SIGNIFICANCE OF SURFACTANT PROTEIN-A IN CHRONIC RHINOSINUSITIS

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ABSTRACT

BackgroundandObjective: Surfactant protein-A (SP-A) is a hydrophobicprotein secreted within pulmonary surfactant that facilitates the adsorption of surface-active lipids to theair-liquid interface of the alveoli and increases alveolarstability. SP-A may also have anti-inflammatory properties. It is implicated in decreasing the pulmonary inflammatory response to bacterial lipopolysaccharide. However, the expression and function of SP-A in the human nasal tissue has not been elucidated. Our objective was to detect the presence of SP-A, measure alterations in several forms of chronic rhinosinusitis (CRS).

Patients and methods:Inferior turbinate and sinus mucosal biopsies were takenfrom 15 patients with chronic sinusitis,15 patients with primary atrophic rhinitis,and 10 healthy controls. Immunohistochemical staining for SP-A and polymerase chain reaction amplification of SP-A messengerRNAwere performed on samples of nasal tissues**.**

Results: Immunostaining localized SP-A to the mucosaand submucosal glands in specimensof chronic bacterial sinusitis,while failed to localize it in primary atrophic rhinitis. Quantitativepolymerase chain reaction showed significantly increased levels of SP-A patients with chronic bacterial sinusitiswhen compared with controls (P<0.0001), also demonstrated significant reduction of SP-A in patients of primary atrophic rhinosinusitis when compared with control(P= 0.0225).

Conclusion:SP-A is significantly increased in chronic bacterial rhinosinusitis,decreased significantly in primary atrophic rhinitis and appears to be expressed by respiratory epithelial cells and submucosal glandular elements of the sinonasal mucosa. Further characterization of this specialized protein is warranted considering the potential therapeutic applications of surfactant in the enhancement of mucociliary clearance.

INTRODUCTION

Pulmonary surfactant is secreted in the form of lamellar bodies from type II pneumocytes in the lung where it reduces surface tension at the air-liquid interface. Over 90% of pulmonary surfactant is lipid, whereas the remainder composed of plasma proteins and the surfactant proteins (SP) A, B, C, and D. The functions andproperties of these proteins appear to be very different. SP-A and SP-D are hydrophilic proteins actively involvedin the innate immune response to inhaled lung pathogens. They are part of the collectin family of proteins that are secreted at a number of epithelial surfaces in the body. In contrast, SP-B and C are veryhydrophobic and secreted within pulmonary surfactant where they assist with a number of biological actions and activities ofthe phospholipids (1).

SP-A is sialoglycoprotein and members of the collectin family, thought to have a role beyond Phosphatidylcholine cycling. It is a hydrophilic protein and is considered to have a critical role in innate immunity. SP-A binds a variety of bacterial, viral and fungal pathogens and is important in the initial phases of host defense.Human SP-A is encoded by two genes,SP-A1 and SP-A2 (2).

SP-A exhibit antimicrobial properties and interact with respiratory tract pathogens such as *Staphylococcus*, *Streptococcus*, *Klebsiella pneumoniae*, *Pseudomonasaeruginosa*, *Escherichia coli*, *Aspergillus*, *Mycobacteriumtuberculosis*, and *Salmonella*.

These bacteria have related molecular structures called pathogen-associated molecular patterns (PAMP) that consist of polysaccharides and Poly-nucleotides, such as lipopolysaccharide (LPS). PAMPs differ little from one pathogen to another but are

not found in the host. SP-A bind PAMPs located on microbial membranes via their calcium-dependent carbohydrate- binding domains.Furthermore, independent of direct binding to pathogens, SP-Aalso interact directly with dendritic cells and modulate subsequent T cell responses, optimize leukocyte function and chemotaxis, modify subsequentcytokine/chemokine profiles, and activate complement. Thus, these proteins are crucial in the initial interaction, recognition, processing, and subsequent adaptive immune response for a wide variety of inhaled pathogens and allergens.In the human respiratory tract, SP-A expression also be elevated in the setting of allergy or infection(3). Bronchoalveolar lavage specimens from patientswith chronic bronchial asthma have demonstratedincreased SP-A, as have reports of differentialSP-A expression in patients with pneumocystis pneumonia.Surfactant protein A expression has also been assessedin the sinonasal mucosa. In a semiquantitativestudy, Dutton et AL.(4) found SP-A to be elevated in the mucosaof rabbits with intercurrent sinusitis or antibiotictreatedsinusitis compared with pathogen-free animals.

