Inhaled Corticosteroids and Their Affect on Reticular Basement Membrane Thickening in Patients with Asthma

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Inhaled Corticosteroids and Their Affect on Reticular Basement Membrane Thickening in Patients with Asthma

**Abstract**

INTRODUCTION: Asthma has been recognized as a disease with two main components: airway inflammation and airway remodeling. One particular aspect of airway remodeling, reticular basement membrane (RBM) thickening has been noted as a feature of asthmatic airways that could contribute to disease severity. The use of inhaled corticosteroids (ICS) has been observed to reduce inflammation in the airways of asthmatics, but its affects on specific components of airway remodeling are still in question.

METHODS: The focus of this study was to review the current literature for the last 10 years on all studies pertaining to RBM thickening in asthmatics and whether the use of ICS can reduce the RBM as determined by bronchial biopsy.

RESULTS: In the four studies reviewed, RBM thickening was noted in mild, moderate, or severe asthmatics as a group when compared to healthy controls. ICS use demonstrated a significant reduction in RBM thickness, when compared to asthmatic subjects who only used bronchodilators for symptom control. The greatest benefit to ICS use was noted when used at moderate to high dosages for periods longer than three months.

CONCLUSION: Long term, high dose ICS are effective at reducing RBM thickness in asthmatics. Although RBM thickening has been correlated with other signs of asthma severity such as airway hyperresponsiveness (AHR), further studies are needed to relate pathological changes to physiological measurements in asthma patients.
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INHALED CORTICOSTEROIDS AND THEIR AFFECT ON RETICULAR BASEMENT MEMBRANE THICKENING IN PATIENTS WITH ASTHMA

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A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
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Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette Sommers MS, PAC
Biography

Amy Scheer was born and raised in Cape Girardeau, MO. She attended Southeast Missouri State University and graduated with a bachelor’s degree in Pre-Med Studies. While in college, she worked at Southeast Missouri Hospital as a monitor tech, OB tech, and finally an ER tech. After college, she landed a position with Surgical Dynamics, a medical device company, which required extensive time spent in surgery to function as a consultant for maxillofacial surgeons. It was there that she was introduced to the PA profession. She applied to Pacific University and in the summer of 2007 began her journey to become a PA. After graduation she plans to work in the Portland area where she can continue to pursue her love for all things outdoors.
Abstract

INTRODUCTION: Asthma has been recognized as a disease with two main components: airway inflammation and airway remodeling. One particular aspect of airway remodeling, reticular basement membrane (RBM) thickening has been noted as a feature of asthmatic airways that could contribute to disease severity. The use of inhaled corticosteroids (ICS) has been observed to reduce inflammation in the airways of asthmatics, but its affects on specific components of airway remodeling are still in question. METHODS: The focus of this study was to review the current literature for the last 10 years on all studies pertaining to RBM thickening in asthmatics and whether the use of ICS can reduce the RBM as determined by bronchial biopsy. RESULTS: In the four studies reviewed, RBM thickening was noted in mild, moderate, or severe asthmatics as a group when compared to healthy controls. ICS use demonstrated a significant reduction in RBM thickness, when compared to asthmatic subjects who only used bronchodilators for symptom control. The greatest benefit to ICS use was noted when used at moderate to high dosages for periods longer than three months. CONCLUSION: Long term, high dose ICS are effective at reducing RBM thickness in asthmatics. Although RBM thickening has been correlated with other signs of asthma severity such as airway hyperresponsiveness (AHR), further studies are needed to relate pathological changes to physiological measurements in asthma patients. KEYWORDS: Reticular basement membrane, inhaled corticosteroids, bronchial biopsy
Acknowledgements

To My Friends and Family: Thank you, thank you, thank you for all of your encouragement and prayers when I had the crazy idea of quitting my job, packing up my car, and moving to the West coast to attend PA school. The sacrifice was worth it!

To Steve Meinhardt: You’re right. You do eat an elephant one bite at a time!
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<tr>
<td>AHR</td>
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Introduction

Asthma is a chronic disease of the airways that is characterized by a group of episodic symptoms such as wheezing, shortness of breath, chest tightness, and cough. The exact cause of asthma isn't known. However, researchers think that a combination of how inherited genes and environmental factors interact early in life, when the immune system is developing, causes asthma to develop. One theory researchers have for what causes asthma is the "hygiene hypothesis." It is thought that our Western lifestyle, with its emphasis on hygiene and sanitation, has improved our living conditions and resulted in less frequent infections in early childhood. Because children no longer experience the same types of environmental exposures and infections as they did in the past, the development of the immune system is altered, increasing the risk for asthma.¹

