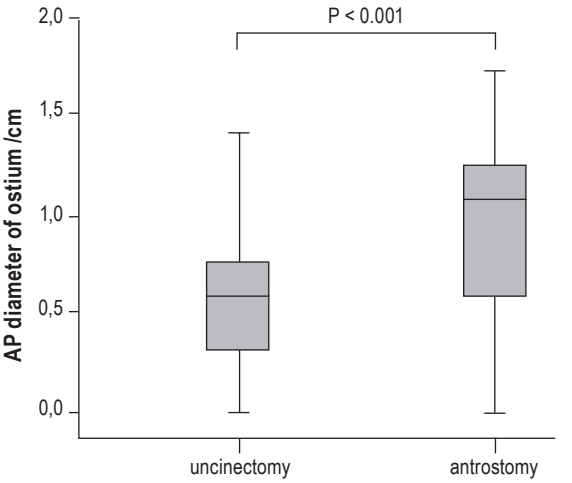

Figure 6. The anterior-posterior (AP) diameter of the maxillary sinus ostium calculated from CT scans taken nine months postoperatively.

Interestingly, the area of ostium correlated significantly with the greater change in Lund-Mackay values for maxillary sinus opacification and values for infundibulum size, indicating that an uncinectomy with additional antrostomy seems to be slightly more effective in healing maxillary mucosal inflammation.

5.4 Long term outcomes (V)

When comparing preoperative and postoperative (nine and 68 months) symptoms (facial pain, nasal obstruction and discharge values and the mean of these values), a significant reduction on both the ostium-preserving and the ostium-enlarging sides was observed. There was no significant difference between the operation techniques. Symptom values for a reduced sense of smell and postnasal drip could not be compared between the sides; however, they declined significantly when comparing preoperative and postoperative values.

When observing satisfaction with the operation at nine and (on average) 68 months postoperatively, the majority of patients expressed good/moderate satisfaction, and there were no differences between operative techniques.

When comparing preoperative and postoperative exacerbation rates, e.g., the number of all reported antibiotic courses for physician-diagnosed sinusitis during the last year, the number decreased significantly. The number of cases of acute sinusitis per year increased slightly between nine and 68 months postoperatively. The AECRS rate could not be compared between sides.

Revision surgery was performed on one antrostomy side and three uncinectomy-only sides during the observation period. This observation was not statistically significant.

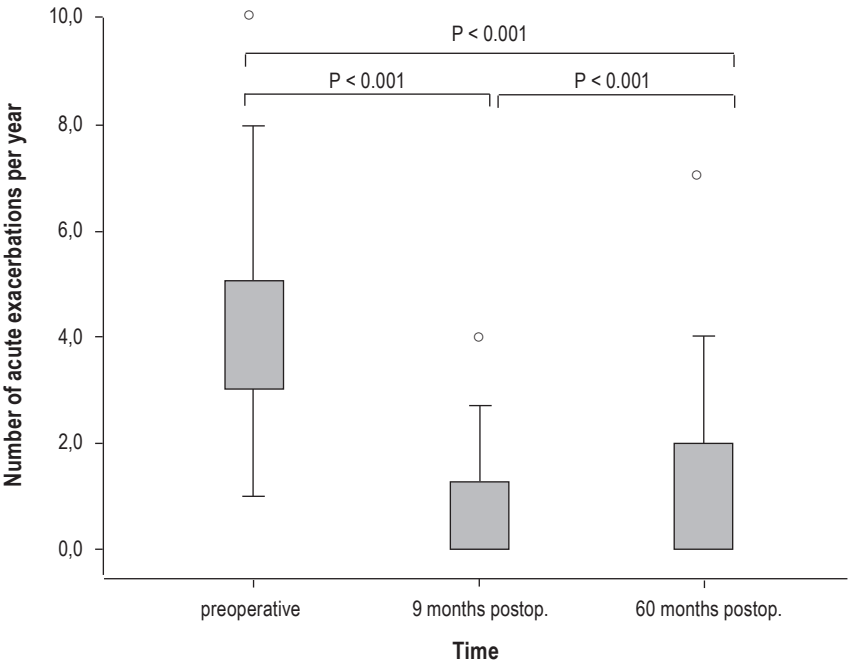

Figure 7. The patient-recorded number of acute exacerbationes, e.g., prescribed antibiotic courses for physician-diagnosed sinusitis, per year.

There was no association with sex, age, number of acute rhinosinusitis/year, allergic rhinitis, asthma, smoking, job exposure, use of intranasal corticosteroid or antihistamine when analysing the median values of pre- or postoperative symptoms and satisfaction for either the ostium-preserving or ostium-enlarging sides. Interestingly, there was a statistically insignificant trend of patients with asthma and/or job exposure more frequently expressing satisfaction only on the antrostomy side or saying that neither technique provided them satisfaction.

5.5 Correlation between different measurements (III, IV, V)

The expression level of endothelial sulfated sialyl-Lewis^X glycans and the number of eosinophils did not correlate with the preoperative symptom score in intraoperative maxillary sinus biopsies. However, the postoperative symptom score correlated with the grade of mucosal eosinophils in the postoperative maxillary sinus samples of both operative techniques. In addition, when comparing the number of intraoperative mucosal

eosinophils and postoperative symptoms, a correlation was found only on the antrostomy side. The postoperative symptom score correlated with the postoperative percentage of mAbs HECA-452^{+} and MECA-79^{+} vessels only on the side with the ostium-preserving technique.

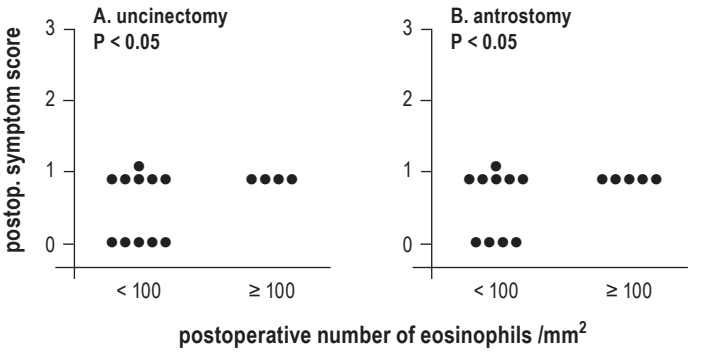

Figure 8. The correlation between the grade of the postoperative number of mucosal eosinophils and postoperative symptom score. (y-axis: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms).

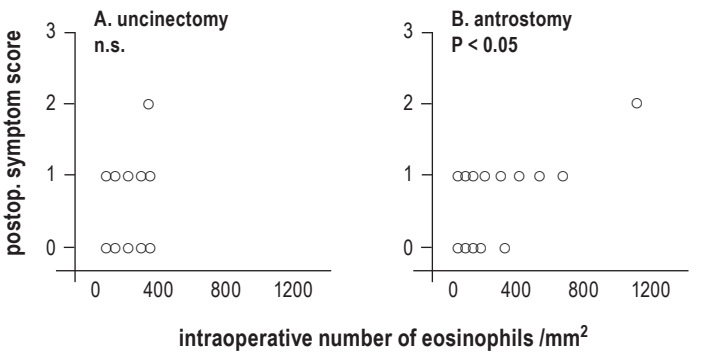

Figure 9. The correlation between the intraoperative number of mucosal eosinophils and postoperative symptom score.

No correlation was observed between pre- or postoperative mucociliary clearance values and the intra- or postoperative presence of endothelial sulfated sialyl-Lewis^{X} glycans or mucosal eosinophils.

A negative correlation was observed between the ostium area and postoperative Lund-Mackay scores, both of which were calculated from CT scans taken nine months postoperatively. However, no correlation was observed either between the postoperative symptoms/symptom sum and postoperative Lund-Mackay score, or between the postoperative symptoms/symptom sum and postoperative size of the ostium.

The age, sex, or patient history of allergic rhinitis and/or asthma diagnosis, hypertrophic polypoid sinus mucosa, smoking, or intranasal corticosteroid and/or antihistamine medication did not associate with the median values of the pre- or postoperative Lund-Mackay scores from either the ostium-preserving or -enlarging side. Similarly, these patient history parameters did not associate with the mean values of the postoperative ostium area from either the ostium-preserving or the ostium-enlarging side.

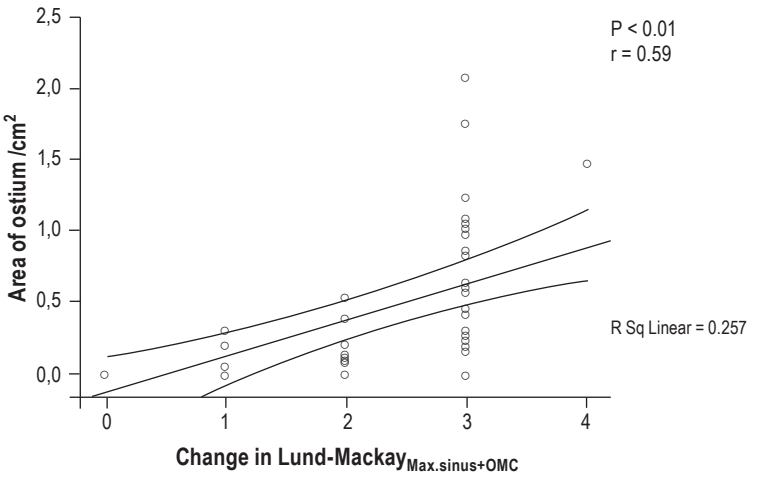

Figure 10. The correlation between the area of maxillary sinus ostium and the unilateral postoperative change in Lund-Mackay (LM) values for maxillary sinus opacification plus ostiomeatal complex obstruction nine months postoperatively.

6 DISCUSSION

6.1 General Discussion

Internationally, endoscopic sinus surgery (ESS) is considered a treatment modality in CRS after the failure of medical treatment, even though the Cochrane Collaboration has stated that ESS offers no additional benefit to that obtained by medical treatment in relieving the symptoms of CRS.

Despite the fact that there are large prospective studies and case series showing the efficacy and safety of ESS in CRS, the evidence is still considered to be insufficient for any statement on the value of ESS compared to medical treatment. Different treatment modalities and schemes are probably needed in the treatment of CRS in its many forms.

Creation of middle meatal antrostomy is sometimes needed for the following cases: biopsy of an antral mass; resection of a maxillary sinus fungal ball or inverted papilloma; presence of accessory ostia leading to maxillary recirculation; and sometimes to allow for the application of topical medication or outpatient antral lavage in selected cases. Questions over the potential risks of middle meatal scarring, interruption of mucociliary clearance, improper ostial function, development of maxillary recirculation by not including the natural ostia in the middle meatal antrostomy, and the likely need for revision maxillary sinus surgery have raised the issue of whether middle meatal antrostomy is necessary in ESS (Catalano 2006).

Topical steroids are beneficial in treating CRS for symptom control. Applying a topical steroid through the nostrils does not imply delivery of the drug to the sinuses, however. For the application of topical medicine to the sinuses, appropriate access and delivery is required (Snidvongs et al. 2013). The oedematous inflammatory mucosa and therefore ostiomeatal occlusion often seen in CRS allows < 1% of solution volume to enter the maxillary sinus before surgery (Snidvongs et al. 2008). It has been postulated that a minimum ostial diameter of 3.95 mm is needed in order to guarantee the penetration of a topical treatment to paranasal sinuses (Grobler et al. 2008).

The present studies revealed that after ESS, most patients reported significant symptomatic relief. There was no statistically significant difference in the subjective or objective measurements between the two operative methods investigated, although there was a tendency to better objective results on the middle meatal antrostomy side.

6.2 Endothelial L-selectin ligands and eosinophils in maxillary sinus mucosa

Study I indicates that normal control samples from the study group without CRS did not express endothelial sulfated sialyl-Lewis^X glycans when detected by mAbs Heca-452 and Meca-79. In patients with CRS, the endothelial expression of sulphated sialyl-Lewis^X oligosaccharides and the number of eosinophils were enhanced in maxillary sinus mucosa specimens. This is in line with the previous findings, which showed that specific modifications of endothelial sulphated sialyl-Lewis^X decorations were induced de novo in bronchial mucosa during bronchial asthma and in other human tissues during chronic inflammation (Toppila et al. 2000, Renkonen et al. 2002).

During chronic inflammation, each organ carries its own modification of sulphated sialyl-Lewis^X glycans, like a postal code, thus providing a possible means for organ-selective leukocyte traffic (Renkonen et al. 2002). The percentages of mAb HECA-452- and mAbMECA-79-positive vessels in the maxillary sinus mucosa during CRS are similar to the postal codes in the bronchial mucosa in asthma, but different from other chronic inflammatory diseases. Thus, the same pattern of endothelial sulphated sialyl-Lewis^X glycans might guide leukocytes to the respiratory mucosa of the maxillary sinuses and the bronchi. This confirms previous postulations made regarding the pathophysiological similarities in the upper and lower airways (Corrigan et al. 1993, Sur et al. 1995), and it also confirms that CRS or unstable allergic rhinitis (AR) might lead to the aggravation of asthma (Murray and Ruszak 2003, Bousquet et al. 2001).

When determined by intraoperative endoscopic findings, computed tomography scans, and histopathological assessments of specimens, the number of mucosal eosinophils and the expression of sulphated sialyl-Lewis^X glycans correlated with the severity of CRS in study I. These findings are comparable to previous findings, which showed that the expression of sulphated sialyl-LewisX glycans correlated with the severity of acute rejection of heart allografts (Toppila et al. 1999). It has been shown that tumour necrosis factor-α, a proinflammatory cytokine, is responsible for the biosynthesis of the sulphated sialyl-Lewis^X epitope in cultured human bronchial mucosa (Delmotte et al. 2002). Thus, cytokines may account for the increase in endothelial sulphated sialyl-Lewis^X decorations guiding leukocyte traffic preferentially to the maxillary sinus mucosa during CRS. An insignificant increase in the number of eosinophils in atopic patients with CRS was found compared to those with nonatopic CRS.

Among the patient sample, the percentage of vessels reacting positively with mAb MECA-79 was significantly increased in patients with CRS and additional AR compared to those with CRS without allergy. This may reflect a different type of pathogenesis between these two conditions. One of the possible mechanisms proposed to explain the interaction between AR and CRS is that AR causes priming and upregulation of adhesion molecules of circulating leukocytes, making them more likely to migrate to sites of ongoing inflammation, such as those caused by bacterial or viral rhinosinusitis (Hamilos et al. 1996).

In study III, patients using a preoperative intranasal glucocorticoid had an increased expression level of sulphated sialyl-Lewis^X glycans compared with those without intranasal glucocorticoid treatment. This may be due to the heterogeneity of the treatment given, or because of the insufficient penetration of the intranasal glucocorticoid to the maxillary sinuses before the surgical opening of the ostia. Nine months after ESS, a significant decrease was found preferentially in patients with intranasal corticosteroid treatment, both in the expression level of mAb HECA- and MECA-positive vessels, and in the number of mucosal eosinophils. This may partly be due to the increased penetration of intranasal corticosteroids into the maxillary sinus.

When comparing the nine-month results between the ostium-preserving and -enlarging techniques using histological parameters, we found that a significant decrease of mucosal eosinophils was achieved only on the antrostomy side. It seems that antrostomy may decrease mucosal inflammation more effectively, but it is not possible to draw definitive conclusions from the small and heterogeneous study population. We also observed that the persistence of postoperative eosinophils correlated positively with the postoperative level of symptoms, and that this correlation was independent of the operation technique. Postoperative uncinate mucosal eosinophils have previously been shown to correlate only with one postoperative symptom (secretion), while other histological markers, e.g., the number of mucosal goblet cells, seemed to be better indicators of subjective recovery (Baudoin et al. 2006).

6.3 Mucociliary clearance

The central dogma in treating CRS has traditionally been the restoration of MCC and disappearance of the stasis of secretions in sinonasal cavities. Reviews of ESS results have reported excellent subjective results, with overall improvement of symptoms in both short- and long-term studies (Hopkins et al. 2006). However, studies often fail to show the correlation of symptom improvement with objective evidence of disease persistence (Vleming and de Vries 1990, Kennendy 1992, Smith et al. 2005, Holbrook et al. 2005).

It has been shown that the mucociliary clearance (MCC) correlates well with the histology and the histological changes of the maxillary sinus mucosa. Slow or sometimes absent mucociliary transport has therefore been regarded as an indication of histological damage in the maxillary sinus mucosa. Recovery of the damaged mucosa after ESS seems to be slow, and pathological findings, with some signs of recovery, are still evident even six months postoperatively (Toskala and Rautiainen 2005).

In study II, mean MCC remained poor even nine months postoperatively. In fact, postoperative mean MCC was even worse than preoperatively on the uncinectomy only side. However, there was no statistical difference between the operative techniques. Despite the poor MCC, a significant reduction of symptoms (facial pain, nasal obstruction, and nasal discharge) was achieved on both the ostium-preserving and -enlarging sides

postoperatively, both in the short-term (nine months) and in the long-term (68 months) surveys. Traditionally, diminution of the symptoms despite the poor recovery of sinus mucosa has been explained by the probable anti-inflammatory effect of improved sinus ventilation, irrespective of MCC (Lund 1986).

Uncinectomy combined with middle meatal antrostomy seemed to restore MCC better than uncinectomy alone among the patients, although there was no statistical difference between the operative techniques. However, it would be tempting to believe that a large antrostomy would offer a better ventilation route to a maxillary sinus, thus enhancing the probable anti-inflammatory effect.

6.4 Computed tomography and Lund-Mackay staging

The Lund-Mackay scoring system was developed for objective quantification of the inflammatory disease in the paranasal sinuses (Lund and Mackay 1993). It is based on a simple numeric score driven from the CT scan as earlier described. In the study group, preoperative and postoperative CT findings in patients with CRS after simple uncinectomy were compared with those after uncinectomy with additional middle meatal antrostomy. Postoperative ostium size was also determined and the correlation of CT findings and symptoms investigated.

In study IV, we were able to show that both the preserving and enlarging techniques occasioned a significant reduction of the LM scores, which is in accordance with the previous observations for the effect of ESS on the LM scores (Sharp et al. 1999). Measurements from the postoperative CT scans showed that the diameter of the ostium remained greater on the antrostomy side than on the ostium-preserving side. This shows that there was no significant postoperative scarring or adhesion formation on either side (especially on the antrostomy side), where the integrity of the ostium was violated. This result was confirmed in another study with the same study population, in which recovery of the middle meatal and ostiomeatal complex area was examined endoscopically (Luukkainen et al. 2012). Postoperatively, endoscopy and CT scans provided identical information about the ostiomeatal complex area and maxillary sinus.