The concept that SP-B could be expressed in the upper airway as well as the lungs is not farfetched considering the similarities between the two systems. Diseases present in the sinonasal system, specifically CRS, are often an extension of the pulmonary system. Individuals with asthma sensitive to the ingestion of aspirin may have associated nasal polyps as part of their disease process. Allergic fungal rhinosinusitis

(AFRS) is the upper airway correlate to allergic bronchopulmonary aspergillosis. Patients with cystic fibrosis (CF) invariably develop CRS in addition to their debilitating pulmonary disease. This is through

the similar mechanisms of inspissated mucus, impaired mucociliary clearance, and persistent bacterial infections and inflammation. Thus, the lungs and the paranasal sinuses share contact with inhaled pathogens and include many of the same epithelial properties (5).

Ultrastructural studies have demonstrated that the phospholipid components of surfactant are present in the form of lamellar bodies in a wide variety of surface cells outside the pulmonary system such asthe gastrointestinaltract, oral cavity, lateral nasal wall, mucosal cells of the stomach(1).

The objective of this study was to investigate whether SP-A is present in sinonasal mucosa and compare expression in distinct types of CRS with healthy control mucosa.

The hypothesis of this study is that SP-A is present in sinonasal mucosa and has altered expression in CRS subtypes when compared with control.

PATIENTS AND METHODS

This study was carried out in Zagazig University hospitals, Otolaryngology; Pathology; and Clinical pathology Departments from Februrary 2008 to March 2010. The subjects were divided into 3 groups, the first group included 15 patients with persistent bacterial CRS inspite of appropriate medical treatment and scheduled for endoscopic surgery in Otolaryngology Department. Preoperative computed tomographic imaging was obtained for each patient, Sinus mucosal biopsies were performed during the course of endoscopic sinus surgery.

Thesecond group included 15 patients with primary atrophic rhinitis randomly selected in the out-patient clinic. Cases with secondary atrophic rhinitis that had been proved clinically and/or histopathologically were excludedfrom this study. Nasal mucosal biopsies were taken from inferior turbinate under local anaesthesia.

The third group included 10 normal controls; nasal mucosal biopsies were obtained from thesesubjects undergoing surgery for other

reasons than CRS including rhinoplastyseptoplasty. All biopsies were obtained from patients and controls after taking consent.

Immunohistochemical staining for SP-A and polymerase chain reaction amplification (PCR) of SP-A messengerRNA were performed on resected nasal tissues.

Immunohistochemical Analysis

Biopsy specimens were washed three times with iced phosphate-buffered saline (PBS) for 5 minutes to remove any exogenous SP-A which may have migrated from the lower airways. After thawing to −20°C and overnight decalcification, followed by fixation in 4% paraformaldehyde,

4-um thick sections were cut from paraffin blocks containing representative tissue samples. Paraffin sections were dewaxed in xylene, rehydrated through a graded alcohol series, placed in 10mmol/L of citrate buffer, and submitted to heat retrieval using a vapor lock for 40 minutes. After heating, the slides were allowed to cool to room temperature and briefly washed with tris (hydroxy methyl) amino methane-buffered saline. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide in methanol for 5 minutes. Normal serum (Novo stain Super ABC kit, Novocastra, Newcastle upon Tyne, England) was used for 30 minutes to block non-specific immunostaining. Immunohistochemical staining was performed using a standard avidin-biotin peroxidase system (Novo stain Super ABC kit).

The primary anti surfactant protein-Aantibodies were incubated overnight at room temperature. Following washing in phosphate –buffered saline, biotinylated universal secondary antibody (Novo stain Super ABC kit) was applied for 30 minutes.