Asthma is recognized as having two main components which can contribute to its severity: chronic airway inflammation and airway remodeling.² Until recently, airway remodeling was thought to develop late in the disease process in response to chronic inflammation.³ However, recent studies show that airway remodeling is present in children with difficult asthma to an extent similar to that seen in adults with a longer history of asthma.⁴

Chronic airway inflammation occurs as a response to injury to the tissues of the airway. The purpose of inflammation in a healthy individual is to repair and restore injured tissues by causing white blood cells, such as neutrophils, to migrate from the blood vessels into the surrounding, injured tissue. Once at the site of injury, the neutrophils, acting as a part of the body’s natural immune response, resolve the inflammation and no lasting damage occurs.⁴ However, in asthma, persistent bouts of inflammation in the airway are detrimental because the inflammation doesn’t ever resolve, becoming chronic in nature. This persistent inflammation
leads to changes in the organization, size, and composition of cells that are present in the airways.⁵ These architectural changes, collectively, are termed airway remodeling.

Histologically, the airways are composed of three layers of cells, the inner wall layer, the outer wall layer, and the smooth muscle layer. Each layer is specialized to perform a specific function to promote a healthy airway. The inner wall layer refers to simple epithelial cells, goblet cells, the basement membrane, and the submucosa. The outer wall layer is composed of connective tissue between the smooth muscle layer and surrounding parenchyma.⁶ The remodeling that occurs within these layers of the airway include: epithelial fragility, goblet cell metaplasia, thickening of the reticular basement membrane (RBM), hyperplasia of airway smooth muscle, and deposition of extracellular matrix.⁵ Airway remodeling can contribute to alterations in airway function such as airway hyperresponsiveness (AHR). This abnormality in asthma occurs when the smooth muscle surrounding the airway overreacts, causing excessive airway constriction and limited airflow. In asthma, this AHR occurs in response to levels of pharmaceutical or nonpharmaceutical stimuli that would be innocuous to a healthy individual.⁴ A combination of airway remodeling and AHR leads to airway obstruction resulting in the classic asthma symptoms of cough, wheezing, chest tightness, and shortness of breath.

Many patients with asthma exhibit persistent AHR, and excessive airway narrowing despite maximal asthma therapy. However, it is not known whether or how each component of airway remodeling alone or in combination, affects patients clinically.⁵ The purpose of this systematic review is to identify one component of airway remodeling and to determine what effect commonly prescribed pharmaceutical treatments can have on its presentation in the disease process of asthma. Thickening of RBM is considered the most consistent structural change in the airways of asthmatics, with some studies suggesting that it is pathognomonic for asthma.⁷

Although there are many components of airway remodeling that could be addressed, due to its focused nature, this paper seeks to address changes in the RBM. Current guidelines recommend using inhaled corticosteroids to inhibit inflammation of the airway in asthmatics,
however, do inhaled corticosteroids mitigate the thickening of the RBM in the airways of patients with asthma?

**Materials and Methods**

A comprehensive literature search was compiled using the keywords: asthma, inhaled corticosteroids, reticular basement membrane, subepithelial reticular layer, bronchial biopsy, and airway remodeling on Ovid:Medline, Web of Science, EBSCO-host, and google. Literature from 1999 to present was reviewed and weighted towards importance at answering the clinical question. These results were then compiled and analyzed. The inclusion criteria were all relevant full text English language articles or data, published after 1999, that aided in explaining the effects of corticosteroids on the RBM in subjects with asthma and utilized bronchial biopsy to determine that thickness. Exclusion criteria included articles published before 1999, animal studies, and studies that utilized any method besides biopsy to determine RBM thickness.

**Results**

A total of four full text English language studies were published between 1999 and 2009 addressing the affects of corticosteroids on the RBM in asthmatic airways utilizing biopsy to evaluate thickness. One of these articles, written by Ward et al, was a continuation of a previous study performed by some of the same researchers two years prior. All of the studies utilized in this systematic review performed and evaluated other tests measuring lung function, AHR, airflow obstruction, and inflammation in addition to measuring RBM thickness by biopsy. Only the information pertaining to RBM thickness or subepithelial reticular layer thickness and the affect that inhaled corticosteroids have on its thickness were considered in the conclusion. Each article was reviewed and graded on the following criteria: randomization, control group, sample size, the dosage and duration of corticosteroids evaluated, and the method used to determine RBM thickness.
In 2002, Ward et al performed a double blinded, randomized, placebo controlled, parallel group study of airway inflammation, RBM thickness and bronchial hyperresponsiveness (BHR) in 35 asthmatics. All subjects had been diagnosed with asthma for at least 12 months. Subjects were using only inhaled salbutamol for relief of symptoms. No subjects had received treatment with regular ICS or inhaled long acting beta agonists for at least 3 months beforehand. In this study, inhaled Fluticasone Propionate (FP) was given via a metered dose inhaler at a dosage of 750 micrograms daily. Control subjects, which consisted of 22 non-asthmatic individuals with no underlying lung disease, were given a physically identical placebo to be used daily. Airway biopsy studies, spirometric tests and methacholine challenge were performed at baseline, three months, six months, and twelve months of treatment. Bronchial biopsies were performed to determine if thickening of the reticular basement membrane was a common characteristic in asthmatics and if it could be mitigated with the use of inhaled corticosteroids (ICS). Results of this study showed that comparison of RBM thickness between asthmatics and normal subjects at baseline was variable, but there was a significantly thicker RBM in patients with asthma. After three months of treatment with FP, there was no significant difference in RBM thickness in asthmatic subjects when compared to placebo. However, there was a significant decrease in RBM thickness in these subjects noted after twelve months of FP use.8