There was a correlation between the postoperative ostium area and postoperative changes in LM values for maxillary sinus opacification and ostiomeatal complex obstruction. Uncinectomy with additional middle meatal antrostomy seemed to be associated with lower LM scores than simple uncinectomy. This observation however was not statistically significant. CT findings did not associate with queried symptoms postoperatively. Poor correlation between symptoms and CT findings has also been detected in other studies (Ryan et al. 2011).

6.5 Long-term outcomes

Our aim was to study and evaluate symptoms, exacerbation rate, and satisfaction after ESS with an ostium-preserving and ostium-enlarging technique at nine and, on average, 68 months postoperatively. We were able to show that all queried sinonasal symptoms decreased significantly during the time period. There was no statistical difference among the symptoms that patients were able to compare between sides, e.g., facial pain, nasal obstruction or discharge. However, if the success of ESS was measured in terms of revision surgery needed, uncinectomy with additional middle meatal antrostomy proved to be more successful. Moreover, patients with asthma and/or job exposure to irritants were more frequently dissatisfied on the uncinectomy side only or on both sides, however these observations were not statistically significant. It is possible that these patients could benefit more from an ostium-enlarging approach in ESS, but this hypothesis requires additional studies to be proven.

In study V, the number of reported antibiotic courses for rhinosinusitis during the last year was used as a sign of the AECRS. It decreased significantly at nine months postoperatively, indicating good recovery with both procedures. However, the AECRS rate began to increase between the period of nine and, on average, 68 months postoperatively, especially in patients with asthma and/or job exposure to irritants. One reason may be that asthma patients or those with job exposure may have persistent mucosal changes that might lead to a poor CRS prognosis (Mendelsohn et al. 2011). The exacerbation episodes could point to an uncontrolled disease and/or poor patient compliance with CRS treatment.

6.6 Limitations of the studies

Measurement methods to analyse symptom outcomes after ESS, such as the Sino-Nasal Outcome Test-20, the 36-Item Short-Form Health Survey, and the Visual Analogue Score, were not used in the studies because conception work began in 2000, when standardized quality-of-life methods were not in general use. We acknowledge the fact that this makes comparison with other studies difficult. On the other hand, because operative methods performed on different sides of each patient were compared, several general QOL parameters would not have been able to be used in analyses.

In study III, postoperative specimens were not taken from seven patients because of a misinterpretation of the study protocol. This may influence the results comparing mucosal eosinophilia and L-selectin ligands pre- and postoperatively, since the number of patients in this study was already limited.

We recognize that a small study group may have affect on the statistical power.

7 CONCLUSIONS

The present dissertation focused on clinical, histopathological, immunohistochemical and radiological findings on a group of patients with CRS without nasal polyposis who underwent ESS with or without additional middle meatal antrostomy.

1. Maxillary sinus mucosa biopsies taken from the control patients without CRS did not essentially express functionally active L-selectin ligands when detected by the mABs HECA-452 and MECA-79. The endothelial expression of L-selectin ligands in maxillary sinus mucosa was enhanced in patients with CRS.

2. MCC of the maxillary sinus mucosa in patients with CRS remained poor even after ESS nine months postoperatively. There was no statistical difference between the operative techniques examined.

3. ESS with conservative therapy decreased the number of L-selectin ligands in maxillary sinus mucosa nine months postoperatively regardless of the type of operation performed. A statistically significant postoperative decrease of the eosinophils in the maxillary sinus mucosa was observed only when a middle meatal antrostomy was performed during ESS.

4. With both ESS techniques, together with the conservative treatment, there was a statistically significant decrease in the LM scores when comparing the preoperative and postoperative LM staging. No statistically significant difference was found between these two groups and the postoperative LM staging.

5. Although the reduction of the sinonasal symptoms remained good even in long-term surveillance, the AECRS rate began to increase after nine months postoperatively. Patients with asthma and/or job exposure seemed to experience less satisfaction with ESS compared with patients without these risk factors. This observation however was not statistically significant.

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10 ORIGINAL PUBLICATIONS

Endothelial L-Selectin Ligands in Sinus Mucosa during Chronic Maxillary Rhinosinusitis

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Rationale: **Chronic rhinosinusitis is characterized by persistent inflammation of the nasal and paranasal mucosa with numerous emigrated leukocytes. L-selectin on leukocytes and its endothelial glycosylated ligands initiate organ-specific leukocyte infiltration into inflamed tissues.** *Objectives:* **The purpose of this study was to evaluate the endothelial expression of functionally active endothelial L-selectin ligands, sulfated sialyl Lewis x, in maxillary sinus mucosa from patients with chronic rhinosinusitis and from normal control subjects.** *Methods:* **Maxillary sinus mucosa specimens (116) were obtained surgically and immunohistochemically stained with monoclonal antibodies detecting sialyl Lewis x or sulfated extended core 1 lactosamines. The severity of the inflammation was determined by intraoperative endoscopic findings, computed tomography scans, and histopathologic assessment of the specimens.** *Measurements and Main Results:* **The percentage of vessels expressing endothelial sulfated sialyl Lewis x epitopes increased during chronic rhinosinusitis compared with uninflamed control tissue, especially in patients with additional allergic rhinitis, and decreased in specimens from aspirin-intolerant patients with preoperative oral corticosteroid treatment. In addition, the expression level of endothelial sulfated sialyl Lewis x epitopes and the number of mucosal eosinophils correlated with the severity of the inflammation, and decreased in specimens taken 9 months postoperatively compared with intraoperative samples, especially in patients with intranasal corticosteroid treatment.** *Conclusions:* **Our results suggest that functionally active L-selectin ligands might guide leukocyte traffic into maxillary sinus mucosa preferentially in patients with severe findings of chronic maxillary rhinosinusitis, thus leading to aggravation of the inflammation.**

Keywords: adhesion molecules; L-selectin; maxillary rhinosinusitis; sialyl Lewis x

Chronic rhinosinusitis is one of the most common chronic conditions with increasing incidence; however, there are limitations in both a plausible etiology and an optimal treatment (1, 2). It shares numerous features with both allergic rhinitis and asthma (2, 3). In the pathophysiology of both chronic rhinosinusitis and allergic rhinitis, eosinophils, helper T lymphocytes, and other leukocytes represent important components of the inflammatory response (3, 4). Allergy is a known contributing factor to chronic rhinosinusitis (4, 5). Patients with rhinosinusitis and concomitant allergic rhinitis have a higher number of eosinophils as well as activated eosinophils infiltrating the sinus mucosa compared with those having only chronic rhinosinusitis (6).

In most organs, leukocyte recruitment proceeds in a cascade-like fashion from capture to rolling to a systematic decrease in rolling velocity to firm adhesion and transmigration (7). Recruitment is initiated by the tethering and rolling of leukocytes on endothelial cells, which is mediated by selectins and their glycosylated ligands (7–9). These interactions are followed by a chemokine-mediated activation of integrins resulting in firm adhesion and, finally, leukocyte migration across the microvascular postcapillary endothelium (10, 11). L-selectin is expressed on most leukocytes and binds to a group of glycoproteins expressed on endothelial cells of high endothelial venules in lymph nodes, on activated endothelial cells, and on other leukocytes. These glycoproteins include CD34, sulfated gp200, endomucin, glycosylation-dependent cell adhesion molecule-1, podocalyxin, endoglycan, mucosal vascular addressin cell adhesion molecule-1, and P-selectin glycoprotein ligand-1 (12–15).

The function of L-selectin counterreceptors depends on their decoration with sialylated, sulfated, and fucosylated oligosaccharides, on the C-6 position of galactose and on the *N*-acetylglucosamine residues of the numerous *O*-glycans (16–23). These sulfated sialyl Lewis x glycans are consistently expressed at least on the CD34 glycans of lymph node high endothelium (24). Under normal conditions, properly glycosylated L-selectin ligands are not expressed on endothelia of other than lymphatic tissues (25). However, the induction of sulfated sialyl Lewis x ligands onto the postcapillary microvascular endothelium occurs both in rodents and humans undergoing allograft rejection as well as chronic inflammatory diseases, such as asthma (25–29). During chronic inflammation, each organ carries its own modification of sulfated sialyl Lewis x glycans, that is, ZIP code (29). In addition, enzymatically synthesized multivalent sialyl Lewis x glycans can prevent selectin-dependent lymphocyte adhesion to properly glycosylated endothelium *ex vivo*, pointing to a putative means to inhibit the inflammatory reaction organ selectively (25, 30).

The previous observations are expanded to study the pathogenesis of chronic maxillary rhinosinusitis. The goal of this study was to analyze whether the expression of functionally active L-selectin ligands and the number of mucosal eosinophils correlate to the severity of chronic allergic and nonallergic rhinosinusitis, and whether they are decreased by medical and operative treatment.

METHODS

Subjects

Forty-eight subjects were enrolled in this study. Characteristics of the groups of patients are shown in Table 1 (*see* the online supplement for

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TABLE 1. CHARACTERISTICS OF PATIENT GROUPS STUDIED

	Control Patients	Maxillary CRS	Maxillary CRS + Allergic Rhinitis	Maxillary CRS + Allergic Rhinitis + Aspirin Sensitivity
Patients, n	8	11	24	5
Patients operated on both sides, n	2	8	18	3
Specimens				
Intraoperative, n	14	19	43	10
Nine months postoperative, n	0	8	22	0
Sex				
Male, n	4	4	9	1
Female, n	4	7	15	4
Age, yr				
Mean	38.4	49.4	45.7	55.4
Min–max	19–56	22–66	20–75	30–73
Patients with associated:				
Nasal polyposis, n	0	4	3	0
Bronchial asthma, n	1	1	4	1
Both, n	0	0	2	4
Patients with medication, preoperative/postoperative				
Nasal corticosteroid, n/n	0/–	3/1	12/2	5/–
Antihistamine, n/n	0/–	1/0	1/1	0/–
Both, n/n	0/–	1/1	4/0	0/–
Oral corticosteroid, n/n	0/–	0/0	0/0	5/–
Patients with CT score, preoperative/postoperative				
0, n/n	8/–	0/0	0/0	0/–
1–3, n/n	0/–	2/3	4/9	0/–
4–7, n/n	0/–	8/2	16/2	0/–
8–12, n/n	0/–	1/0	4/0	5/–

Definition of abbreviations: CRS = chronic rhinosinusitis; CT score = sinus computed tomography values according to Lund and MacKay (33).

additional detail about the subjects and methods). Uninflamed normal control subjects had never suffered from chronic rhinosinusitis or allergic rhinitis. Chronic maxillary rhinosinusitis was diagnosed by the presence of sinus-related symptoms for at least 12 weeks despite medical treatment, associated with abnormalities of mucosal thickening or sinus opacification on sinus computed tomography scan (31). Patients with allergic rhinitis had at least a 2-year history of allergy confirmed by a positive skin prick test reaction for at least one inhalatory allergen (32). Patients who had, in addition, aspirin sensitivity and oral corticosteroids for 5 days before surgery were studied as a separate group. The study was supported by the ethics committee of Tampere University Hospital (Tampere, Finland).

For subjects with chronic rhinosinusitis, endoscopic sinus surgery was performed under local or general anesthesia. Intra- or postoperative endoscopic findings noted were the condition of antral mucosa. Endoscopic findings were graded according to the following scale: 0 = no inflammation, 1 = mild edema, 2 = moderate edema and inflammation, 3 = severe edema and inflammation. Biopsies of the maxillary sinus mucosa were performed during operation and 9 months postoperatively. The radiologic stage of inflammation was based on opacification of the sinuses and occlusion of the osteomeatal complex on the computed tomography scans according to Lund and coworkers (33, 34). Here, radiologic Stages 0, 1, 2, and 3 indicate scores 0, 1–3, 4–7, and 8–12, respectively, according to Lund and coworkers. Additional detail about the subjects and sample collection is provided in the online supplement.

Immunohistochemistry

L-selectin ligands were studied with two monoclonal antibodies (mAbs). mAb HECA-452 recognizes α-2,3-sialylation and α-1,3-fucosylation of lactosamine, and mAb MECA-79 recognizes an extended sulfated core 1 lactosamine structure (35–38). mAb HECA-452 (rat IgM; 2 μg/ml) and mAb MECA-79 (rat IgM; 1 μg/ml) were kindly provided by S. Jalkanen (University of Turku, Turku, Finland). Anti-human CD34, Class II (mIgG1; 2 μg/ml; DakoCytomation, Glostrup, Denmark), was used as a positive control for the detection of endothelial cells. mAbs 7C7 (mouse IgM; 1.2 μg/ml) and TIB-146 (rat IgM; 10 μg/ml), both kindly provided by S. Jalkanen, were used as negative controls. For immunohistochemical techniques and microscopic analysis of the specimens, previously described protocols were used (27–29). Briefly, the mean number of mAb HECA-452– and mAb MECA-79–vessels was divided by the mean number of CD34-positive vessels from the whole specimen, yielding the percentage of sialyl Lewix x (sLe^x)- or sulfated sialyl Lewis x (sulfo sLe^x)-reactive vessels. From hemalum–eosin-stained tissue sections, the number of eosinophils per millimeter squared was microscopically calculated and the histopathologic assessment of inflammation was based on the mucosal edema, and the quantity and composition of leukocyte infiltrate, which was semiquantitatively scored as 0 = no inflammation, 1 = mild, 2 = moderate, or 3 = severe.

Statistical Analysis

Statistics were performed with the SPSS Base 11.0 Statistical Software Package (SPSS, Chicago, IL). Data values were expressed as means ± SD. Results were analyzed first by nonparametric Kruskal–Wallis one-way analysis of variance by ranks and then by nonparametric Mann–Whitney U test for multiple comparisons in different groups. The nonparametric Spearman rank correlation test was used to study the correlation between ranks of the percentage of positive vessels and the severity of inflammation. The Spearman rank-order correlation coefficient (r) was used to assess bivariate association. A two-tailed p value less than 0.05 was considered significant with all tests.

RESULTS

In maxillary sinus specimens from normal control patients, the level of endothelial sulfated sialyl Lewis x epitopes, that is, the mean percentage ± SD of mAb HECA-452– and mAb MECA-79–positive vessels, was 0.2 ± 0.3 and 0.3 ± 0.4%, respectively,

and the mean number ± SD of mucosal eosinophils was 18.5 ± 27.0/mm^2. However, during chronic maxillary rhinosinusitis the percentage of mAb HECA-452– and mAb MECA-79–positive vessels, and the number of mucosal eosinophils, were significantly increased compared with healthy control subjects ($p < 0.0001$ by Mann–Whitney U test; Figure 1). Moreover, the percentage of mAb MECA-79–positive vessels, that is, expressing the extended core 1 polylactosamine structure, was significantly increased in patients with chronic rhinosinusitis with additional allergic rhinitis compared with patients with chronic rhinosinusitis without atopy (mean percentage ± SD: 6.5 ± 5.1 and 4.6 ± 6.1%, respectively; $p < 0.05$ by Mann–Whitney U test) as shown in Figure 1B. Interestingly, the percentages of mAb HECA-452– and MECA-79–positive vessels were significantly decreased in specimens from aspirin-sensitive patients with chronic rhinosinusitis, allergic rhinitis, and preoperative oral glucocorticoid treatment (1.5 ± 1.0 and 1.7 ± 2.0%, respectively) compared with aspirin-tolerant patients with chronic rhinosinusitis and with allergic rhinitis but without oral corticosteroid treatment (6.5 ± 5.1 and 3.9 ± 3.2%; $p < 0.001$ by Mann–Whitney U test) as shown in Figures 1A and 1B. All these differences were independent of the intranasal corticosteroid drug used by the patients with chronic rhinosinusitis (data nor shown).

When studying specimens taken from patients during and 9 months after functional endoscopic sinus surgery, the intraoperative number of mucosal eosinophils was independent of preoperative intranasal corticosteroid treatment (Figure 2C). Interestingly, in specimens from patients with intranasal corticosteroid treatment, the expression level of mAb HECA-452– and mAb MECA-79–positive vessels (4.6 ± 3.5 and 6.6 ± 4.5%, respectively) was increased compared with patients without intranasal corticosteroids (3.0 ± 2.4% and 5.0 ± 5.9%; $p < 0.05$ by Mann–Whitney U test) as shown in Figures 2A and 2B. However, the expression level of mAb HECA-452– and mAb MECA-79–positive vessels and the number of mucosal eosinophils were decreased significantly in 9-month follow-up specimens, especially in patients with postoperative intranasal corticosteroid treatment (1.5 ± 0.9%, 1.0 ± 1.0%, and 43 ± 47 cells/mm^2, respectively) compared with the patients without postoperative intranasal corticosteroid treatment (1.8 ± 2.3%, 1.4 ± 1.7%, and 135 ± 188 cells/mm^2, respectively; $p < 0.01$ by Mann–Whitney U test) as shown in Figures 2 and 3. All these differences were independent of atopic status of the patients (data not shown).

The expression levels of endothelial sulfated sLe^x glycans, as well as the number of mucosal eosinophils in intraoperative biopsies, correlated significantly with the severity of inflammation determined by three different methods: histologic score, endoscopic grade, and radiologic stage. There was already a significant correlation between the number of mucosal eosinophils as well as the percentages of mAb HECA-452– and mAb MECA-79–positive vessels, and radiologic stage and endoscopic grade of the chronic maxillary rhinosinusitis (all had a p value of less than 0.01, and a correlation coefficient value r ranging from 0.6 to 0.7, Spearman rank correlation test). However, the correlation was strongest between mucosal eosinophils, mAb HECA-452– or mAb MECA-79–positive vessels, and histologic score ($p < 0.01$, $r = 0.7$; $p < 0.01$, $r = 0.8$; and $p < 0.01$, $r = 0.8$ by Spearman rank correlation test, respectively) as shown in Figure 4. In addition, the percentages of mAb HECA-452– and mAb MECA-79–positive vessels correlated with the number of mucosal eosinophils in intraoperative biopsies from patients with chronic maxillary rhinosinusitis ($p < 0.05$, $r = 0.5$ and $p < 0.01$, $r = 0.7$ by Spearman rank correlation test, respectively) as shown in Figure 5.

The number of mucosal eosinophils and the expression level of activated endothelial cells endothelial (sulfated sialyl Lewis x epitope) in intraoperative maxillary sinus biopsies was independent of antihistamine treatment, asthma, or nasal polyposis status of the patients with chronic rhinosinusitis (data not shown). Interestingly, the percentage of mAb MECA-79–positive vessels was significantly increased in intraoperative maxillary sinus mucosa from aspirin-tolerant patients with chronic rhinosinusitis with additional allergic rhinitis and nasal polyposis compared with aspirin-insensitive patients with chronic rhinosinusitis with allergic rhinitis but without nasal polyposis (mean percentages ± SD: 10.0 ± 5.4 and 5.7 ± 4.7%, respectively; $p < 0.05$ by Mann–Whitney U test) (data not shown). This was independent of intranasal corticosteroid treatment (data not shown).