The sections then were incubated with the avidin- biotin complex reagent (Novo stain Super ABC kit) for 30 minutes and developed with 3, 3- diaminobenzidine tetra hydrochloride in phosphate- buffered saline

(PH 7.5), containing 0.036% hydrogen peroxide for 5 minutes. Light Mayer hematoxylin was applied as a counter stain. The slides then were dehydrated in a series of ethanol and mounted with permount. Cytoplasmic and/or membranous staining was considered as positive.Two negative control sections were used in each case; one was incubated with the secondary antibody only, the other with the primary antibody only. Sections of human lung stained with anti surfactant-A antibodies were used for positive control.Cells were considered positive for anti SP-A antibodieswhen at least 10% of cells show diffusecytoplasmic or membranous staining.

Quantitative Reverse-Transcriptase Polymerase Chain Reaction

Total RNA purification was performed on all specimens (using an Aurum Total RNA Mini Prep-Kit; Bio-Rad, Hercules, Calif), including a DNase 1 digest, according to the manufacturer's instructions. Reverse transcriptase PCR was performed on a portion of the purified RNA for each specimen to create complementary DNA (cDNA) libraries using the iScript cDNA Synthesis Kit (Bio-Rad) under the following conditions in a conventional thermocycler: 5 minutesat 25°C, 30 minutes at 42°C, and 5 minutes at 85°C

Qunatitative PCR

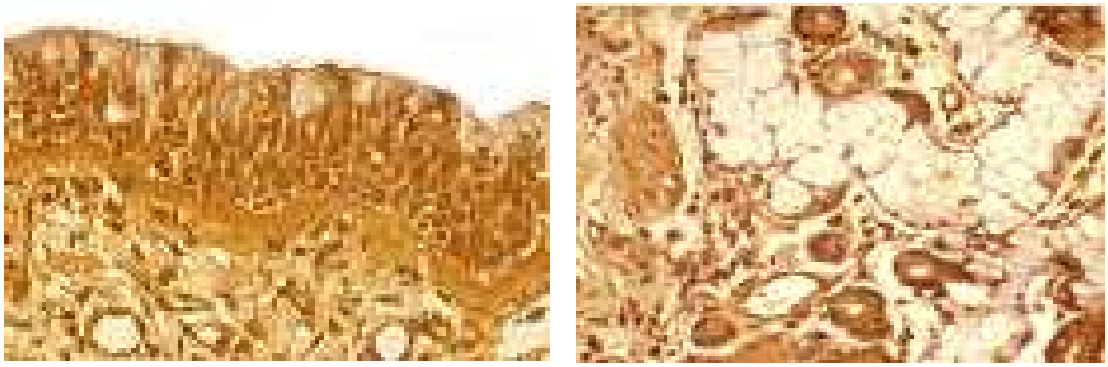
Intron-exon spanning SP-A primers were used in the quantitative PCRamplification reactions with the following design: 5_-AAGCCACACTCCACGACTTTAGA-3_and 5_-CCCATTGCTGGAGAAGACCT- 3_ (Integrated DNA Technology Inc, Coralville, Iowa). Commercially available _-actin primers for the amplification of the housekeeping gene were used: 5-TCATGAAGTGTGACGTTGACATCCGT-3and5_CTTAGAAGCATTTGCGGTGCACGATG-3(Promega,Madison, Wis).