In 2005, Ward et al also performed a follow up study to the one performed in 2002. In this study, he performed a double-blind, randomized, placebo-controlled, parallel group study of ICS in 35 asthmatics, with bronchoalveolar lavage (BAL) and airway endobronchial biopsy (EBB) for inflammatory cell profiles, spirometry, methacholine challenge, and EBB for airway remodeling carried out at baseline, three and 12 months. The subjects were mild-to-moderate yet symptomatic, steroid naïve, atopic asthmatics. All were using Albuterol as needed for relief of symptoms, with no long acting beta agonists. Controls were 22 normal healthy volunteers. Like the previous study, the asthmatics were divided into two groups. One group was given 750 micrograms of FP twice daily while the other group was given a placebo. Spirometry improved
following three months of daily FP with no further improvement with up to 12 months of daily FP. AHR to methacholine improved throughout the study, with the most significant improvement being from three to 12 months. BAL inflammatory cells such as esosinophils, neutrophils, mast cells, and leucocytes decreased following three months of daily FP with no further improvement with 12 months. RBM thickness decreased in the FP group, but only after 12 months of treatment. EBB cell counts showed a decreased in esosinophils, mast cells, and leucocytes following three months of daily FP, with no further changes between three and 12 months.9

Shiba et al conducted a cohort study to evaluate the difference in RBM thickness and lung function in mild asthma. The study included 13 healthy control subjects, 17 subjects with newly diagnosed mild asthma, nine subjects with mild asthma diagnosed more than 12 months previously, and ten subjects with mild-to-moderate asthma diagnosed more than 12 months previously. The group of mild-to-moderate asthmatics had been using a daily inhalation of greater than or equal to 600mg of beclomethasone dipropionate (BDP) since the diagnoses of asthma, while the other subjects with asthma had only been using a bronchodilator. Spirometry and methacholine challenge tests were performed to evaluate airflow obstruction and airway hyperresponsiveness. Bronchial biopsies were obtained from each subject and the RBM was measured by a single pathologist in a blinded fashion. It was concluded that the RMB thickness was greater in subjects with mild asthma not treated with inhaled steroids, than it was in healthy subjects. Additionally, RBM thickness was significantly less in subjects who suffered from mild-to-moderate asthma in excess of 12 months and who were treated with 600mg daily BDP than in subjects with mild asthma in excess of 12 months who were only treated with a bronchodilator.10

Sont et al conducted a randomized, single-blinded, prospective, parallel trial involving 75 adults with mild-to-moderate asthma who visited a clinic every three months for two years. The purpose of the study was to investigate whether a treatment strategy of ICS aimed at reducing
airway hyperresponsiveness (AHR strategy), in addition to the existing guidelines for asthma control (reference strategy), led to more effective control of asthma and greater improvement of chronic airway inflammation. In the reference strategy, the current NIH guidelines that determine the dosage of ICS to be used evaluate asthma symptoms, bronchodilator use, peak flow variability, and forced vital capacity (FEV₁). Subjects were required to keep a diary of their symptoms, then a step-wise dosage of ICS was prescribed based on four different classes of symptom severity. In the AHR strategy, the NIH guidelines plus another variable, AHR to methacholine, was evaluated. Depending on class of symptom severity, subjects took no ICS, 200 micrograms of Budesonide or BDP twice daily, 400 micrograms twice daily, or 800 micrograms twice daily plus five days of low dose oral steroids. Airway inflammation was measured based on the eosinophil count in the subepithelial reticular membrane and the thickness of the subepithelial reticular membrane as determined by fiberoptic bronchial biopsy at entry and after two years. Only 55 patients agreed to undergo fiberoptic bronchoscopy. During the two year follow-up, there was a significant decrease in thickness of the subepithelial reticular membrane within the AHR strategy group, which was much greater than the change seen in the reference strategy group. Similar results were obtained when restricting the analysis to subjects who were already using inhaled steroids at entry into the study.¹¹

**Discussion**

The limitation of performing any study on the RBM, is that the best way to assess its characteristics, is through direct visualization. This can only be achieved through performing a bronchial biopsy. Unfortunately, due to the invasive nature of this procedure, it is often difficult to recruit subjects who are willing to undergo this kind of testing. Therefore, the number of studies that have been performed utilizing bronchial biopsy to evaluate RBM thickness, before and after the use of inhaled corticosteroids, is limited.