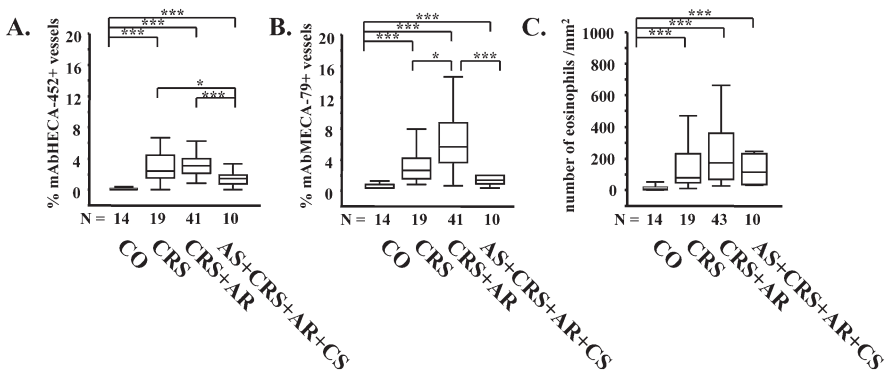

Figure 1. Comparison of the percentages of vessels expressing sulfo sLe^x epitopes analyzed with (*A*) anti-sLe^x antibody (mAb HECA-452) and (*B*) an anti-sulfated extended core 1 lactosamine antibody (mAb MECA-79) in intraoperative maxillary sinus mucosa from the following groups of subjects: normal control subjects (*CO*) as well as patients with chronic maxillary rhinosinusitis (*CRS*), with chronic maxillary rhinosinusitis and allergic rhinitis (*CRS+AR*), and aspirin-sensitive patients with chronic maxillary rhinosinusitis, allergic rhinitis, and preoperative oral corticosteroid treatment (*AS+CRS+AR+CS*). (*C*) Comparison of the number of eosinophils in maxillary sinus mucosa in the same groups of subjects. *N* = number of specimens. Only the significant differences are marked: ***$p < 0.001$; *$p < 0.05$. *Horizontal lines* represent medians; *upper* and *lower vertical bars* represent 75th and 25th percentile ranges, respectively; and *vertical lines* represent the 99th percentile range.

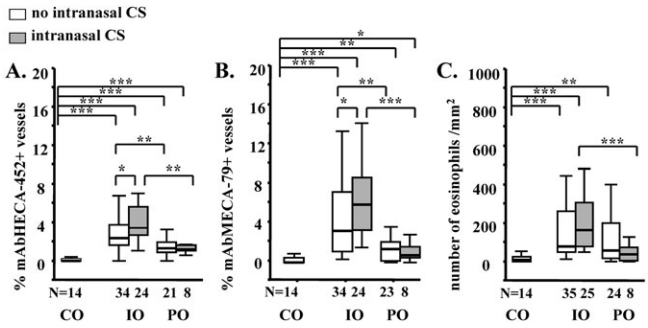

Figure 2. Comparison of the percentages of vessels expressing sulfo sLe^x epitopes analyzed with (*A*) anti-sLe^x antibody (mAb HECA-452) and (*B*) an anti-sulfated extended core 1 lactosamine antibody (mAb MECA-79), as well as (*C*) the number of eosinophils in maxillary sinus specimens from normal control subjects (*CO*) and patients with chronic rhinosinusitis taken intraoperatively (*IO*) or 9 months postoperatively (*PO*). Patients either used intranasal corticosteroids (*CS*) or did not. Patients with aspirin sensitivity were excluded. *N* = number of specimens. Only the significant differences are marked: ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$. *Horizontal lines* represent medians; *vertical bars* (*upper* and *lower*) and *lines* represent the 75th, 25th, and 99th percentile ranges, respectively.

DISCUSSION

The present study with 116 biopsies from maxillary sinus mucosa showed that normal control samples did not essentially express endothelial sulfated sialyl Lewis x glycans when detected by mAbs HECA-452 and MECA-79. However, the endothelial expression of sulfated sialyl Lewis x oligosaccharides as well as the number of eosinophils were enhanced in mucosa during chronic maxillary rhinosinusitis. This is in line with our previous findings that specific modifications of endothelial sulfated sialyl Lewis x decorations were induced *de novo* in bronchial mucosa during bronchial asthma as well as in several other human tissues during chronic inflammation (28, 29).

Previously, we have found that during chronic inflammation, each organ carries its own modification of sulfated sialyl Lewis x glycans, that is, ZIP code, thus providing a possible means for organ-selective leukocyte traffic (29). Here, the percentages of mAb HECA-452– and mAb MECA-79–positive vessels, that is, the ZIP codes, in respiratory mucosa of maxillary sinus during chronic rhinosinusitis are similar to the ZIP codes in bronchial mucosa during asthma, and, different from other chronic inflammatory diseases. Thus the same pattern of endothelial sulfated sialyl Lewis x glycans might guide leukocytes to the respiratory mucosa of maxillary sinuses and bronchi. This confirms previous postulations that there are similarities in the pathophysiology of upper and lower airways (39, 40), and that chronic rhinosinusitis or unstable allergic rhinitis might lead to aggravation of asthma (41–44).

Studies demonstrate that mouse and human L-selectin ligand sulfotransferases are capable of forming 6-sulfo sialyl Lewis x on core 2-branched *O*-glycans and, together with core 1 extension enzyme it forms the MECA-79 epitope, defined as Galβ1–4 (sulfo-6)GlcNAcβ1–3Galβ1–3GalNAcα1-R, which is a partial structure of 6-sulfo sialyl Lewis x on extended core 1 *O*-glycans (26, 45–48). The MECA-79 antibody also binds to 6-sulfo sialyl Lewis x on extended core 1 *O*-glycans and inhibits both *in vivo* and *ex vivo* lymphocyte attachment to high endothelial venules by neutralizing L-selectin ligands (37, 48, 49).

According to our results, the number of mucosal eosinophils and the expression of sulfated sialyl Lewis x glycans correlated with the severity of chronic maxillary rhinosinusitis, when determined by intraoperative endoscopic findings, computed tomography scans, and histopathologic assessment of specimens. These findings are comparable to our previous findings that the expression of sulfated sialyl Lewis x glycans correlated with the severity of acute rejection of heart allografts (26). Four major pathophysiological processes are supposed to be responsible for chronic rhinosinusitis: (*1*) rarely, a chronic infectious disorder with prominent hyperplasia of immune cells; (*2*) chronic eosinophilic rhinosinusitis; (*3*) allergic fungal rhinosinusitis, which is a severe variant of chronic eosinophilic rhinosinusitis with fungal colonization within the sinus cavities; and (*4*) a chronic inflammatory disorder characterized by a mononuclear cell infiltrate and primarily mucus gland hyperplasia but with few eosinophils (5). In this study, expression of endothelial sulfated sialyl Lewis x decorations correlated with the number of mucosal eosinophils in intraoperative biopsies from patients with atopic or nonatopic chronic maxillary rhinosinusitis. Although the prevalence of mucosal eosinophils was not systematically analyzed, they seemed to be situated in the vicinity of mAb HECA– and MECA-positive vessels (Figure 3). Delmotte and coworkers have shown that tumor necrosis factor-α, a proinflammatory cytokine, is responsible for the biosynthesis of sulfated sialyl Lewis x epitope in cultured human bronchial mucosa (50). Thus, cytokines might account for the increase in endothelial sulfated sialyl Lewis x decorations, which might guide leukocyte traffic to the maxillary sinus mucosa preferentially during chronic rhinosinusitis.

Among our patients, the percentage of vessels reacting positively with the antibody recognizing the extended core 1 polylactosamine structure, mAb MECA-79, was significantly increased in patients with chronic rhinosinusitis and additional allergic rhinitis compared with those with chronic rhinosinusitis but without allergy. This might reflect the fact that the pathogenesis of chronic allergic rhinosinusitis might differ from that of nonallergic chronic rhinosinusitis. One of the possible mechanisms proposed to explain the interaction between allergic rhinitis and rhinosinusitis is that allergic rhinitis causes priming and upregulation of adhesion molecules of circulating leukocytes, making them more likely to migrate to sites of ongoing inflammation such as those caused by bacterial or viral rhinosinusitis (51). Ogata and coworkers found increased number of mucosal activated eosinophils in subjects with allergic chronic rhinosinusitis compared with those with nonallergic chronic rhinosinusitis (52). Moreover, the prevalence of eosinophilic rhinosinusitis is increased compared with noneosinophilic rhinosinusitis in patients with allergic rhinitis (5). In our study, there was an insignificant increase in the number of eosinophils in atopic patients with chronic maxillary rhinosinusitis compared with nonatopic patients with chronic maxillary rhinosinusitis.

Interestingly, among our subjects with aspirin sensitivity, allergic rhinitis, and chronic rhinosinusitis, preoperative oral glucocorticoid treatment was associated with decreased expression of sulfated sialyl Lewis x-bearing glycoforms, whereas there was an insignificant decrease in the number of mucosal eosinophils compared with atopic patients who did not have aspirin sensitivity and oral glucocorticoid treatment. Although the comparison between aspirin-intolerant subjects with or without oral glucocorticoid treatment was not done, it can be postulated that the susceptibility of eosinophils to glucocorticoids (53) might be partly due to the inhibitory effect of glucocorticoid on L-selectin–mediated migration. In patients with acute conjunctival inflammation after cataract surgery, we showed similarly that preoperative intravenous hydrocortisone inhibited leukocyte rolling and trafficking detected by an *in vivo* reflected-light confocal microscopy technique

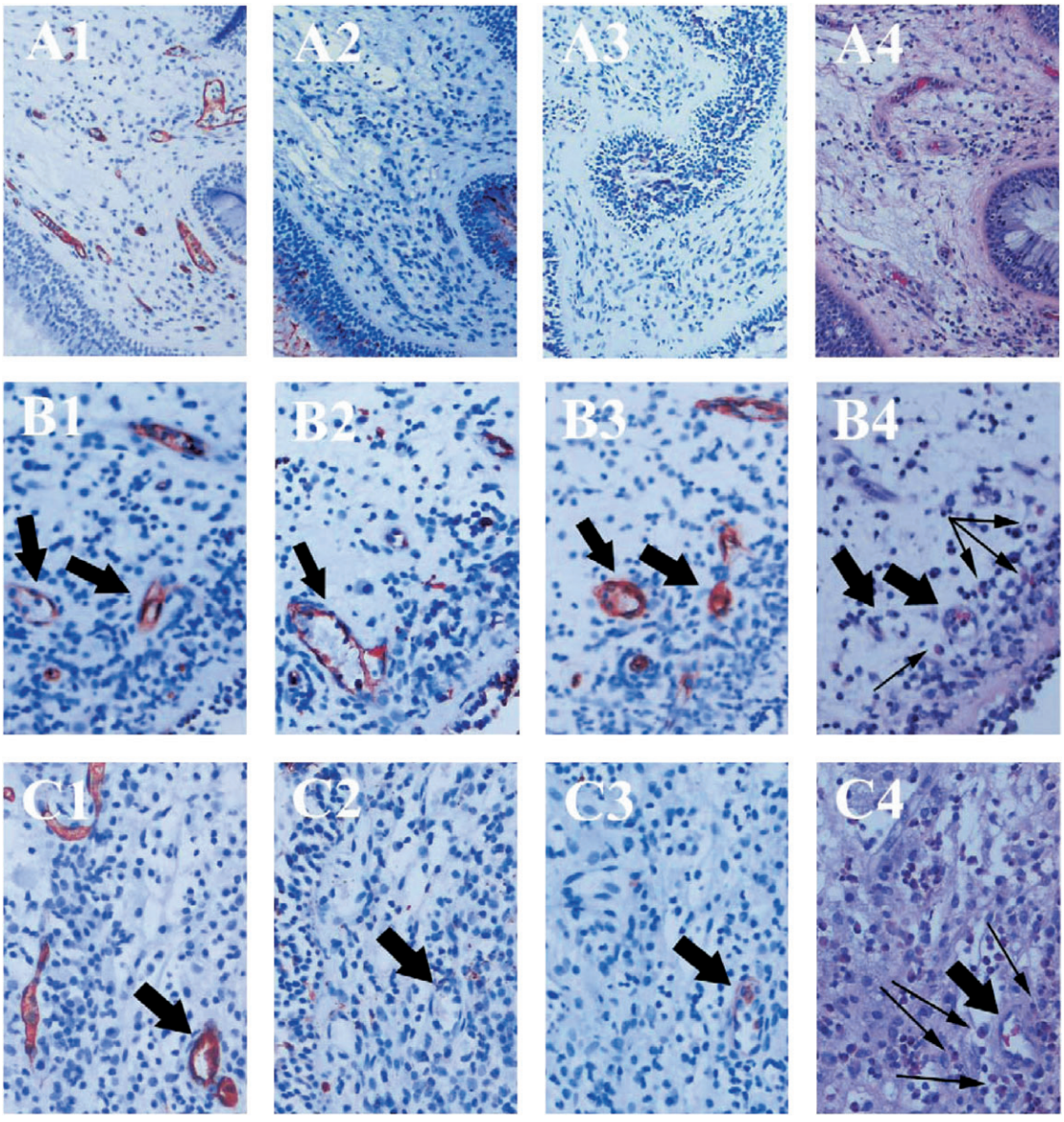

Figure 3. Endothelial expression of CD34, sulfated sialyl Lewis x epitopes, and the number of eosinophils in healthy control and inflamed maxillary sinus mucosa. (*A1–A4*) The same region from a normal control sample, where anti-CD34 antibody showed a strong positive reaction with the endothelium of all vessels (*A1*), mAbs HECA-452 and MECA-79 showed no endothelial reactivity (*A2–A3*), and hematoxylin and eosin staining showed only few mucosal eosinophils and other leukocytes (*A4*). (*B1–B4*) The same region of an intraoperative biopsy from a patient with chronic rhinosinusitis and allergic rhinitis, where anti-CD34 antibody stained strongly all vessels (two venules shown by *arrows*; *B1*), mAbs HECA-452 and MECA-79 also stained strongly many of the capillaries and venules (the identical venules shown by *arrows*; *B2* and *B3*), and strong leukocytosis with a high number of eosinophils (*small arrows*, *B4*) is apparent in the vicinity of the mAb HECA– and MECA-positive vessels (*large arrows*). (*C1–C4*) The same region of an intraoperative biopsy from a patient with chronic rhinosinusitis, allergic rhinitis, aspirin sensitivity, and preoperative oral corticosteroid treatment, where anti-CD34 antibody stained strongly essentially all vessels (a venule shown by an *arrow*, *C1*), mAb HECA-452 did not essentially react with the vessels (the identical venule shown by an *arrow*, *C2*), mAb MECA-79 stained weakly the identical venule (*arrow*, *C3*), and eosinophils (*small arrows*, *C4*) were found in the vicinity of the mAb MECA-positive venule (*large arrow*). Original magnification: (*A1–A4*) ×100; (*B1–C4*) ×200.

(54, 55). However, in the present study, patients using preoperative intranasal glucocorticoid had an increased expression level of sulfated sialyl Lewis x glycans compared with those without intranasal glucocorticoid treatment, possibly because of the heterogeneity of the treatment given or because of the insufficient penetration of intranasal glucocorticoid to maxillary sinuses before surgical enlargement of the ostia. Nine months after sinus surgery, a significant decrease both in the expression level of mAb HECA– and MECA-positive vessels and the number of mucosal eosinophils was found preferentially in patients with intranasal corticosteroid treatment, despite the small number of postoperative biopsies. This might be partly due to the increased penetration of intranasal corticosteroids to maxillary sinuses.

Others have shown that endothelial P-selectin was strongly expressed in nasal polyp tissue and that treatment with intranasal corticosteroids reduced it (56, 57). Monoclonal antibody against L-selectin inhibited significantly *in vitro* T cell adhesion to nasal polyp endothelium (58), and budesonide treatment led to a significantly decreased sialyl Lewis x-binding site concentration in nasal polyp cultures (59). In the present study, the percentage of mAb MECA-79–positive vessels was significantly increased in maxillary sinus mucosa from atopic patients with chronic rhinosinusitis, and was even higher in patients with nasal polyposis compared with atopic patients with chronic rhinosinusitis but without diagnosed nasal polyposis. Subjects with aspirin intolerance, nasal polyps, and asthma are more likely to have eosinophilic chronic rhinosinusitis than a noneosinophilic disorder (5). Therefore, further studies about the role of L-selectin ligands in the pathogenesis of eosinophilic chronic rhinosinusitis, espe-

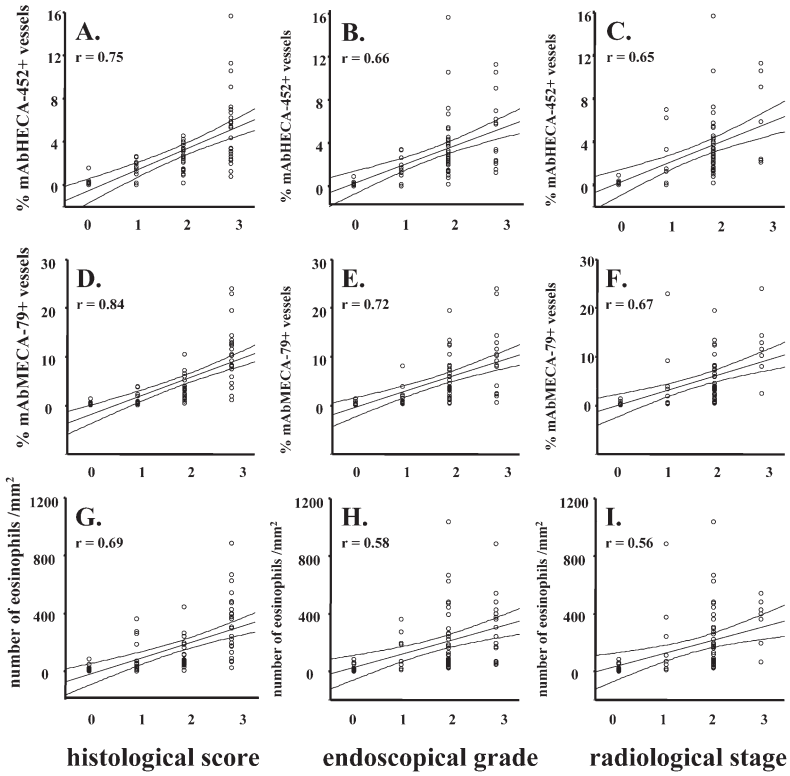

Figure 4. Percentages of vessels expressing sulfo sLe^x epitopes analyzed with mAbs HECA-452 (*A–C*) and MECA-79 (*D–F*), as well as the number of eosinophils (*G–I*) in maxillary sinus mucosa from healthy control subjects and patients with chronic maxillary rhinosinusitis. The panel of nine curves shows that the percentage of mAb HECA-452– and MECA-79–positive vessels, and the number of eosinophils, correlate positively with the severity of inflammation as detected by three methods: histologic score (*A*, *D*, and *G*), endoscopic grade (*B*, *E*, and *H*), and radiologic stage (*C*, *F*, and *I*). Each zero value of histologic score, endoscopic grade, and radiologic stage represents a maxillary sinus sample from normal control subjects, and the values 1–3 represent intraoperative specimens from patients with chronic maxillary rhinosinusitis. Patients with aspirin sensitivity were excluded. The curves were significant at $p < 0.01$. The correlation coefficient (r) indicates the strength of the correlation ($0 \leq r \leq 1$; where $r = 1$ means perfect correlation). The strongest correlation was found between the percentages of mAb HECA-452– and MECA-79–positive vessels and the histologic score of the inflammation. *Lines* represent the mean with 95% confidence intervals.

cially in patients with these associated diseases, need to be performed.