In a quantitativePCRdetection system (My iQ Thermal Cycler; Bio-Rad), 96-well reaction plates were used to perform real-time, quantitative PCR with the sample wells containing the following: 25-µL consist of 1 µL of 2 × Supermix with SYBRgreen (a fluorescent double-stranded DNA-binding reporter molecule), 1 µL each of SP-A primer (100 ng/µL) or _-actin primers (100 pmol/µL) for control wells, a 1-µL sample complementary DNA, and 22 µL of nuclease-free water. After an initial activation step at 95°C for 3 minutes, amplification was performed across 45 cycles with the following parameters: denaturation for 30 seconds at 95°C, annealing for 20 seconds at 58°C, and elongation for 30 seconds at 72°C. Digital capture of SYBRgreen fluorescence was performed during the annealing phase for threshold cycle assessment. The threshold cycle values were automatically stored in an output file, and these were analyzed to determine relative starting messengerRNA (mRNA) concentrations according to the 2-__threshold cycle method16 using a proprietary macro (Bio-Rad) with Excel 2003 XT (Microsoft Corp, Redmond, Wash). A melt-curve analysis confirmed specimen uniformity and estimated product size in each sample well in the 96-well plate. The following protocol was programmed into the My iQ Thermal Cycler (Bio-Rad) to produce the melt curves for each sample well after amplification using SYBRgreen as the reporter: 1 minute at 95°C, 1 minute at 55°C, and 10 seconds at 55°C for80 cycles. Finally, to verify PCR product sequence, random samples were prepared and sequenced by the Vanderbilt Universitym(Nashville, Tenn) DNA sequencing core laboratory. Data were compared with the human genome via BLAST downloadable software (http://www.ncbi.nlm.nih.gov/genome/seq/BlastGen BlastGen.cgi?taxid=9606).All data compiled in this study were analyzed statistically using SigmaStat software (version 2.03; SPSS Inc, Chicago, Ill).

RESULTS

Forty subjects were recruited for the present study, including 15 patients with chronic bacterial sinusitis, 15 patients with primary atrophic rhinitis and 10 healthy control. The mean age of the group was 42 years, with a 1.8:1 male-female distribution.SP-A protein expression was studied in nasal tissuebiopsies by immunohistochemistry. There was strong positivestaining in thein human nasal mucosa and submucosa of a case of chronic bacterial sinusitis, as shown in Figure 1.This indicates that SP-A is secreted by nasal epithelium and glandular epithelium. Faint staining for SP-A was also detected in biopsies of control group as shown in figure 2 and was not detected in the atrophic rhinitis patiens (figure3).As a negative staining control, sections were incubated with nonimmune rabbit serum instead of SP-A antibody, resulting in loss of staining (Fig. 4).

Quantitative PCR (reported asΔCT± SD) (Fig. 5) showed significantly increased levels ofSP-A (4.73 ±2.8, 80-fold) mRNA (t=4.687; P<0.0001) from chronic bacterial sinusitis patients when compared with controls (10.4 ± 3.2). AlthoughSP-A mRNA was decreased in patients with atrophic rhinitis (15.7 ±6.3,) when compared with control (10.4±3.2), these decrease was statistically significant(t= 2.4462; P= 0.0225).



A B

Figure 1:
Photomicrograph of chronic rhinosinusitis showing strong cytoplasmic immunostaining of surfactant protein-A in both nasal mucosa (A); and submucosal glands (B); hematoxylin counterstain X 400.

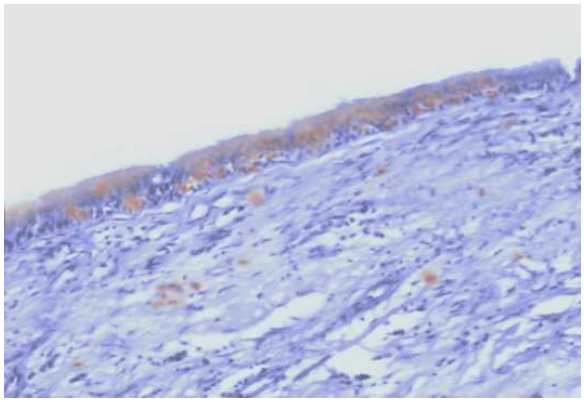


Figure 2: Photomicrograph showing faint immunostaining of surfactant protein A (SP-A) in human nasal mucosa and submucosa of the control group; hematoxylin counterstain X 400.