In the four studies reviewed, there were differences in methodology, sample size, severity of asthma, length of study, corticosteroid utilized and dosage of corticosteroid utilized. Also,
there was considerable variability noted in the RBM thickness between asthmatic and normal subjects. This finding might suggest that the presence of RBM thickness doesn’t discriminate individual asthmatic patients from healthy subjects in the unequivocal manner implied by some researchers. However, in all of the studies reviewed, a significantly thickened RBM was present in asthmatic patients as a group and was shown to be reduced with at least three month use of moderate to high dose ICS. However, a reduction in the thickness of the RBM by use of ICS is only helpful information if it can provide a correlation in a clinical setting.

In the 2002 study performed by Ward et al, it was determined that after three months of treatment with 750 micrograms of FP, the asthmatic subjects had very little change in AHR as determined by methacholine challenge, even though lung function was improved as determined by FEV₁. Between three and 12 months, there was a much greater improvement in AHR, while asthma symptoms continued to be stable and controlled. This greater secondary improvement in AHR was associated with a concurrent reduction in RBM thickness, 90% of which also occurred from the time frame of three to 12 months. This finding suggests that there is a significant link between AHR and RBM thickening in asthma, even if the symptoms of asthma appear to be in good control.

In the 2005 Ward et al follow up study, inflammatory parameters measured in solid tissue, airway biopsies, were used to better demonstrate airway inflammation, RBM thickening, and AHR. The strength of this study is that it was performed in the same manner that the previous one was and proceeded to show the same results as the first study in regards to a decrease of RBM thickening from three to 12 months use of 750 micrograms of FP daily. Additionally, endobronchial biopsies (EBB) were performed to determine if there was a significant correlation between eosinophil cell count and AHR. After three months of treatment with FP, the eosinophil cell counts had decreased in the asthmatic subjects, but there were no further changes from three to 12 months. However, AHR did improve from three to 12 months of daily FP, as previously demonstrated. This finding indicates that the improvement in AHR
was not related to decreased airway inflammation, but instead could be related to a decrease in RBM.

In the 2002 Shiba et al study, ten of the 49 subjects had mild-to-moderate asthma and used ICS to prevent exacerbations. The remaining 39 subjects had mild asthma and used only bronchodilators to treat symptoms. The results of this study showed that RBM thickening was present even in subjects with mild asthma. Additionally, there was significant RBM thickening in mild asthmatics that had been diagnosed within 1 year, as compared to non-asthmatic controls. These findings confirm the idea that airway remodeling takes place early in the disease process and even with a mild form of the disease. Also it was shown that RBM thickening in mild asthmatics not treated with ICS was negatively correlated with FEV₁ and AHR. This suggests that even in mild disease, the presence of RBM thickening could be responsible for decreased lung function and airflow.

In the Sont et al study, the dosage of ICS utilized by one group of subjects was determined by asthma symptoms, bronchodilator use, peak flow variability, and FEV₁. The other group of subjects was evaluated with the additional variable of AHR to methacholine. These subjects were consistently found to have AHR and thus were prescribed higher dosages of ICS. This indicates that the added variable of increased AHR can be present when all the other tests for evaluation of asthma severity indicate that the condition is stable and controlled. Furthermore, this study showed that the subjects whose ICS dosage was determined by evaluating AHR had a 1.8 fold lower exacerbation rate than the group of subjects whose ICS dosage was determined by evaluating conventional asthma severity markers. This finding suggests that perhaps AHR is a better marker of asthma severity than FEV₁, peak flow, and subjective asthma symptoms. If this is the case, and AHR has been shown to be linked to RBM thickening, perhaps the current clinical management of asthma should center around treating AHR which has been shown to improve with use of daily ICS to target RBM thickening.
Conclusion

Airway remodeling is a complex phenomenon that includes a variety of structural changes whose specific contribution to the clinical presentation of asthma needs further analysis. One specific component of airway remodeling, RBM thickening, is an early, persistent finding in histological studies of asthmatic airways of all ages. Even though its studies are limited in number, it appears that this thickening can be mitigated with a course of moderate to high dose ICS for greater than three months. Additionally, it appears that the current objective indicators of asthma severity such as FEV₁ and peak flow are not nearly as important as AHR in the long term control of exacerbations. Finally, because there is some evidence that AHR and RBM thickening are correlated, ICS should be initiated with the diagnosis of asthma, even in patients with a mild form of the disease.