Taken together, the *de novo* expression of endothelial sulfated sialyl Lewis x glycans in maxillary sinus mucosa might provide a means for organ-selective inhibition of leukocyte trafficking. Moreover, expression of these glycans correlated with the severity and extent of sinus disease present on computed tomography imaging, endoscopic grading, and histologic grading, thus suggesting that they may be important in the pathogenesis of chronic rhinosinusitis.

Conflict of Interest Statement: S.K.T.-S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.P.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; T.V.M.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.V.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.A.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.E.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; R.L.O.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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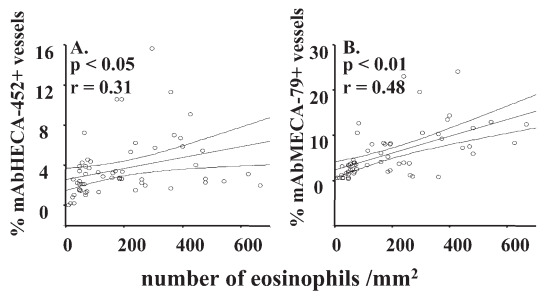

Figure 5. Correlation between the percentage of mAb HECA-452– and MECA-79–positive vessels, and the number of mucosal eosinophils in intraoperative maxillary sinus biopsies from patients with chronic rhinosinusitis. Patients with aspirin sensitivity were excluded. *Lines* represent the mean with 95% confidence intervals.

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Effect of endoscopic sinus surgery on antral mucociliary clearance*

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SUMMARY

Endoscopic sinus surgery (ESS) is the most used surgical approach in the treatment of chronic and recurrent maxillary rhinosinusitis. However, it still remains unclear how well surgery restores the mucociliary function in damaged maxillary sinus mucosa. There is also controversy whether to enlargen the natural ostium or not.

We examined the mucociliary clearance (MCC) of maxillary sinuses in 27 patients with chronic and recurrent rhinosinusitis. On one side only an uncinectomy was done, on the contralateral side a middle meatal antrostomy was additionally performed. The mucociliary clearance (MCC) was measured in both sides preoperatively and 9 months after the operation. Measurements of the mucociliary clearance in maxillary sinuses were done using an isotope method.

Preoperative mean residual activity on the uncinectomy side was 87.2 % and postoperative mean residual activity 94.1 %. On the middle meatal antrostomy side mean preoperative residual activity was 92.3 % and postoperative mean residual activity 88.4 %.

Residual activity was considered as good (≤50%) on the uncinectomy side in 2 sinuses (7.4 %) preoperatively and in 1 sinus (3.7 %) postoperatively. On the middle meatal antrostomy side residual activity was considered good in 1 sinus (3.7 %) preoperatively and in 4 sinuses (14.8 %) postoperatively.

Mucociliary function remained poor even 9 months postoperatively. Surgery did not significantly improve the mucociliary function of maxillary sinus mucosa in chronic or recurrent rhinosinusitis. There was no statistical difference between operative techniques. In this study it seemed however, that uncinectomy combined with the enlargening of the natural ostium may restore maxillary sinus mucociliary clearance (MCC) better than uncinectomy alone.

Key words: chronic rhinosinusitis, endoscopic sinus surgery, middle meatal antrostomy, mucociliary clearance, uncinectomy

INTRODUCTION

Mucociliary clearance (MCC) is a major element of the defence system in the respiratory tract. Effective mucociliary function is based on a proper functional relationship between the moving cilia, mucus and periciliary fluid. In chronic rhinosinusitis, lacking of ciliated epithelia or nonfunctional cilia are regarded as the most important reasons for the impaired mucociliary clearance [(1,2)].

Endoscopic sinus surgery (ESS) is the main surgical approach for the treatment of chronic and recurrent rhinosinusitis (CRS) after failure of medical treatment. ESS is based on the theory that the maxillary sinus ostia are the most important areas in the pathogenesis of chronic and recurrent rhinosinusitis. Obstruction in the ostia is believed to lead to chronic inflammation and eventually to pathological alterations in maxillary sinus mucosa and in mucociliary clearance. Based on this theory, surgical opening of the ostia and improved ventilation of the sinuses should restore the normal mucosal function [(3,4)].

There are different opinions conserning the extent of surgery in the ostiomeatal complex. It is considered, that uncinectomy alone would be enough to restore the ventilation into the maxillary sinus, and that enlargening the ostium would interfere the normal function of the maxillary sinus [(3)].

Mucociliary function can be examined by measuring the ciliary beat frequency, the mucociliary transport rate or the mucociliary clearance. In the mucociliary clearance measurement the decrease of the radioactivity of the tracer (^{99}m-Techenetium-labeled human serum) per unit is measured from a certain

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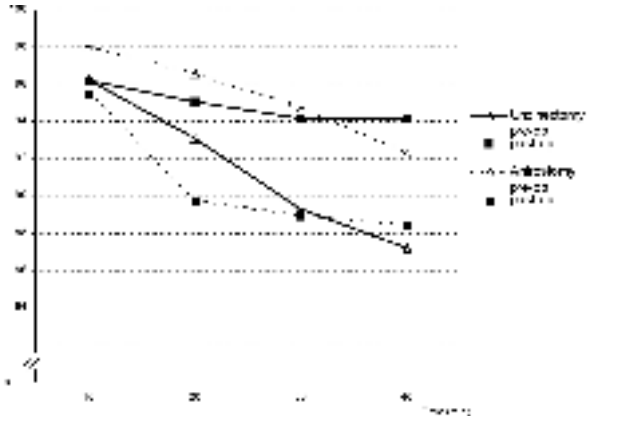

Figure 1. Mean residual mucociliary activity preoperatively and postoperatively in uncinectomy alone (n=27) and in uncinectomy combined with the enlargening of the ostium (antrostomy, n=27).

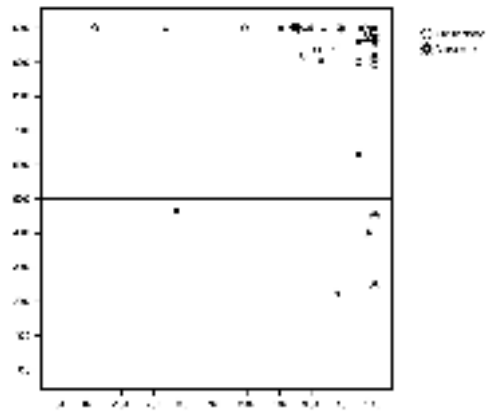

Figure 2. Residual mucociliary activity in the maxillary sinuses (n=54) preoperatively and postoperatively. Lower left quadrant indicating good mucociliary clearance in the maxillary sinus both preoperatively and postoperatively, lower right quadrant indicating restored mucociliary clerance after ESS. Upper left quadrant indicates worsened mucociliary clearance after ESS and upper right quadrant indicates poor mucociliary clearance both preoperatively and postoperatively.

area. The results are reported in percentages or in minutes needed for halving of radioactivity (T1/2).

There are studies, which involve the examination of the mucociliary clearance in chronic or recurrent rhinosinusitis [5,6]. It has been shown that the maxillary sinus mucosa recovers slowly after surgery and that there are still pathological histological findings in the sinus mucosa even 6 months postoperatively [7,8]. It has been also stated that in most cases the mucociliary clearence improves only slightly after surgery [5].

There have not been studies comparing uncinectomy and middle meatal antrostomy and the effectiveness of these operative techniques in the mucociliary clearance of the maxillary sinus. The purpose of this study was to determine the functional recovery of the maxillary sinus mucosa after ESS and to examine the possible difference between two operative techniques.

METHODS

Patients

This study was carried out at the Department of Otorhinolaryngology, Tampere University Hospital, Finland and Mikkeli Central Hospital, Mikkeli, Finland. The Committee of Ethics approved the study, and all subjects gave their informed consent. The study group comprised of 30 patients, 20 women and 10 men, age range 22 to 66 years with a mean of 47 years. In 27 patients we were able to measure the maxillary sinus mucociliary clearance (MCC) both preoperatively and postoperatively.

Diagnosis

Patients suffered from chronic or recurrent maxillary rhinosinusitis. Chronic maxillary sinusitis was diagnosed by the presence of sinus related symptoms for at least 12 weeks despite maximal medical treatment, associated with abnormalities of mucosal thickening or sinus opacification on computed tomography scan. A nasal endoscopy was performed and patients with visible polyposis in the middle meatal area were excluded from the study. There was no difference in the symptoms between sides. In preoperative CT-scan both sides had similar, moderate findings. None of the patients had aspirin intolerance, gross immunodeficiency, chronic bronchitis or cystic fibrosis. Patients with polyposis or previous sinus surgery were excluded from the study group.

Surgery

The study group underwent endoscopic sinus surgery in local anesthesia. Uncinectomy alone was done on the other side; on contralateral side a middle meatal antrostomy was additionally performed. Anterior ethmoidectomy was done, if it was considered necessary. The light middle meatal tamponation was removed on the first postoperative day. Nasal endoscopy was performed and operation field cleaned 2 weeks after surgery. Follow-up was done at 9 months after the surgery.

Measurements

MCC measurements were taken preoperatively and 9 months after the operation. Irrigation tubes (Sinoject, Atos, Hörby) were introduced through the inferior meatus into the maxillary sinuses at least 30 minutes before the measurement to avoid any reflectory ciliostasis due to puncture. The procedure was done under local anesthesia, with 4% lidocain adrenaline cotton administered in the inferior meatus for 10 minutes. With a thin catether and 1 ml syringe, a drop (0.03-ml) of sterile human serum albumin labeled with ^{99}mTc (Venticol, Sorin Biomedica, Saluggia) was applied through the irrigation tube into the bottom of both maxillary sinuses at the the same time. Each patient was seated in front of a gamma camera (Picker SX-300, Elscint 409 ECT, Siemens Ecam) with an all-purpose parallel-hole collimator (high-resolution in Siemens) connect-

ed with a Gamma-11, Elscint or Siemens computer system for processing. Clearance of the tracer in both sinuses was monitored at the same time from an anterior view for 40 minutes. Area of the initial tracer in the sinuses was marked and clearance of tracer from the sinuses, as well as the possible appearance of activity in the pharynx, was measured with gamma imaging at time-points 0, 10, 20, 30 and 40 minutes from the anterior view, with residual activity (percentage from the initial) determined in the sinuses. Two cobalt buttons were fixed on the forehead and one on the upper part of the sternum for control of errors caused by patients` movements. Radiation activity of the amount of tracer used for both sides totalled 40 μCi; the dose of radiation for each patient was 50 μSv.

RESULTS

Preoperative mucociliary clearance

The mean residual activity on the uncinectomy side after 40 minutes in 27 sinuses was 87.2 %. On the middle meatal antrostomy the mean residual activity after 40 minutes was 94.2 %.

Preoperatively there were 13 (48.1 %) sinuses on the uncinectomy side and 15 (55.5%) sinuses on the middle meatal antrostomy side where no clearance was seen during 40 minutes follow-up time. Residual activity was considered as good (< 50 %) in 2 (7.4 %) sinuses on the uncinectomy side and in 1 (3.7 %) sinus on the middle meatal antrostomy side.

Postoperative mucociliary clearance

The mean residual activity on the uncinectomy side after 40 minutes was 94.1 %. On the middle meatal antrostomy side the mean residual activity was 88.4%.

Postoperatively there were 14 (51.9 %) sinuses on the uncinectomy side and 14 (51.9 %) sinuses on the middle meatal antrostomy side where no clearance was seen during 40 minutes follow-up. Residual clearance was concidered good (< 50 %) in 1 (3.7 %) sinus on the uncinectomy side (not the same sinus as in preoperative measurements). On the middle meatal antrostomy side residual clearance was considered good in 4 (14.8 %) sinuses (1 same sinus as in preoperative measurements).

DISCUSSION

Reviews of the results of endoscopic sinus surgery have reported excellent subjective results with overall improvements of about 90 % in both short and long term [9,10]. However studies have demonstrated that symptom improvement does not correlate well to objective endoscopic evidence of disease persistence [13,14].

Previous studies have shown that patients undergoing sinus surgery had histological changes, such as damage and metaplasia of the sinus mucosa, as well as ciliary changes preoperatively. The sinus mucosa seemed to recover histologically slowly and there were still remaining pathological findings, with some signs of recovery, even 6 months postoperatively [5,11].

It has been shown that the mucociliary clearance (MCC) correlates well with the histology and the histological changes of the maxillary sinus mucosa [11]. In chronic rhinosinusitis a very slow and sometimes absent mucociliary transport has been found indicating histological damage in maxillary sinus mucosa [5,12].

Measurements of the mucociliary transport in the nasal cavity after ESS have shown that after 3 months the mucociliary activity was better than preoperatively but still significantly impaired compared to healthy controls [16].

Restoration of mucociliary clearance in the maxillary sinuses is believed to be essential to the success of ESS. This study supports previous findings about poor recovery of the mucociliary function after ESS in chronic and recurrent maxillary rhinosinusitis [5,6]. Despite the fact, that histological changes in maxillary sinuses do not seem to disappear even 6 months postoperatively, a large number of patients consider themselves recovered. Diminution of the symptoms has been explained by better postoperative sinus ventilation [15,17]. Normal ventilation has probably an anti-inflammatory effect diminishing the inflammation somewhat irrespective of mucociliary clearance effects.

Although about 90 % of the patients have been reported to benefit from sinus surgery [10], ESS does not seem to effect significantly to the mucociliary function of the maxillary sinus mucosa. In our study uncinectomy alone seemed to impaire mucociliary function and uncinectomy combined with middle meatal antrostomy seemed to improve MCC only slightly during 9 months of follow-up.

The change in postoperative mucociliary clearance values was independent of the operation technique. Thus, according to our results, we are not able to say which operative technique is more effective when considering the mucociliary clearance results. However, further studies are required to find out if there are differencies between the two operative techniques when observing other subjective and objective findings.

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Mucosal eosinophils and L-selectin ligands are associated with invasive and noninvasive sinus surgery outcomes

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ABSTRACT

Background: *Chronic rhinosinusitis (CRS) is characterized by persistent inflammation of the nasal and paranasal mucosa with numerous emigrated leukocytes. L-Selectin on leukocytes and its endothelial glycosylated ligands initiate leukocyte infiltration into inflamed tissues. Endoscopic sinus surgery (ESS) is the major approach for restoring sinus physiology after failure of conservative therapy; however, the effect of enlarging the maxillary sinus ostium is still unknown. Here, we compared two histological markers of local inflammation, the number of mucosal eosinophils, and the expression of endothelial L-selectin ligands, with clinical outcomes after enlarging or saving the maxillary sinus ostium.*

Methods: *Twenty-three patients with CRS underwent uncinectomy on one side and additional middle meatal antrostomy on the other side. Maxillary sinus mucosa biopsy specimens from these patients and nine healthy subjects were taken for immunohistochemical evaluations of the number of mucosal eosinophils and endothelial L-selectin ligands. Also, symptoms and mucociliary clearance were measured.*

Results: *The postoperative reduction of the endothelial L-selectin ligands was independent of the operation technique. There was a correlation between postoperative number of mucosal eosinophils and symptom score, which was also independent of the surgical technique. The postoperative decrease of mucosal eosinophils, as well as the correlation of the intraoperative eosinophils with the postoperative symptom score, was found only on antrostomy side.*

Conclusion: *ESS decreases the expression of endothelial L-selectin ligands, which might lead to decreased eosinophil traffic into maxillary sinus mucosa, putatively more when enlarging the maxillary sinus ostium. Both intra- and postoperative low number of eosinophils seem to be indicators of good subjective recovery.*

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Key words: Adhesion molecule, chronic sinusitis, endoscopic sinus surgery, eosinophils, L-selectin, mucociliary clearance, sialyl Lewis x

Chronic rhinosinusitis (CRS) is considered to have a multifactorial etiology. The mucosal lining in CRS is characterized by basement membrane thickening, goblet cell hyperplasia, and subepithelial edema, as well as mononuclear cell and, less abundantly, eosinophil infiltration.[1] The infiltration of leukocytes to sites of inflammation is accomplished by the coordinated actions selectins, integrins, and immunoglobulins. L-Selectin is broadly distributed on most leukocytes and their endothelial counterreceptors are decorated with sialylated, sulfated, and fucosylated glycans.[2–9] During normal conditions, properly glycosylated L-selectin ligands are not expressed on endothelia of other than lymphatic tissues.[10] However, the induction of sulfated sialyl Lewis x ligands on the postcapillary microvascular endothelium occurs during several inflammatory conditions, such as asthma and CRS.[10–15]

Here, we expanded our previous observations to compare functionally active endothelial L-selectin ligands and mucosal eosinophils with subjective and objective recovery after endoscopic sinus surgery (ESS) with two techniques. After failure of conservative therapy, the goal of ESS is to restore the normal mucosal physiology by enabling mucociliary clearance and ventilation through the natural ostia.[1] ESS with standard technique is usually initiated with uncinectomy and middle meatal antrostomy and usually followed by opening of the anterior ethmoidal cells.[16,17] ESS with minimal invasive technique aims at achieving normal sinus function and preventing sinus exposure to environmental irritants, by causing minimal opening of the sinonasal structures.[18–20] Although promising results exist of limited approach of sinuses, statement of evidence is not available concerning the enlarging of the maxillary sinus ostium.[21–23] We study here whether the reduction of expression of endothelial L-selectin ligands and mucosal eosinophils could be more pronounced with ostium-saving than ostium-enlarging surgery and could these histologic endpoints predict clinical outcomes.