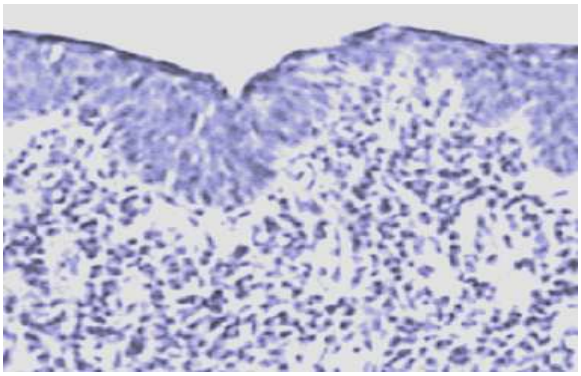
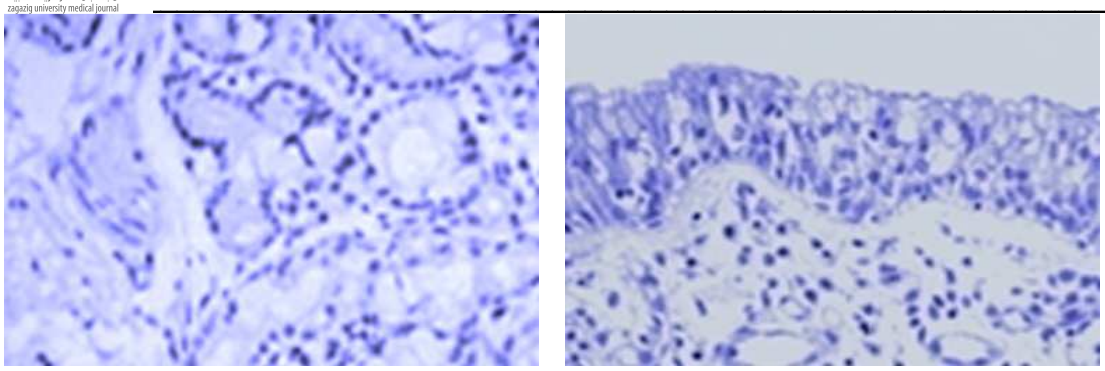


Figure 3: Photomicrograph of atrophic rhinitis showing negative immunostaining for surfactant protein-A (SP-A) in human nasal mucosa and submucosa; hematoxylin counterstain X 400.



A B

Figure 4. Photomicrograph showing negative control with negative immunostaining for surfactant protein-A (SP-A) in nasal mucosa (A) and submucosa (B); hematoxylin counterstain X 400.

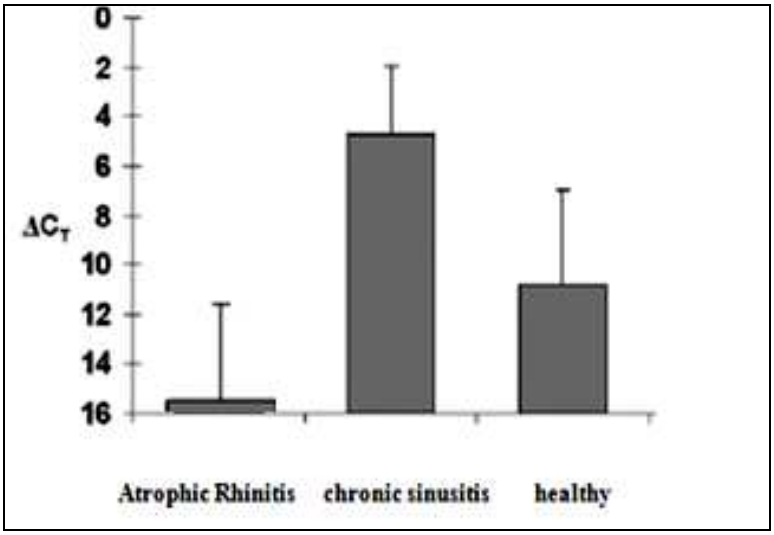


Figure 5: Quantitative polymerase chain reaction (PCR) analysis of the expression of SP-A mRNA in the sinus and nasal mucosa of patients with chronic sinusitis, and atrophic rhinitis. SP-A has an average C_t value of 4.73±2.8 in chronic sinusitis patients when compared with healthy (P<0.0001), while in atrophic rhinitis the value was 15.7 ±6.3 compared with healthy (P=0.0225).

DISCUSSION

Surfactant-associated protein-A (SP-A) is inthe family of collectin proteins that play an integral part in the innate defense system. SP-A expression and function are altered in a variety of inflammatory and infectious diseases. However, the presence of SP-A in the human paranasal sinus mucosa is not well known (6).

There are few of previous studies investigating surfactant and surfactant protein (SP) in the upper airway. The presence of lamellar bodies and SP-A, -B, and -D have been described in the porcine eustachian tube, indicating that the apparatus for a surfactant-like system is present outside the pulmonary system(7). Woodworth et al.demonstrate the presence of lamellar bodies; SP; and mRNA in both diseased and normal human sinus tissueand reported that SP-A and SP-D immunolocalized to the sinonasal epithelium andsubmucosal gland secretory ducts (8). The discovery of surfactant production and secretion in sinonasal mucosa indicates that initial contact and interaction between pathogens and SPs occurs after inhalation and deposition into the mucus of the upper respiratory tract.

This studycharacterizes the differential expression of SP-A in the nasal mucosal samples of patientswith chronic rhinosinusitis using immuno-histochemical staining and quantitative PCR.

By immunohistochemistry, we detected strong SP-A staining in the epithelial cells and lumen of thesubmucosal glands in the chronic bacterial sinusitis patients (figure 1). Alsothe results of the present study indicate that SP-A mRNA are significantly increased in chronic sinusitis patients and significantly decreased in patients with atrophic rhinitis(figure5).

The findings in cases of chronic sinusitis may be explained on the basis ofthe different histological findings present in normal mucosa and chronic sinusitis mucosa, since SP production mostly occurs in submucosal glandular pathways and these patients exhibit glandular hyperplasia. This hyperplasia is more pronounced inpatients with chronic sinusitis. This mayhave contributed more mRNA transcripts due to a relativeabundance of these cell types. In agree,Bradford et al. (5) reported a significant elevation of SP-A and D in patients with chronic bacterial sinusitis associated with cystic fibrosis. In the sinonasal tissue of rabbits with acute bacterial sinusitis (inflammation but not allergy), SP-A was more prevalent than in pathogen-free animals (9).

The SP-A protein levels were significantly reduced compared with controls in the atrophic rhinitis patients (figure5) in support of our immuno-histochemistry results with no immunostaining of SP-A (figure3).

A possible explanation for thisobservation is that absence of significant SP-A geneup-regulation and depletion of SP-A protein reserves in the presence of atrophic changes of the submucosal glands and mucosa.This is in agreement with the results obtained by Ramadan et al. (10)who had demonstrated a significant decrease in phospholipid and surfactant concentrationsin the cases with primary atrophic rhinitis compared to normal cases.

Several theories tried to explain the etiology of primary atrophic rhinitis. Infection, one of the theories explaining the etiology of primary atrophic rhinitis, can affect the surfactant system leading to surfactant deficiency through several mechanisms including:Inflammatory cytokines produced in response to sepsis inhibit thesynthesis of surfactant (11),Activated neutrophils are capable of cleaving SP-A and impairing surfactant function(13).Ramadan et al.(10)reported that abnormal surfactant function in the larger airwaysmight be expected to decrease the efficiency of mucociliary clearance and also adversely lead to stasis of mucus, In addition, surfactantdeficiency will impair opsonization and phagocytosis of bacteriaby macrophages, thusfavouring bacterial multiplication and leucocytes infiltration.On account of lacking the opsonizing effect (due to decreased concentration of secretory IgA and surfactant deficiency) the leucocytes cannot phagocytoze and destroythe bacteria with continuous production of proteolytic enzymes in the secretion which are probably harmful to the mucous membrane, as it is known that inhalation of proteolytic enzymes produces emphysema in animals .