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Table 1 **The characteristics of patient groups used in this study**

Patient	Age (yr)	Patient History	Smoking	Medication	Symptom Score	Biopsy	Number of Eosinophils/mm^2
Male	33	Co	−	−	0, 0	+, +	0, 0
Female	56	Co	+	−	0, 0	+, +	3, 6
Female	54	Co	−	−	0, 0	−, +	−, 60
Male	56	Co	+	−	0, 0	+, +	0, 0
Male	45	Co, AR§	−	−	0, 0	+, −	13, −
Male	30	Co, AR§	+	−	0, 0	+, −	2, −
Male	32	Co, AR§	−	−	0, 0	+, −	0, −
Female	20	Co, AR§	−	−	0, 0	−, +	−, 22
Female	19	Co, AR	−	−	0, 0	+, −	51, −
Female†	43	CRS	+	A/−	2, 2/0, 0	+, ±/−, −	48, 48/−, −
Female	64	CRS	−	−/−	3, 3/1, 1	+, ±/+, ±	393, 27/72, 13
Female	60	CRS	−	C/C	2, 2/1, 1	±, +/−, −	470, 76/−, −
Female	22	CRS	−	C/C	3, 3/0, 0	+, ±/+, ±	68, 47/20, 1
Female	40	CRS, NP*	+	−/−	1, 1/1, 1	+, ±/+, ±	56, 48/400, 720,
Male	42	CRS, HP, AR	−	−/−	1, 1/0, 0	±, −/−, −	240, −/−, −
Female	50	CRS, HP, AR	−	C/−	3, 3/2, 2	+, ±/−, −	296, 1040/−, −
Female	42	CRS, HP, AR	−	C/C	2, 2/1, 1	±, /−, −	115, −/−, −
Female	53	CRS, HP, AR, A	−	−/−	2, 3/1, 1	+, ±/+, ±	194, 176/49, 0
Male	31	CRS, HP, A	−	−/−	2, 2/1, 1	±, +/−, −	30, 74/−, −
Male	56	CRS, AR	+	−/−	2, 2/1, 1	+, ±/+, ±	64, 25/521, 21
Female	55	CRS, AR	−	−/−	1, 1/1, 1	+, ±/+, ±	667, 626/48, 341
Male	52	CRS, AR	−	−/−	2, 2/1, 1	+, ±/+, ±	56, 48/160, 17
Male	46	CRS, AR	−	−/−	2, 2/1, 1	+, ±/−, −	445, 80/−, −
Male	30	CRS, AR	+	A/A	2, 2/1, 0	±, +/±, +	261, 186/246, 64
Female	62	CRS, AR	+	−/−	2, 2/0, 0	±, +/±, +	69, 40/5, 16
Female	38	CRS, AR	−	AC/AC	2, 2/1, 1	±, +/±, +	171, 51/48, 50
Female	21	CRS, AR	−	AC/−	1, 1/0, 0	+, ±/+, ±	129, 69/29, 40
Female	45	CRS, AR, A	−	−/−	3, 3/1, 1	±, +/±, +	360, 260/88, 0
Male	58	CRS, AR, A	−	C/−	2, 2/1, 1	±, +/±, +	480, 160/101, 170
Female	30	CRS, AR, A	+	−/−	2, 2/1, 1	+, ±/+, −	192, 272/208, 0
Male	62	CRS, A	+	−/−	1, 1/0, 0	±, +/±, +	85, 224/0, 4
Female	66	CRS, A	−	C/C	3, 2/1, 1	±, +/±, +	68, 185/125, 96

The age (yr) of the patients is shown at the time of operation.
Patient history: Co = control patient; AR = allergic rhinitis; CRS = chronic rhinosinusitis; HP = hypertrophic polypoid maxillary sinus mucosa, found by microscopic evaluation; A = asthma; AR§ = asymptomatic AR; NP = postoperative nasal polyposis with one exceptional case, which was withdrawn from data analysis. Medication: A = antihistamine; C = intranasal corticosteroid. The backslash (/) between the letters indicates preoperative/postoperative medication. Symptom score: The backslash (/) separates preoperative/postoperative scores. Biopsy: The backslash (/) separates preoperative/postoperative biopsies. The comma (,) separates the right and left maxillary sinuses. The underline (_) stands for the side on which middle meatal antrostomy was performed; + = representative biopsy, − = nonrepresentative or absence of biopsy; † = the patient died accidentally before the last follow-up. Thus, the symptom and sign score are shown 3 months postoperatively. Number of eosinophils/mm^2: The backslash (/) separates preoperative/postoperative values. The comma (,) separates the right and left maxillary sinuses. The underline (_) stands for the side on which middle meatal antrostomy was performed.*

MATERIALS AND METHODS

Subjects

This study was performed at the Department of Otorhinolaryngology, Tampere University Hospital, Finland, and Mikkeli Central Hospital, Mikkeli, Finland, during 2001–2003. Characteristics of groups of patients are shown in Table 1. The control maxillary sinus biopsy specimens from nine subjects without CRS were obtained during orbital decompression or bimaxillary osteotomy. Exclusion criteria were age <18 years; medication for respiratory diseases; clinically demonstrable infection in the respiratory tract during the month preceding

the surgery; previous sinonasal surgery; or a history or physical examination suggestive of CRS, nasal polyposis, or moderate, or severe symptoms of allergic rhinitis, asthma, tumor, or disease with severe impact on general immunity.

Twenty-three patients with CRS were enrolled this study. Inclusion criteria were at least 12 weeks of moderate–severe sinus-related symptoms despite maximal medical treatment, *e.g.*, at least two major factors (facial pain, nasal obstruction, nasal discharge, hyposmia, and anosmia), or at least one major and two minor factors (fever, halitosis, fatigue, dental pain, cough, and ear pain); endoscopic findings (mucosal thickening and purulent discharge); and sinus computed tomography score according to Lund-McKay at least 6/24 but not >18/24. Exclusion criteria were age of <18 years; oral corticosteroid treatment during the last 2 months before surgery; previous sinonasal surgery; a history or physical examination suggestive of severe nasal septal deviation, unilateral sinusitis, nasal polyposis of grade 1 or more according to endoscopic examination and computed tomography scan, aspirin sensitivity, chronic bronchitis, cystic fibrosis, tumor, or disease with severe impact on general immunity; mild sinus-related symptoms; and the following computed tomography findings: severe chronic pansinusitis (total opacification in posterior ethmoidal and/or sphenoidal and/or frontal sinuses and/or total obstruction of frontal recess) and Lund-McKay score of <6/24 or >18/24. Withdrawals from the result analysis: one patient was withdrawn because of the regrowth of nasal polyps 9 months postoperatively with high endoscopic scores as well as high number of postoperative eosinophils and endothelial L-selectin ligands in sinus mucosa. Dropouts from the study: one patient died accidentally before the last postoperative control; thus, the postoperative samples were not taken and the symptom and endoscopic scores are based on the control 3 months postoperatively. Disabilities in the following with the study protocol: from the seven patients at Mikkeli central hospital, the postoperative biopsy specimens were not taken because of the misinterpretation of the study protocol. In addition, from three patients one or two pre- or postoperative samples were nonrepresentative. Altogether, the number of patients with acceptable intra- and postoperative specimens from both sinuses comprised only 16 patients. Diagnosis of nasal polyposis was based on endoscopic examination and pathological evaluation of polyp tissue. Diagnosis of hypertrophic polypoid mucosa of maxillary sinus was based on microscopic evaluation. The patients with hypertrophic polypoid maxillary sinus mucosa did not have macroscopic sinonasal polyps detected by nasal endoscopy or computed tomography scans. Diagnosis of allergic rhinitis was based on skin-prick test positivity and at least a 2-year history of major symptoms (rhinorrhea, nasal obstruction, nasal itching, and sneezing). Of those who were taking nasal corticosteroids for at least 2 months before performing biopsies, seven patients had momethasone furoate (Schering-Plough, Kenilworth, NJ), 50 μg/nostril twice a day, and one patient had fluticasone propionate (GlaxoSmithKline, London, United Kingdom), 50 μg/nostril twice a day. Of those who used oral antihistamines with or without oral decongestant for at least 2 weeks before taking biopsy specimens, one subject used cetirizine hydrochloride (UCB, Brussels, Belgium), 10 mg/day and three subjects used a combination of acrivastine and pseudoephedrine hydrochloride (GlaxoSmithKline), 8 + 60 mg/once or twice a day.

Sinus Surgery

For subjects with CRS, ESS was performed as previously described.[15,24] Briefly, the uncinectomy was performed on both sides, in which the lower two-thirds of the uncinate process was removed. Additional middle meatal antrostomy was randomized on either the right or the left side of each patient. It was performed by removing with cutting forceps the posterior connective tissue of the natural ostium to duplicate the diameter. If large ethmoid bulla was disturbed doing uncinectomy and/or antrostomy, it was opened. The light middle meatal tamponation was removed on the 1st postoperative day. Nasal endoscopy was performed and the operation field was cleaned 2 weeks after surgery.

Histological Specimens

The biopsies of the maxillary sinus mucosa were performed intraoperatively from all subjects. The postoperative biopsy specimens were taken from the patients with CRS 9 months after ESS under local anesthesia with small maxillary sinus forceps from the lateroinferior part of the maxillary sinus. Sections of paraffin-embedded tissue samples were stained with hemalaun-eosin for calculating the number of mucosal eosinophils per squared millimeter. L-Selectin ligands were studied immunohistochemically with two monoclonal antibodies (mAb). The mAb HECA-452 recognizes α2,3-sialylation and α1,3-fucosylation of lactosamine, and mAb MECA-79 recognizes an extended sulfated core 1 lactosamine structure.[25–28] The mAb HECA-452 (rat IgM; 2 μg/mL) and mAb MECA-79 (rat IgM; 1 μg/mL) were kindly provided by Dr. S. Jalkanen (University of Turku, Turku, Finland). Anti-human CD34, class II (mIgG1; 2 μg/mL; DAKO, Glostrup, Denmark), was used as a positive control for the detection of endothelial cells. The mAb 7C7 (mouse IgM; 1.2 μg/mL) and TIB-146 (rat IgM; 10 μg/mL), both kindly provided by Dr. S. Jalkanen, were used as negative controls. For immunohistochemical techniques and microscopic analysis of the specimens, previously described protocols were used.[15] Briefly, the mean number of mAb HECA-452$^+$ and mAb MECA-79$^+$ vessels was divided by the mean number of CD34$^+$ vessels from the whole specimen yielding the percentage of sialyl Lewis x– or sulfated lactosamine-reactive vessels.

Symptom Score

All subjects filled out a questionnaire of symptoms 1–78 days (mean ± SD, 25 ± 22 days) before the operation, and those with CRS diagnosis, 3, 6, and 9 months postoperatively. The symptoms of nasal obstruction, the amount and consistency of nasal discharge, epistaxis, tears, and facial pain were asked from each side separately. The symptoms of headache, postnasal drip, sense of smell, and cough were not asked from each side separately. The total symptoms were scored for each side as follows: 0, asymptomatic; 1, mild; 2, moderate; and 3, severe symptoms. In this study we used symptom scores preoperatively and 9 months postoperatively.

Mucociliary Clearance

Mucociliary measurements were performed only for patients with CRS diagnosis, during the same preoperative visit

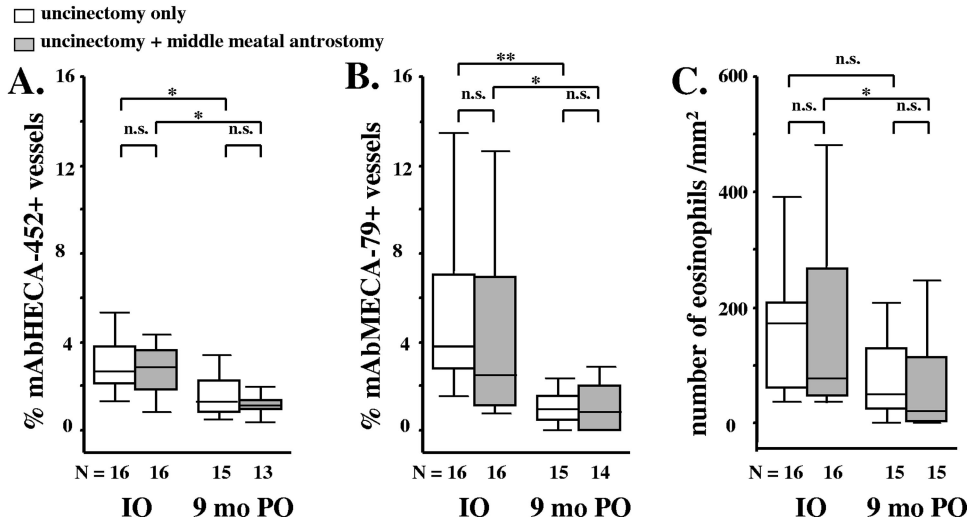

Figure 1. Comparison of the percentages of vessels expressing sulfated sialyl Lewis x epitopes analyzed with (A) antisialyl Lewis x antibody (monoclonal antibody [mAb] HECA-452) and (B) an antisulfated extended core 1 lactosamine antibody (mAb MECA-79), as well as (C) the number of eosinophils in maxillary sinus specimens and patients with chronic rhinosinusitis taken intraoperatively (IO) or 9 months postoperatively (9 mo PO). The patients underwent endoscopic sinus surgery (ESS) with uncinectomy only on one side (white bar) and ESS with additional middle meatal antrostomy on the contralateral side (black bar). N indicates the number of specimens, n.s. indicates no significant difference. The significant differences are marked with asterisks: $^{**}p < 0.01$; $^{*}p < 0.05$.

when the first questionnaire was taken and 9 months postoperatively. We used the previously described technique.[24] Briefly, a drop of sterile human serum albumin labeled with 99mTc (Venticol; Sorin Biomedica, Saluggia, Italy) was applied through the irrigation tube into the bottom of both maxillary sinuses. Area of the initial tracer in the sinuses was marked and clearance of tracer from the sinuses, as well as the possible appearance of activity in the pharynx, was measured with γ-imaging at specified time points from the anterior view. The percentage of the residual activity in each maxillary sinus after 40 minutes was used in this study.

Statistical Analysis

Statistics were performed with the SPSS Base 11.0 Statistical Software Package (SPSS, Chicago, IL). Data are expressed as median and interquartile ranges. For multiple comparisons, the results were analyzed by the nonparametric Kruskal-Wallis one-way analysis of variance by ranks and then by nonparametric Mann-Whitney *U* test. The nonparametric Wilcoxon rank sum test was used for comparison of matched pairs. The nonparametric ordinal regression analysis was used to study the correlation between the ranks. A two-tailed value of $p < 0.05$ was considered significant with all tests.

RESULTS

Compared with control specimens, intraoperative samples of CRS are characterized by increased number of mucosal eosinophils and percentages of endothelial sulfated sialyl Lewis x epitopes ($p < 0.001$ by Mann-Whitney *U* test; data not shown). A higher number of mucosal eosinophils were observed for intraoperative specimens obtained from CRS patients with allergic rhinitis than from CRS patients without allergic rhinitis ($p < 0.05$ by Mann-Whitney *U* test; data not shown). The mucosal parameters did not differ significantly between CRS groups with or without hypertrophic polypoid mucosa of the maxillary sinus ($p > 0.05$ by Mann-Whitney *U* test; data not shown) or between CRS groups with or without medication ($p > 0.05$ by Mann-Whitney *U* test; data not shown).

When observing the two sides of each CRS patient before operation, there were no statistically significant differences in the presence of endothelial sulfated sialyl Lewis x glycans, mucosal eosinophils, symptom score, or mucociliary clearance values ($p > 0.05$, Wilcoxon test, data not shown). Therefore, any postoperative difference in these parameters between the sides was considered to be caused by the difference between ostium-saving and -enlarging techniques.

When comparing the specimens taken from patients during and 9 months after ESS, the expression level of mAb HECA-452^{+} and mAb MECA-79^{+} vessels decreased significantly postoperatively with both ostium-enlarging or ostium-saving techniques shown in Fig. 1 ($p < 0.05$, Wilcoxon test). The postoperative decrease of mucosal eosinophils reached significance only on the antrostomy side but not on the side with uncinectomy only, as shown in Fig. 1 ($p = 0.02$ and $p = 0.18$, respectively, Wilcoxon test). No differences were observed in the presence of tissue eosinophils or sulfated sialyl Lewis x epitopes when comparing the postoperative specimens from each side (Fig. 1; $p > 0.05$, Wilcoxon test).

The expression level of endothelial sulfated sialyl Lewis x glycans or the number of eosinophils did not correlate with the preoperative symptom score in intraoperative maxillary sinus biopsy specimens ($p > 0.05$, ordinal regression, data not shown). However, the postoperative symptom score correlated with the grade of mucosal eosinophils in postoperative maxillary sinus samples with both operative techniques as shown in Fig. 2 ($p < 0.05$, ordinal regression). In addition, when comparing the number of intraoperative mucosal eosin-

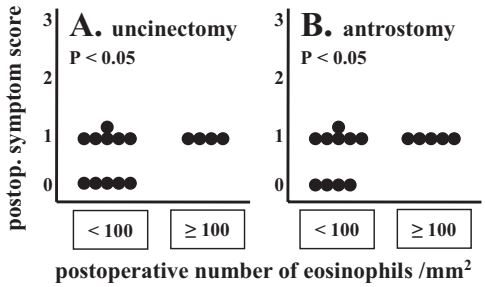

Figure 2. The correlation between the grade of the postoperative number of mucosal eosinophils and postoperative symptom score on the side (A) with uncinectomy and (B) with additional middle meatal antrostomy. The x-axis represents the grade of eosinophils from maxillary sinus biopsy taken 9 months postoperatively (<100 eosinophils/mm²; ≥100 eosinophils/mm²). The y-axis represents the postoperative symptom score taken 9 months postoperatively: 0 = resolved, 1 = mild, 2 = moderate, and 3 = severe symptoms. The high number of eosinophils (i.e., ≥100 eosinophils/mm²) correlates positively with the high postoperative symptom score on both the side with uncinectomy and the side with additional middle meatal antrostomy.

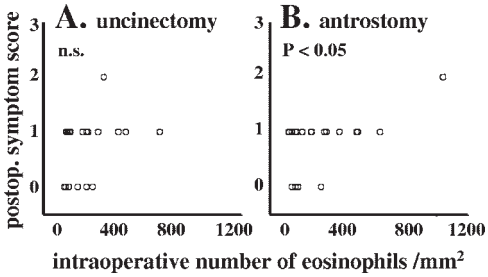

Figure 3. The correlation between the intraoperative number of mucosal eosinophils and postoperative symptom score on the side (A) with uncinectomy and (B) with additional middle meatal antrostomy. The x-axis represents the number eosinophils from maxillary sinus biopsy taken intraoperatively. The y-axis represents the postoperative symptom score taken 9 months postoperatively: 0 = resolved, 1 = mild, 2 = moderate, and 3 = severe symptoms. The number of eosinophils correlates positively with the postoperative symptom score only on the side with additional middle meatal antrostomy. n.s., No significant difference.

ophils and postoperative symptoms, there was found a correlation only on the antrostomy side as seen in Fig. 3 ($p < 0.05$, ordinal regression). The postoperative symptom score correlated with the postoperative percentage of mAb's HECA-452$^+$ and MECA-79$^+$ vessels only on the side with the ostium-saving technique ($p < 0.05$ ordinal regression, data not shown). No correlation was observed between pre- or postoperative mucociliary clearance values and intra- or postoperative presence of endothelial sulfated sialyl Lewis x glycans or mucosal eosinophils ($p > 0.05$, Spearman rank correlation test, data not shown).

DISCUSSION

This study was performed to compare the ostium-saving and -enlarging techniques by evaluating histological parameters and to observe the correlation between histological and clinical recovery of ESS. L-Selectin ligands were chosen because they might have a significant impact on eosinophil traffic into chronically inflamed sinus mucosa.[15] In addition, others have shown that the presence of eosinophilia during CRS is frequently associated with severe objective findings and decreased likelihood of surgical success.[29–33] We showed that CRS with allergic rhinitis is more pronounced with tissue eosinophilia than CRS without allergic rhinitis, which is in line with the previous observations of others.[34,35] Although the influx of eosinophils in nasal polyp tissue has been well reported by others, we did not observe a difference in eosinophilia of maxillary sinus mucosa between patients with or without hypertrophic polypoid mucosa of the maxillary sinuses.[36] This is probably because of the fact that the hypertrophic sinus mucosa was found only microscopically.

The main finding of this study was that when antrostomy was performed, a significant decrease in the endothelial L-selectin ligands and mucosal eosinophils was observed. By contrast, when maxillary sinus ostium was not enlarged, the expression of endothelial L-selectin ligands decreased but not the number of mucosal eosinophils. Although it seems that antrostomy might decrease more effectively the mucosal inflammation, it is not possible to draw final conclusions from our small and heterogenous patient population. We also observed that the persistence of a high grade of postoperative eosinophils correlated positively with the postoperative level of symptoms, but this correlation was independent of the two different operation techniques. On the other hand, we found an antrostomy-dependent correlation between the intraoperative mucosal eosinophils and postoperative symptom score, putatively meaning that intraoperative low tissue eosinophilia may be a marker for better postoperative symptom relief. When the ostium was not enlarged, the postoperative number of eosinophils did not significantly alter, which might have led to the persistence of postoperative symptoms compared with the antrostomy side (unpublished data of our own experiment Mar. 12, 2007). Others have shown that cellular infiltration and local cytokine activity in the sinus or uncinate mucosa collected at surgery may have high prognostic value for outcome.[37–41] Baudoin *et al.* showed that the number of postoperative uncinate mucosal eosinophils correlated with only one postoperative symptom (secretion), while other histological markers, *e.g.*, the number of mucosal goblet cells, seemed to be better indicators for subjective recovery.[42] In contrast with the postoperative histological findings, we did not find a significant correlation between the preoperative symptoms and intraoperative histological findings. This might be due to the fact that preoperative symptoms and intraoperative histology are not fully comparable because of time delay (in average, 25 days) between performing the preoperative questionnaire and the operation.

CONCLUSION

When observing the decreased presence of mucosal eosinophils, an uncinectomy with additional antrostomy seems to be a more effective technique than uncinectomy without antrostomy. However, before concluding the real role of antrostomy, additional studies are required with a population increased in number and decreased in variation, such as the presence of allergic rhinitis. The pathophysiological mecha-

nisms underlying the reduction in the level of L-selectin ligands and eosinophils after ESS still remains to be resolved. The persistence of postoperative eosinophils seems to indicate worse symptom relief. We advocate that more frequently taken intraoperative sinus biopsy specimens with pathological evaluation of mucosal eosinophils and other inflammatory factors might be a useful tool to predict postoperative outcomes and to encourage certain patients for intensive therapy and follow-ups.

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ORIGINAL CONTRIBUTION

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Computed tomography findings after endoscopic sinus surgery with preserving or enlarging maxillary sinus ostium surgery*

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SUMMARY

Endoscopic sinus surgery (ESS) is the main surgical approach in the treatment of chronic rhinosinusitis (CRS) after failure of medical treatment. ESS is based on the theory that obstruction of the maxillary sinus ostium is mainly behind the pathogenesis of CRS. Controversy remains concerning the enlargement of the natural maxillary sinus ostium. The aim of this study was to compare computed tomography (CT) findings after preservation or enlargement of the maxillary sinus ostium. Thirty patients with non-polypous CRS underwent randomized endoscopic sinus surgery with uncinectomy on one side and additional middle meatal antrostomy on the other side. Lund-Mackay (LM) scores and the ostium diameters were analysed from CT scans taken preoperatively and nine months postoperatively, and were used for comparison of the two operative techniques. In addition, the correlation between CT findings and subjective outcomes was studied. Comparison of the preoperative and postoperative CT scans revealed that significant reduction of LM score was achieved on both sides, regardless of the type of procedure performed. The postoperative area of the ostium remained significantly larger on the antrostomy side compared to the uncinectomy side. A large maxillary sinus ostium size seems to associate with lower postoperative LM score, but does not seem to provide superior symptom relief.

Key words: *chronic rhinosinusitis, endoscopic sinus surgery, computed tomography, Lund-Mackay score.*

INTRODUCTION

Since its introduction, endoscopic sinus surgery (ESS) has been widely accepted in the treatment of chronic rhinosinusitis (CRS) after failure of medical treatment [(1)]. Reported results have been good both in short- and long-term surveys [(2,3)].

ESS is based on the theory that the maxillary sinus ostium is the most important area in the pathogenesis of chronic and recurrent rhinosinusitis [(15,16)]. Obstruction of the ostium is believed to lead to chronic inflammation and eventually to pathologic alterations of the maxillary sinus mucosa. Therefore, surgical opening of the ostium and thus improved drainage and ventilation of the sinus should restore the normal mucosa [(4)].

There are different opinions concerning the extent of surgery of the ostiomeatal complex. It is considered that removal of the uncinate process alone would be enough to restore the ventilation of the maxillary sinus. ESS with the minimally invasive technique aims to achieve normal sinus function and prevent sinus exposure to environmental irritants, by causing minimal opening of the sinonasal structures [(5,6)].

Despite the fact that the ostium is considered to be the most

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important area in the pathogenesis of CRS, few studies have addressed the role of middle meatal antrostomy in patient symptoms and in objective postoperative findings [7,17,19]. Although promising results exist about limited approach of the maxillary sinus ostia, there are no results available concerning the computed tomography outcomes of preservation vs. enlargement of the maxillary sinus ostium [7-9].

The Lund-Mackay (LM) scoring system was developed for objective quantification of the inflammatory disease in the paranasal sinuses [10]. It is based on a simple numeric score driven from the CT scan in which every sinus group is assigned a numeric grade depending on the extent of the disease [10]. Although CT and endoscopic scores correlate well, the correlation between CT findings and symptom scores has generally shown to be poor and is not a good indicator of the outcomes [1,11,12].

The purpose of this study was to compare preoperative and postoperative CT findings in patients with CRS after uncinectomy with additional middle meatal antrostomy to those after uncinectomy without enlarging the natural ostium. For assessment of the clinical relevance of these results, we also studied correlation between postoperative CT findings and symptoms asked.

MATERIALS AND METHODS

Subjects

This prospective, randomized, single-blinded study was carried out at the Department of Otorhinolaryngology, Tampere University Hospital, Finland and Mikkeli Central Hospital, Mikkeli, Finland between 2001 and 2003. The ethical committees of the Tampere University Hospital and Mikkeli Central Hospital approved the study. Informed consent was obtained from the patients in this study. Thirty patients having non-polypous CRS, and not responding to maximal medical treatment, were enrolled in this study. They underwent randomly and single-blindly uncinectomy-only on one side and additional middle meatal antrostomy on the contralateral side. The study methods were symptom questionnaire and sinus CT scans performed prior to and nine months after the ESS. Characteristics about the groups of patients are shown in Table 1.

Inclusion criteria were: moderate to severe sinus-related symptoms during at least 12 weeks, despite maximal medical treatment, e.g. at least two major factors (facial pain, nasal obstruction, nasal discharge, hyposmia, and anosmia), or at least one major and two minor factors (fever, halitosis, fatigue, dental pain, cough, and ear pain); endoscopic findings (mucosal thickening, purulent discharge); and total Lund-Mackay sinus computed tomography scores of at least 6/24 but no more than 18/24.

Exclusion criteria were: age less than 18 years; oral corticosteroid treatment during the last two months prior to surgery; previous sinonasal surgery; a history or physical examination suggestive of severe nasal septal deviation (that causes only unilateral nasal obstruction and/or requires septoplasty before performing ESS), unilateral sinusitis, nasal polyposis > grade 1, aspirin sensitivity, chronic bronchitis, cystic fibrosis, tumor or disease with severe impact on general immunity; mild sinus-related symptoms; and the following computed tomography findings: severe chronic pansinusitis (total opacification in posterior ethmoidal and/or sphenoidal and/or frontal sinuses and/or total obstruction of frontal recess) and Lund-Mackay score less than 6/24 or more than 18/24.

Dropouts from the study: one patient died accidentally prior to the postoperative control, thus the postoperative CT-scans were not taken.

Diagnosis of nasal polyposis was based on endoscopic examination and pathological evaluation of polyp tissue. Diagnosis of allergic rhinitis was based on skin prick test positivity and at least a two-year history of major symptoms (rhinorrhea, nasal obstruction, nasal itching, and sneezing). Of those who were taking nasal corticosteroids for at least two months before computed tomography scans, 10 had momethasone furoate 50 ug / nostril twice a day (Schering-Plough, Kenilworth, NJ, USA), and 2 had fluticasone proprionate 50 ug / nostril twice a day (Glaxosmithkline, London, UK). Of those who used oral antihistamines with or without oral decongestant for at least 2 weeks before taking biopsies, 1 subject used cetirizine hydrochloride 10 mg / day (UCB, Brussels, Belgium), 1 used a combination of cetirizine hydrochloride and pseudoephedrine hydrochloride 5 mg + 120 mg / day (UCB, Brussels, Belgium), and 4 used a combination of acrivastine and pseudoephedrine hydrochloride 8 mg + 60 mg / once or twice a day (Glaxosmithkline).

Sinus surgery

Patients underwent endoscopic sinus surgery as previously described [17,18]. Briefly, randomized, standardised uncinectomy alone and uncinectomy with additional middle meatal antrostomy were performed on each side of each patient. Uncinecomy was performed similarly on both sides. The patient was blinded for the procedures performed on each side. On the antrostomy side, the size of the natural ostium was duplicated in the posterior direction by using cutting forceps. If necessitated, a large ethmoid bulla was opened on both ostium-preserving and enlarging sides in 25 patients. Posterior ethmoidal cells, sphenoidal sinuses and frontal sinuses were left undisturbed.

Computed tomography scans

High resolution CT imaging of the nasal airways and paranasal sinuses was performed on a ProSpeed PLUS scanner (General Electric, Miwaukee, WI, USA) equipped with a helical CT having a tube voltage of 120 kV and tube current of 200 mA. The thickness of the coronal slices was 3 mm with no intervening gap, a field of view of 25 cm and matrix size of 512. Reconstructions were acquired post examination and were 1 mm thick. The extent of the inflammatory disease in computed

tomography scans of the paranasal sinuses was determined by using the Lund-Mackay staging for rhinosinusitis [10]. LM staging is based on a simple numeric score derived from the CT scan. Each sinus group (maxillary, frontal, sphenoidal, anterior ethmoidal, and posterior ethmoidal) is assigned a numeric grade: 0 = no abnormality, 1 = partial opacification, and 2 = total opacification. The ostiomeatal complex is scored as 0 (not obstructed) or 2 (obstructed). Thus a total score of 0 to 24 is possible, and each side can be considered separately (0 to 12). Analysis of the preoperative and postoperative CT scans and the staging of the CT scans were done on one occasion by two blinded authors (JPM and SKT-S).

The ostiomeatal complex was reconstructed with 1 mm slice thickness. The anteroposterior (AP) and cephalocaudal (CC) dimensions of the ostium were calculated by two blinded authors (JPM and PD) from the distance measurement data on the postoperative CT scan database. The maxillary sinus ostium was considered to be an ellipse with AP and CC dimensions as major and minor axes respectively. Thus the postoperative ostium size was determined to be $0.25\pi APCC$.

Patient questionnaires

The symptoms questionnaires were filled at one month preoperatively and at one, nine months and three years postoperatively. In this study we used the questionnaires filled at nine months postoperatively. We used total symptom score that was the sum of the following questions: facial pain/pressure (min-max 0-3), nasal obstruction (0-3), nasal discharge (0-3), posterior nasal drip (0-2), number of acute purulent sinusitis during the past 12 months (0 = zero, 1 = one or two, 2 = three or more), and sense of smell (0-3). Total symptom score may thus range from 0 to 16, with lower scores representing better outcomes.

Statistical analyses

Statistics were performed with the SPSS Base 11.0 Statistical Software Package (SPSS, Chicago, IL, USA). Data is expressed as median and interquartile ranges. The nonparametric Wilcoxon rank sum test was used for comparison of matched pairs. The nonparametric spearman rank correlation test was used to study the correlations. The nonparametric Mann Whitney U test was used for comparisons of median or mean values in two groups. A two-tailed p-value of less than 0.05 was considered significant in all tests.

RESULTS

Observation of both sides of each CRS patient before operation revealed no significant differences statistically in the LM scores ($p > 0.05$, Wilcoxon test, Figure 1) or LM values for maxillary sinus opacification (0-2) or values for **ostiomeatal complex obstruction** (0 or 2) ($p > 0.05$, Wilcoxon test, data not shown). Therefore, any postoperative differences in CT-parameters between the sides were considered to be due to the difference between ostium-preserving and enlarging techniques.

Comparison of the LM scores to CT scans taken prior to and 9 months postoperatively exposed a statistically significant difference on both ostium enlarging and preserving sides ($p < 0.001$, Wilcoxon test, Figure 1). Similarly, a significant improvement was achieved in postoperative LM values for maxillary sinus opacification and values for ostiomeatal complex obstruction on both sides ($p < 0.001$, Wilcoxon test, data not shown). In contrast, when comparing both sides, no statistically significant difference was observed in the postoperative LM scores ($p > 0.05$, Wilcoxon test, Figure 1) or in postoperative LM values for maxillary sinus opacification and values for ostiomeatal complex obstruction ($p > 0.05$, Wilcoxon test, data not shown).

When observing both sides from postoperative CT scans, the anteroposterior (AP) diameter of the antrostomy side was statistically significantly greater than that of the uncinectomy side (mean values 0.98 cm, 0.52 cm respectively, $p < 0.001$, Wilcoxon test, Figure 2). Similar significant differences were found for the cephalocaudal (CC) diameter from postoperative CT-scans (mean values 0.75 cm, 0.41 cm, respectively, $p < 0.001$, Wilcoxon test, Figure 3). Moreover, the ostium area was also significantly greater on the antrostomy side in calculations from postoperative CT scans (mean values 0.70 cm^2, 0.23 cm^2, respectively, $p < 0.001$, Wilcoxon test, data not shown).

A correlation was observed between the postoperative ostium area and postoperative change in LM values for maxillary sinus opacification and ostiomeatal complex obstruction ($p < 0.01$, $r = 0.59$, Spearman rank correlation test, Figure 4). However, the postoperative symptoms/symptom sum did not correlate to any of the postoperative CT-values: postoperative size of ostium, postoperative LM score, change in LM score or change in LM values for maxillary sinus/ostiomeatal complex ($p > 0.05$, Spearman rank correlation test, data not shown).

The age, sex, or patient history of allergic rhinitis and/or asthma diagnosis, hypertrophic polypoid sinus mucosa, smoking, or intranasal corticosteroid and/or antihistamine medication, or the additional opening of the ethmoidal bulla, did not associate with the median values of the pre- or postoperative LM scores from either ostium preserving or enlarging side ($p > 0.05$, by Mann Whitney U test, data not shown). Similarly, these parameters did not associate with the mean values of postoperative ostium area from either ostium-preserving or enlarging side ($p > 0.05$, by Mann Whitney U test, data not shown).

DISCUSSION

This study was performed to compare two operative techniques in endoscopic sinus surgery: uncinectomy vs. uncinectomy with middle meatal antrostomy. The comparison was made by observing Lund-Mackay scores and ostium size prior to and 9 months after the operation. The correlation between the postoperative CT findings and subjective outcomes was studied in order to evaluate if larger ostium size or low LM score indicate better symptom relief.

Patient	Age	Patient history	Smoking	Medication	LM-score	Postop. area of ostium (cm^2)
female†	43	CRS	+	A/-	5,5/-,-	- , -
female	64	CRS	-	-/-	5,8/2,3	0.65 , 1.05
female	60	CRS	-	C/C	5,5/2,4	0.19 , 0.00
female	22	CRS	-	C/C	5,5/5,3	0.00 , 0.88
female	42	CRS	-	-/-	5,5/4,4	0.52 , 0.26
male	52	CRS	-	C/C	6,6/3,3	0.16 , 0.12
female	40	CRS,NP*	+	-/-	5,5/5,2	0.00 , 1.06
female	37	CRS,HP	-	-/-	5,5/1,1	0.57 , 1.22
female	40	CRS,HP	+	-/-	7,7/2,2	0.20 , 0.10
male	42	CRS,HP,AR	-	-/-	3,3/2,2	0.06 , 0.07
female	50	CRS,HP,AR	-	C/-	5,5/5,2	0.00 , 0.28
female	42	CRS,HP,AR	-	C/C	5,5/0,2	0.21 , 0.13
female	53	CRS,HP,AR,A	-	-/-	5,5/2,2	0.33 , 1.01
female	49	CRS,HP,AR,A	-	AC/AC	6,6/3,3	0.19 , 0.05
male	58	CRS,HP,A	-	-/C	7,7/3,3	1.00 , 0.20
male	31	CRS,HP,A	-	-/-	4,4/4,2	0.00 , 0.19
male	56	CRS,AR	+	-/-	4,4/0,0	0.41 , 0.95
female	55	CRS,AR	-	-/-	5,5/2,2	0.66 , 0.47
male	52	CRS,AR	-	-/-	6,5/2,2	0.02 , 0.88
male	46	CRS,AR	-	-/-	5,5/3,3	0.05 , 0.42
male	30	CRS,AR	+	A/A	5,5/1,1	1.75 , 0.08
female	62	CRS,AR	+	-/-	4,4/0,0	1.10 , 0.83
female	38	CRS,AR	-	AC/AC	4,4/2,1	0.61 , 0.14
female	21	CRS,AR	-	AC/-	5,6/1,1	0.55 , 1.45
female	45	CRS,AR,A	-	-/-	5,5/2,2	0.15 , 0.14
male	58	CRS,AR,A	-	C/-	4,5/1,2	1.12 , 0.61
female	30	CRS,AR,A	+	-/-	5,5/5,2	0.00 , 2.09
male	62	CRS,A	+	-/-	7,6/1,1	0.01 , 0.01
female	66	CRS,A	-	C/C	5,6/2,2	0.99 , 0.28
female	30	CRS,A	-	AC/AC	3,5/1,1	0.26 , 0.36

Table 1. The characteristics of the patient groups used in this study. The age (years) of the patients is shown at the time of operation. Abbreviations: *Patient history*: Co = control patient, AR = allergic rhinitis, CRS = chronic rhinosinusitis, NP = nasal polyposis, A = asthma. NP* indicates postoperative nasal polyposis with one exceptional case. *Medication*: A = antihistamine, C = intranasal corticosteroid. The backslash (/) between the letters indicates preoperative / postoperative medication. *LM-score*: Lund-Mackay score for computed tomography (CT) scans. The backslash (/) separates preoperative / postoperative CT-scans. The comma (,) separates the right and left side of the sinonasal tract. The underline (_) stands for the side on which middle meatal antrostomy was performed. *Postop. area of ostium (cm^2)*: The area (in square centimeters) is counted from the CT-scans taken 9 months postoperatively. The comma (,) separates the right and left side of the sinonasal tract. The underline (_) stands for the side on which middle meatal antrostomy was performed. † = the patient died accidentally before the last follow-up. Thus the patient was withdrawn from the analysis.