The therapeutic potential of correcting abnormalities in surfactant proteins has already been demonstrated in thelower airways. The correction of SP-D deficiencies with topical SP-D reverses emphysema, pulmonary lipidosis and macrophage infiltrations in diseased mice (13). Gesche et al. (14)found that human (rh)KGF, betamethasone, or their combination treatment increased secreted surfactant phosphatidalcholines (PC) in neonatal rats with lung injuriesFurthermore, topical SP-A and SP-D have decreased IgE and eosinophilia in mouse models of allergic bronchopulmonary Aspergillosis (15).Since allergic bronchopulmonary Aspergillosis is very similar to allergic fungal rhinosinusitis and can be considered its counterpart in the lower airway, this

holds future therapeutic options for difficult to treat sinus disease.

CONCLUSION

This study characterized the detection and expression, of SP-A in human sinus mucosa. SP-A is significantly increased in chronic bacterial rhinosinusitis,decreased in primary atrophic rhinitis and appears to be expressed by respiratory epithelial cells and submucosal glandular elements of the sinonasal mucosa. Further characterization of this specialized protein is warranted considering the potential therapeutic applications of surfactant in the enhancement of mucociliary clearance.

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أهمية سيرفاكتا نت بروتين (أ) فى الالتهابات المزمنة بالأنف و الجيوب الأنفية

المقدمة : سيرفاكتانت بروتين (أ) هواحد البروتينات الهيدروفوبية التى تفرز كجزء من سيرفاكتانت الرئة الذى ييسر امتصاص الدهون السطحية النشطة الى منطقة التلاقى المائى الهوائى للحويصلات الهوائيةويزيد ثباتها.
سيرفاكتانت بروتين (أ) ربما له أيضا دور فى الخواص المضادة الالتهابات وهو متداخل فى تقليل الاستجابة الالتهابية ضد الدهون السكريةالمتعددة البكتيرية. أما وجود ووظيفة سيرفاكتانت بروتين (أ) فى أنسجة الأنف للانسان لم يتم التأكد منه بشكل واضح.

الهدف من البحث : كان البحث يهدف الى اثبات وجود سيرفاكتانت بروتين (أ) وقياس التغير فيه فى الأنواع المختلفة الالتهابات المزمنة بالأنفو الجيوب الأنفية.

طريقة البحث : أجرى البحث على15 مريضا بالالتهاب المزمن البكتيرى للجيوب الأنفية و 15 مريضا بالالتهاب الصخرى الأولى للأنف و10 ليس لديهم أمراض بالأنف أوالجيوب الأنفية كعينة حاكمة للمقارنةتم أخذ عينات من القرينة السفلية للأنف و من الجيب الأنفى ثم تم الصبغ المناعى الكيميائى وفحصها باستخدام جهاز بى سى لقياس سيرفاكتانت بروتين (أ).

النتائج : حدد صبغ الخلايا المناعى وجود سيرفاكتانت بروتين (أ) بالغشاء المخاطى والغدد تحت المخاطية بالعينات من الالتهاب البكتيرى المزمن للجيوب الأنفية. وبالقياس الكمى لسيرفاكتانت بروتين (أ) وجد زيادة نات دلالة احصائية في الالتهاب المزمن البكتيرى للجيوب الأنفية ونقص ذو دلالة احصائية فى الالتهاب الصخرى الأولى بالمقارنة للخلايا الأنفية فى الاشخاص السليمة.

الأستنتاج : بمراجعة النتائج وجد أن مستوى سيرفاكتانت بروتين (أ) يزيد زيادة نات دلالة احصائية فى الالتهاب البكتيرى المزمن للجيوب الأنفية. و يقل احصائيا فى الالتهاب الصخرى الأولى للأنف ويتواجد سيرفاكتانت بروتين (أ)فى خلايا الجهاز التنفسى السطحيةوالغدد تحت المخاطية بالغشاء المخاطى للأنف والجيوب الأتفية مما يجعل تطبيق ذلك فى العلاج بأستخدام سيرفاكتانت بروتين لتحفيز التنظيف المخاطى الهدبى هو أمر مشجع.