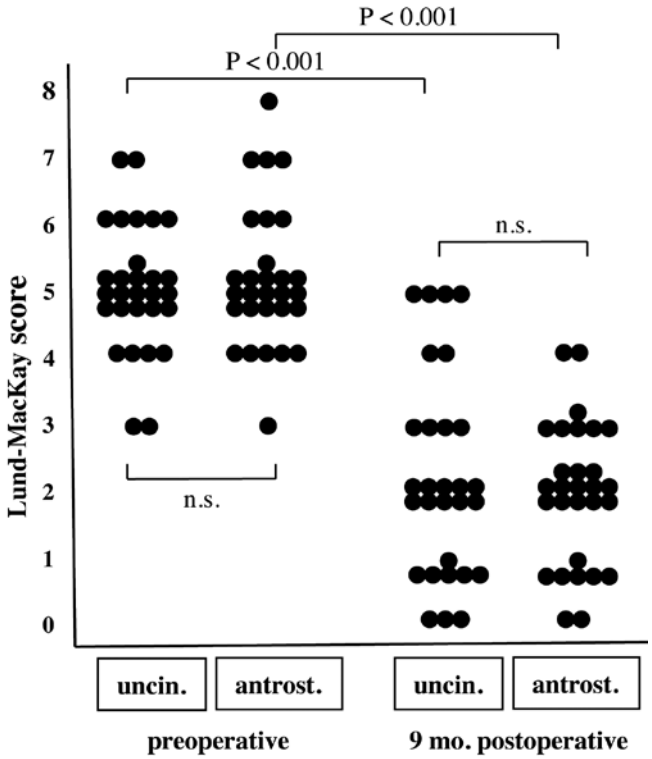

Figure 1. Comparison of the unilateral Lund-Mackay (LM) scores for computed tomography scans taken preoperatively and 9 months postoperatively in patients who had undergone uncinectomy on one side and additional middle meatal antrostomy on the other side. There was a significant decrease in the postoperative LM scores for computed tomography scans in comparison to preoperative LM scores (by Wilcoxon test). When comparing uncinectomy and antrostomy sides with each individual, there was not a significant difference (n.s.) between these sides in either preoperatively or 9 months postoperatively taken computed tomography scans (by Wilcoxon test).

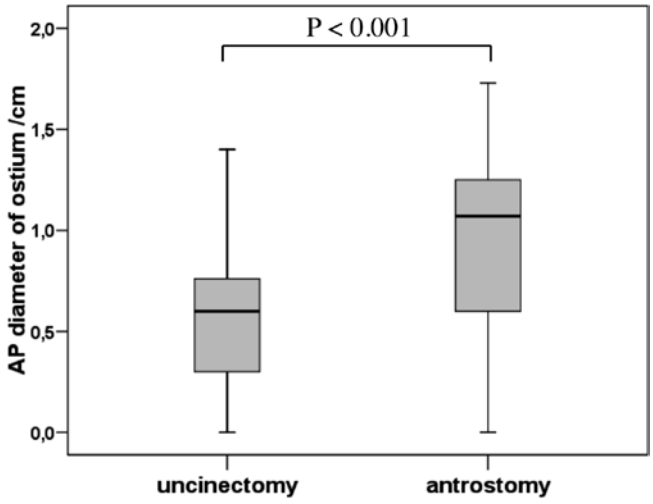

Figure 2. The y-axis represents the anterior-posterior (AP) diameter of the maxillary sinus ostium calculated from the computed tomography scans taken 9 months postoperatively in patients who had undergone uncinectomy on one side and additional middle meatal antrostomy on the other side. The AP-diameter of the ostium remained greater on the antrostomy side than on the uncinectomy side 9 months postoperatively (by Wilcoxon test).

Others have also compared uncinectomy and additional middle meatal antrostomy on each side of each CRS patient [19]. In contrast to our study, the patients had additional nasal polyps and the CT-findings were not evaluated. Wadwongtham et al., found in this prospective randomized study that a large middle meatal antrostomy had a better patency rate than an undisturbed maxillary sinus ostium only in the early phase of evaluation (3 months postoperatively). From the 6th month to the final evaluation (1 year) there was no statistically significant difference between the surgical techniques, recurrent polyposis being the main reason for re-occclusion of the drainage system [19].

Although clinical studies have shown that Lund-Mackay scores have little correlation in symptom severity, it is still the most widely used radiological method for assessing the diagnosis and the severity of CRS [9,13]. We showed that both the preserving and enlarging techniques occasioned a significant reduction of the LM scores. This is in accordance with the previous observations for the effect of ESS on the LM scores [14].

On one hand, measurements from the postoperative CT scans showed that the diameter of the ostium remained greater on the antrostomy side than on the ostium preserving side. On the other hand there was a correlation between the postoperative ostium area and postoperative change in LM values for maxillary sinus opacification and ostiomeatal complex obstruction. Thus, an uncinectomy with additional middle meatal antrostomy seemed to be associated with lower LM scores than uncinectomy without antrostomy.

We have previously shown with these subjects, that the number of eosinophils in the sinus mucosa decreased only on the side on which the ostium was enlarged, not on ostium preserving side [18]. Thus, antrostomy might normalize more effectively not only the severity of the mucosal inflammation but also the volume of the inflamed sinus mucosa. Yet, because we were not able to show that achieving lower LM scores by larger ostium size provided superior symptom relief, additional middle meatal antrostomy might not be expected to be more effec-

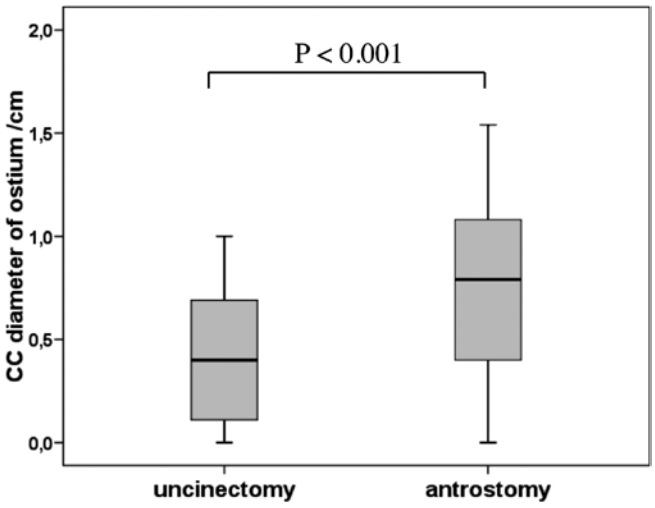

Figure 3. The y-axis represents the cephalocaudal (CC) diameter of the maxillary sinus ostium calculated from the computed tomography scans taken 9 months postoperatively in patients who had undergone uncinectomy on one side and additional middle meatal antrostomy on the other side. The CC-diameter of the ostium remained greater on the antrostomy side than on the uncinectomy side 9 months postoperatively (by Wilcoxon test).

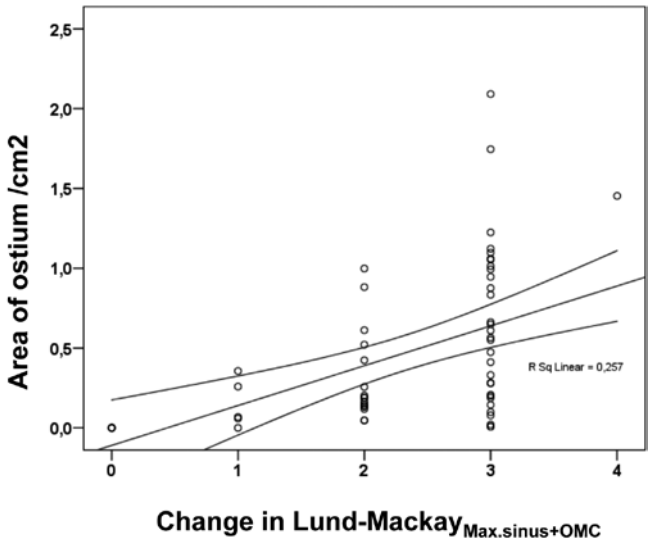

Figure 4. The correlation between the area of the maxillary sinus ostium and the unilateral postoperative change in LundMackay (LM) values for maxillary sinus opacification plus ostiomeatal complex obstruction (= Max.sinus+OMC). The values were evaluated from the computed tomography scans taken 9 months postoperatively. The area was calculated from the mathematical equation 0.25πAPCC. Increased postoperative area of the maxillary sinus ostium correlated with greater postoperative change in LM values for maxillary sinus opacification and ostiomeatal complex obstruction (by Spearman rank correlation test). r = correlation coefficient.

tive than simple uncinectomy only. However, further studies with larger numbers of patients are required to study this.

By using the reconstructed 1 mm CT slice thickness of the ostiomeatal complex, we were able not only to calculate the ostium area, but also to show that there was no significant postoperative scarring or adhesion formation on either side. This might thus, indicate good recovery of the ostiometal complex with both procedures.

Measurement methods, such as SinoNasal outcome Test-20, 36-Item Short-Form health Survey, and Visual Analogue Score, to analyze symptom outcomes after ESS were not used in this study as conception work began in 2000, when standardized Quality of Life methods were not in general use. We acknowledge the fact that this makes comparison to other studies difficult.

CONCLUSION

The postoperative decrease of the Lund-McKay scores on both sides seems to indicate the good outcomes of ESS, regardless of the type of procedure performed. When observing the postoperative postoperative change in LM values for maxillary sinus opacification and ostiomeatal complex obstruction, an uncinectomy with additional antrostomy seems to be slightly more effective than uncinectomy without antrostomy. However, these CT findings did not associate to symptoms asked postoperatively. Thus, uncinectomy with additional middle meatal antrostomy seems to have no benefit over simple uncinectomy.

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Satisfaction with maxillary sinus surgery might be influenced by risk factors

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Tommi V. M. Torkkeli, M.D., Ph.D.,[4] Markus E. P. Rautiainen,[1,5]
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AQ: 3 **ABSTRACT**

Chronic rhinosinusitis (CRS) is an inflammation of the nose and paranasal sinuses lasting for ≥12 weeks. Endoscopic sinus surgery (ESS) is considered during difficult to treat CRS. The minimally invasive technique focuses on the transition areas rather than on the ostia. The aim of this study was to evaluate symptoms, the number of acute sinusitis episodes, and satisfaction after ESS with either preservation or enlargement of the maxillary sinus ostium. Thirty patients with moderate nonpolypous CRS were enrolled. Uncinectomy only and additional middle meatal antrostomy were randomized for each side of each patient and performed single blindly. The symptoms questionnaires were filled at four time intervals. Significant symptom reduction was achieved independently of operation technique. The number of acute sinusitis episodes indicating the exacerbation rate decreased significantly at 9 and, on average, 68 months postoperatively. However, the exacerbation rate began to increase after 9 months postoperatively. Three revisions were performed on the side with uncinectomy only and one on the side with additional antrostomy. Most patients reported good satisfaction with both procedures. There was a trend for patients with asthma and/or job exposure to report insignificantly more frequently no satisfaction with surgery, especially with the uncinectomy-only procedure. Both procedures seem to be efficient in providing symptom relief and satisfaction. More studies are needed to evaluate if patients with risk factors benefit more from an ostium-enlarging procedure.

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Chronic rhinosinusitis (CRS) is a versatile, multifactorial disease of the nose and paranasal sinuses with a prevalence of ~10%.[1,2] Several diseases coexist with CRS by partly unknown mechanisms: asthma, aspirin sensitivity, atopy, chronic rhinitis, depression, anxiety, and fatigue.[3] It is known that biological and chemical agents associate with work-related asthma, and occupational exposure causes 10–20% of adult-onset asthma.[4–6] However, only few studies address the influence of occupational exposure on CRS.[7–9] Primary management of CRS is conservative. It is composed of nasal saline irrigations and corticosteroids. Depending on the comorbidities and hyperinflammatory or infective exacerbations, additional treatment might be used. Quality of life (QoL) questionnaires are not able to estimate exacerbations, *e.g.*, to what extent CRS is under control.[10] Even so, only few studies have observed the influence of CRS management on the exacerbation rate.

Endoscopic sinus surgery (ESS) is considered during recalcitrant and difficult-to-treat CRS.[2] It is based on the theory that obstruction of the ostium leads to chronic inflammation and eventually to pathological alterations of the maxillary sinus mucosa. Others have shown that ostiomeatal complex obstruction does not correlate with adjacent sinus status in CRS with nasal polyps.[11] Nevertheless, it seems that surgical opening of the ostium improves drainage and ventilation of the sinus and thus might restore the normal mucosa during CRS without nasal polyps.[11–13] Ragab *et al.* were not able to prove ESS to be superior to conservative therapy in controlled studies.[14] Uncontrolled studies have shown QoL improvement after ESS, also in CRS patients with high age, ASA intolerance, depression, fibromyalgia, and chronic fatigue AQ: 4 syndrome.[3,15–19] However, ESS seems to, at least partially, provide symptom relief and/or decrease inflammatory findings.[20–24]

Despite the fact that the ostium is considered to be the most important area in the pathogenesis of CRS, few studies have addressed the extent of sinus surgery on the ostiomeatal area. Other studies have previously indicated

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Table 1

Characteristics of Patients	Preoperatively	9 mo Postoperatively	68 mo Postoperatively
Age at the operation, yr			
Median	50	54	56
Range	21–66	22–66	27–72
No. of male patients	11	10	8
Allergic rhinitis	16	16	14
Asthma	10	10	10
No. of patients with job exposure	15	15	12
Nasal polyps	0	1	1
Smokers	7	7	7
Medication			
Antihistamine	1	2	3
Intranasal CCS ± antihistamine	11	10	18

CCS = corticosteroid.

that removal of the uncinate process alone might be enough to restore the ventilation of the maxillary sinus.[25–28] There is also evidence that the effect of minimally invasive ESS is comparable with invasive ESS.[26,28–33] On the other hand, uncontrolled studies suggest that the presence of biofilms, osteomyelitis, and other factors favor invasive approaches toward the osteomeatal unit.[34–39] Our aim was to evaluate symptoms, exacerbation rate, and satisfaction after ESS with either the ostium-preserving or the ostium-enlarging technique.

MATERIALS AND METHODS

Subjects

This study was performed at the Department of Otorhinolaryngology, Tampere University Hospital, Finland, and Mikkeli Central Hospital, Mikkeli, Finland. The study was approved by the Institutional Review Boards of the Tampere University Hospital and Mikkeli Central Hospital. J.P. Myller and A.T. Luukkainen contributed equally to this work. Informed consent was obtained from all patients. Thirty patients with CRS were enrolled in this study. Characteristics of groups of patients can be seen in Table 1 and in a previous publication.[40] Inclusion criteria were moderate to severe sinus-related symptoms, according to patient interview, during at least 12 weeks, despite maximal medical treatment and a Lund-McKay sinus computed tomography score[41] of at least 6/24 but no more than 18/24. Exclusion criteria were age <18 years; oral corticosteroid treatment during the last 2 months before surgery; previous sinonasal surgery; a history or physical examination suggestive of severe nasal septal deviation (that causes only unilateral nasal obstruction and/or requires septoplasty before ESS can be performed), unilateral sinusitis, nasal polyposis of more than grade 1[42], aspirin sensitivity, chronic bronchitis, cystic fibrosis, or a tumor or a disease with a severe impact on general immunity; and mild sinus-related symptoms. Dropouts from the study included one patient who died accidentally before the last postoperative control. Three additional patients missed the last follow-up (68 months postoperatively); we were unable to contact them by telephone.

Job exposure was evaluated according to reported current occupation and characterization of workplace. The positive job exposure group was determined according to international categorization of high-risk occupations.[4,6] The substances causing job exposure were bioaerosols (four patients), flour (four patients), mites (three patients), wood dust (two patients), reactive chemicals/metalwork (two patients), molds (one patient), and agricultural organic particles (one patient). The determination of the patients' other comorbidities was based on medical records, interview, and medical examination as previously described.[40]

Sinus Surgery

ESS was performed by two authors (Myller and Torkkeli) as previously described.[40,43,44] Both procedures were standardized. Briefly, the uncinectomy was performed on both sides, in which the lower two-thirds of the uncinate process was removed. Additional middle meatal antrostomy was randomized on either the right or the left side of each patient. Randomization was performed by allotment. Two identical pieces of paper, one with the caption "sinistrum" and the other with the caption "dextrum," were placed in an envelope. Each time a new patient was recruited, the operating surgeon pulled out a piece of paper. Additional meatal antrostomy was performed on the side of the pulled caption. If mucosa blocked the maxillary sinus ostium on the uncinectomy-only side, as little as pos-

sible was carefully removed from it, without disturbing the bony ostium. On the additional middle meatal antrostomy side, the diameter of the ostium was duplicated in the posterior direction with cutting forceps. If necessary, a large ethmoid bulla was opened on both ostium-preserving and -enlarging sides (Table 1).

Questionnaires

Patients filled the symptom questionnaire 1–77 days (mean ± SD, 26 ± 23 days) preoperatively. The same questionnaire was filled during a control visit to the operating surgeon 9 months postoperatively, and later on, based on patients' answers during telephone calls made, blindly at 56–86 months (mean ± SD, 68 ± 6.5 months) postoperatively. During the telephone call, if the patient had undergone revision surgery, he/she was asked to answer the questions according to the situation before revision surgery was performed. The following questions were asked preoperatively, and at 9 and, on average, 68 months postoperatively: the number of acute bacterial sinusitis episodes diagnosed or suspected by a doctor during the previous year and the existence of the symptoms of facial pain/pressure, nasal obstruction, nasal discharge, postnasal drip, and decreased sense of smell (no = 0, mild or moderate = 1, and severe = 2). In addition, lacrimation (none = 0, mild = 1, moderate = 2, severe = 3) and postoperative bleeding (absent = 0, mild or moderate = 1, and severe = 2) were asked during the debridement follow-up visit at 7–30 days (mean ± SD, 16 ± 5 days) postoperatively and at 9 months postoperatively. Satisfaction with the operation was scored according to two questions asked at 9 and 68 months postoperatively on each side separately: "How is the situation in the maxillary sinuses now compared with the situation before the operation" (no symptoms, clearly decreased symptoms, slightly decreased symptoms, no change, or more symptoms) and "If you could choose, would you now be willing for a similar operation?" (yes, maybe, or no, and reason why if no). The satisfaction was scored in the following way: 0 = good, patient benefited clearly from the operation; 1 = moderate, patient experienced only slight benefit from the operation and is unsure about the willingness for a similar operation if it was performed now; 2 = poor, patient experienced no change or worsening after the operation and is unwilling/unsure for a similar operation.

Statistical Analysis

Statistics were performed with SPSS Base 11.0 Statistical Software Package (SPSS, Chicago, IL). Data are expressed as medians and interquartile ranges. The nonparametric Wilcoxon test was used for comparison of matched pairs. Mann-Whitney *U* tests were used for comparisons of two groups. Spearman rank correlation test was used for correlations. For comparisons of dichotomous data in matched pairs, McNemar's test was used. A two-tailed value of $p < 0.05$ was considered significant in all tests.

RESULTS

Results were analyzed on an intent-to-treat basis and each patient was analyzed according to the randomly allocated treatment.

Symptoms during the Debridement Visit

During the debridement visit at 7–30 days (mean ± SD, 16 ± 5 days) postoperatively, the patients were asked about symptoms during immediate postoperative recovery: pain, bleeding, lacrimation, and nasal obstruction. There were no significant differences between the operation techniques in the median values of each of these four symptoms ($p > 0.05$; Wilcoxon test; data not shown). The median sum of these four symptoms as well as the median points of pain, obstruction, and bleeding decreased on both sides between the debridement visit and a visit at 9 months postoperatively, indicating good recovery on both sides ($p < 0.001$; Wilcoxon test; data not shown). Lacrimation remained at the same low level on both sides; thus, there was no a significant difference in the medians at 16 days and 9 months postoperatively ($p > 0.05$; Wilcoxon test; data not shown).

Long-Term Outcomes

When comparing preoperative and postoperative (9 and 68 months) symptoms, facial pain, nasal obstruction, and discharge values and the mean of these three values, a significant reduction on both the ostium -preserving and the -enlarging sides was observed ($p < 0.001$, by Wilcoxon test; data partly shown in Fig. 1 *A*). F1
There was no significant difference between the operation techniques in these values ($p > 0.05$, by Wilcoxon test; data partly shown in Fig. 1 *A*). Moreover, the delta-values indicating the change of these three symptoms before and after the operation did not differ between the operation techniques at the 9 and, on average, 68 months postoperative values ($p > 0.05$, by Wilcoxon test; data not shown). Symptom values for reduced sense of smell and postnasal drip could not be compared between the sides; however, they declined significantly when comparing preoperative and postoperative (9 and 68 months) values ($p < 0.001$, by Wilcoxon test; data not shown).

When observing satisfaction with the operation at 9 and, on average, 68 months postoperatively, the majority of patients expressed good/moderate satisfaction and there were no differences between operative techniques in the reported satisfaction ($p > 0.05$, by Wilcoxon test; Fig. 1 *B*).

COLOR

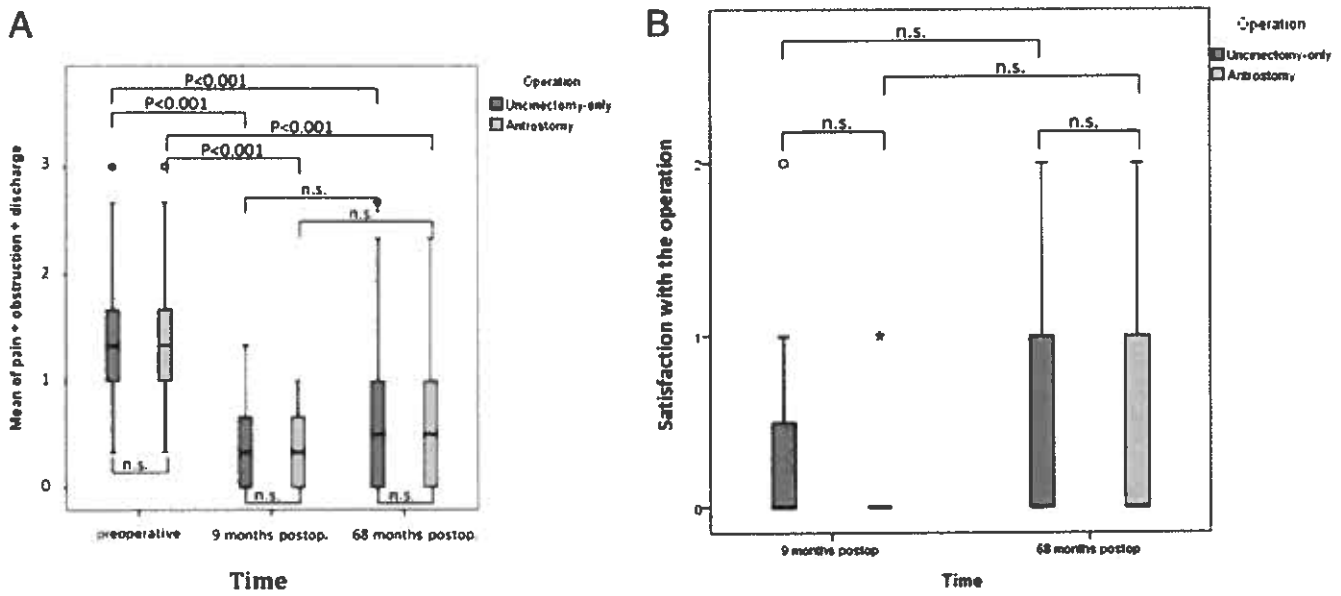

Figure 1. Comparisons of medians indicating (A) mean value of pain + obstruction + discharge scores and (B) satisfaction (0 = yes, 1 = partly, and 2 = no) between the operation techniques and the time points. The p values by Wilcoxon test (n.s. = not significant). Horizontal lines represent medians; upper and lower vertical bars represent the 75th and 25th percentile ranges; vertical lines represent the 99th percentile range.

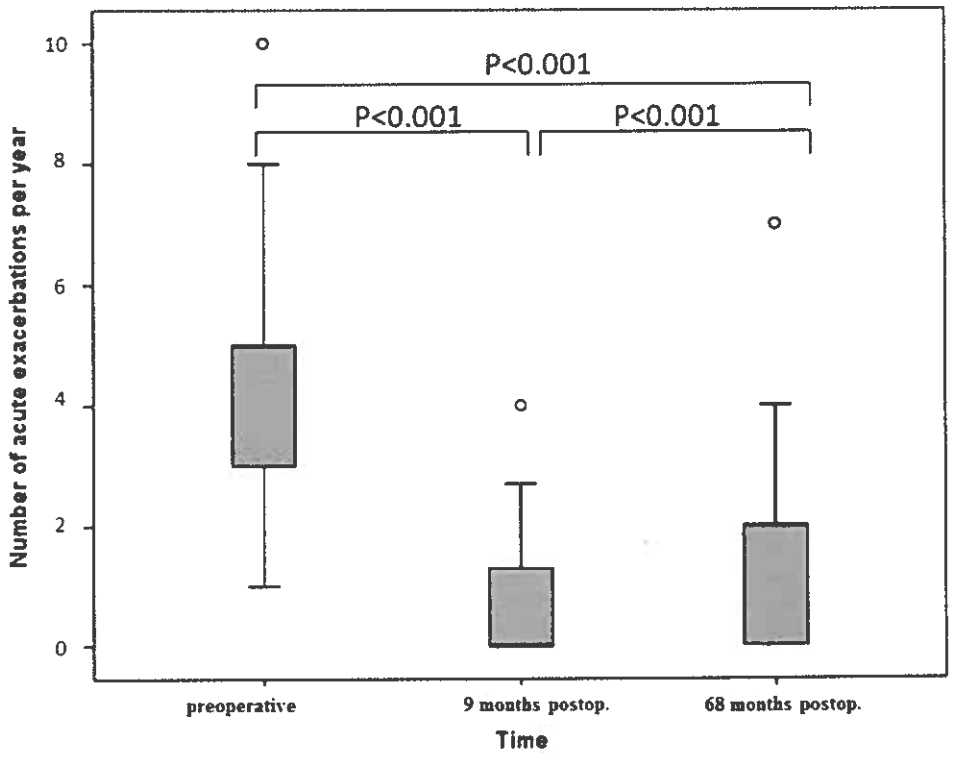

Figure 2. The patient-reported number of acute exacerbations, e.g., prescribed antibiotic courses for doctor-diagnosed sinusitis, per year. At 9 months postoperatively the patients reported the number of antibiotics prescribed during the postoperative follow-up time period (9 months). Thus, this value was multiplied by 12/9 = 1.33 for the analysis and the presentation in the figure.The P values by Wilcoxon test. Horizontal lines represent medians; upper and lower vertical bars represent the 75th and 25th percentile ranges; vertical lines represent the 99th percentile range.

The exacerbation rate could not be compared between sides. When comparing preoperative and postoperative (9 and 68 months) exacerbation rates, *e.g.*, the numbers of reported antibiotic courses for doctor-diagnosed sinusitis during the last year, the number decreased significantly ($p < 0.001$, by Wilcoxon test; F2 Fig. 2). Interestingly, the number of acute sinusitis per year increased slightly but significantly between 9 and 68 months postoperatively ($p < 0.001$, by Wilcoxon test; Fig. 2).

Revision surgery was performed on one antrostomy side and three uncinectomy-only sides for 3 of 26 patients during the observation period; however, this difference between the sides remained statistically in-

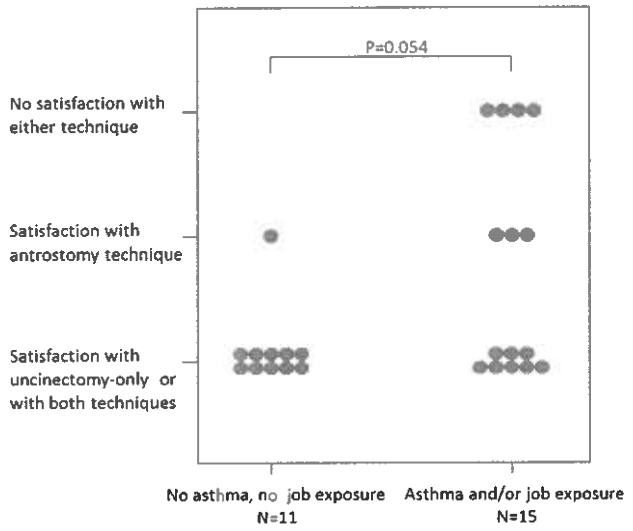

Figure 3. Observation of two patient groups: the one without asthma or job exposure, and the other one with asthma and/or job exposure. Comparison of the operation technique with which the patient experienced greater satisfaction, between the patient groups, on average at 68 months postoperatively. The p value by Mann Whitney U test.

significant ($p > 0.05$, McNemar test; data not shown). The two patients (one man and one woman) that underwent revision surgery only on the uncinectomy side had complaints solely on this side before revision antrostomy was performed. Of the three patients that underwent revision surgery, all were nonsmokers and had allergic rhinitis but not asthma. The patient with bilateral revision surgery, additionally, had job exposure (for case report see Fig. 4).

The Influence of Patient History

When analyzing the median values of pre- or postoperative symptoms and satisfaction for either ostium-preserving or -enlarging sides, there was no association to sex, allergic rhinitis, and/or asthma; smoking; job exposure; or intranasal corticosteroid and/or antihistamine medication ($p > 0.05$, Mann-Whitney U test; data not shown). Moreover, these symptom and satisfaction values did not correlate with age or the number of acute sinusitis/year ($p > 0.05$, Spearman rank correlation test; data not shown). Interestingly, there was a trend that patients with asthma and/or job exposure expressed more frequently satisfaction only on the side with antrostomy or neither technique provided them satisfaction ($p = 0.054$, Mann-Whitney U test; Fig. 3). The unsatisfied patients had the possibility to come for an extra control visit with nasal endoscopy at, on average, 68 months postoperatively (Fig. 4).

DISCUSSION

Our aim was to evaluate symptoms, exacerbation rate, and satisfaction after ESS with either the ostium-preserving or the ostium-enlarging technique at 9 and, on average, 68 months postoperatively. Only a few studies have previously addressed the long-term outcomes of ESS. We showed that all asked sinonasal symptoms decreased significantly postoperatively. The reduction of the symptoms that the patient was able to compare between sides, *e.g.*, facial pain, nasal obstruction, and discharge, were similar both on the uncinectomy-only and the additional middle meatal antrostomy sides. However, three revision surgeries were required during the observation time on the uncinectomy side and one on the antrostomy side.

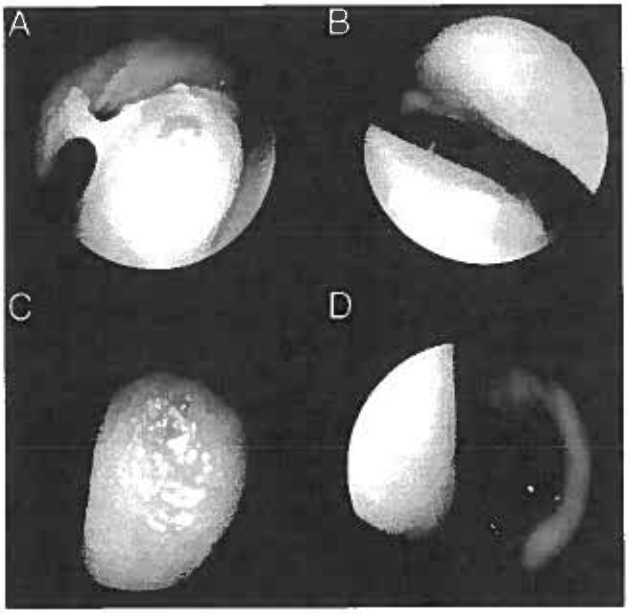

Figure 4. Two cases at 6 years postoperatively. The first patient was a 50-year-old nonsmoking woman with allergic rhinitis and job exposure (cold storage room worker). She had undergone (A) uncinectomy only on the right side and (B) additional middle meatal antrostomy on the left side. However, she underwent revision surgery on both sides 19 months after the primary operation because of the continuation of the symptoms and exacerbations. At 73 months postoperatively, there was a continuation of symptoms, e.g., the mean score of pain + obstruction + discharge was 2.33 on both sides. However, the number of acute exacerbations was 0 during the past 12 months, and she expressed good satisfaction with both techniques. Endoscopy at 79 months postoperatively showed that both sides were open narrowly. The second patient was a 53-years-old nonsmoking woman with allergic rhinitis, asthma, and job exposure (nurse). She had undergone (C) uncinectomy only on the right side and (D) additional middle meatal antrostomy on the left side. At 69 months postoperatively, the mean score of pain + obstruction + discharge was 1 on both sides, indicating good recovery. However, she reported that the number of acute exacerbations was 4 during the past 12 months, and she expressed no satisfaction with either technique. Endoscopy at 75 months postoperatively showed that the uncinectomy side was not open and the antrostomy side was widely open.

COLOR

Moreover, patients with asthma and/or job exposure expressed more frequently satisfaction only on the side with antrostomy or neither technique provided them satisfaction. Thus, uncinectomy may not be sufficient in providing lasting symptom relief, especially in patients with risk factors, such as asthma and/or job exposure. Irritant exposure has been less investigated in CRS, whereas, it is known to influence asthma onset and exacerbations.[4,5,8] Chronic infection, biofilms, or other factors might play a role in CRS pathogenesis, especially in patients with asthma and/or occupational exposure. These patients could benefit more from an ostium-enlarging approach. This hypothesis requires additional studies to be proven. Others have shown that two-thirds of patients with recalcitrant CRS have biofilms in the sinonasal mucosa, but their influence on disease or ESS outcomes still needs to be elucidated.[34,36–39,45] Zhang *et al.* showed that both asthma and biofilm-forming bacteria were associated with revision ESS after adjustment for other CRS risk factors; however, neither asthma nor biofilms modified each other's association with revision ESS.[46] Other studies suggest that CRS patients with asthma might have different bacterial colonization and different responses to bacteria colonizing the sinuses, thus putatively leading to or worsening sinonasal inflammation.[7,47,48]

The number of reported antibiotic courses for doctor-diagnosed sinusitis during the last year was used in this study as a sign of exacerbation rate. It decreased significantly at 9 months postoperatively, indicating good recovery with both procedures. What is interesting is that exacerbations began to increase after the 9-month postoperative follow-up time. We suggest that as in asthma, these episodes would seem to point at uncontrolled disease and/or poor patient compliance with CRS treatment. It has been shown that patients with Samter's triad suffer usually from difficult-to-treat CRS.[49] Although we did not observe this patient group, this could partly explain our finding that patients with CRS and asthma or job exposure were less satisfied after ESS with either technique or with the uncinectomy-only technique. Asthma patients or those with job exposure might have mucosal changes that might lead to poor CRS prognosis.[49] More studies of ESS with long-term follow-up and with observations of both QoL and exacerbation rate are needed.

Albu *et al.* did not find differences in subjective outcomes after performing a large (>16 mm) or small (<16 mm) middle meatal antrostomy, which is in accordance with the findings of our study.[26,28,50] We have previously indicated within these patients that at 9 months postoperatively, there was a good and relatively similar recovery of the maxillary sinus mucosa, radiologically evaluated; however, the maxillary sinus mucociliary clearance remained poor on both sides.[40,44] Moreover, six obstructed maxillary sinus ostia were found endoscopically on the uncinectomy-only side in contrast to four on the antrostomy side.[51]

CONCLUSION

The exacerbation rate began to increase between the 9- and, on average, 68-month period postoperatively, whereas the reduction in sinonasal symptoms remained the same during this period. There were no significant differences between uncinectomy with additional antrostomy and uncinectomy-only sides in terms of satisfaction with the operation, facial pain, nasal obstruction, and discharge values. It seems that patients with asthma or job exposure might experience less satisfaction with any procedure or might benefit more from maxillary sinus surgery with the ostium-enlarging than the ostium-preserving technique, compared with patients without these risk factors. Moreover, additional middle meatal antrostomy might be slightly superior to uncinectomy only in terms of the need for revision operations.

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