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**Urinary Glycosaminoglycans as a Marker  
of Treatment Response in Asthmatic Children  
on Inhaled Corticosteroids**

*Thesis*

*Submitted for Partial Fulfillment of Master Degree  
In Pediatrics*

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا سُبْحَانَكَ لَا  
عِلْمَ لَنَا إِلَّا مَا  
عَلَّمْتَنَا إِنَّكَ أَنْتَ  
الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم  
سورة البقرة الآية (٣٢)



# Dedication

*To my Dear Father  
Who gave me too much  
and received too little*

*My mother*

*My Husband Mohamed*

*♀*

*My Children Ahmed & Rawan*

*To my sister Hend*

*♀*

*My Brother Mohamed*



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## List of Abbreviation

<b>ADAM33</b>	: Adesintergrin and metalloproteinase 33
<b>ANOVA</b>	: Analysis Of Variance
<b>β-Blockers</b>	: Beta-Blockers
<b>BDP</b>	: Budesonide
<b>BSA</b>	: Body surface area
<b>CBC</b>	: Complete blood picture
<b>Cm</b>	: Centimeter
<b>COPD</b>	: Chronic obstructive pulmonary disease
<b>CPC</b>	: Cetylpyridinium chloride
<b>Creat.</b>	: Creatinine
<b>DMB</b>	: Dimethylmethylene blue
<b>DPP10</b>	: Dipeptidyl peptidase 10
<b>ECG</b>	: Electrocardiograph
<b>ECM</b>	: Extracellular matrix
<b>EDTA</b>	: Ethylenediaminetetraacetic acid
<b>EIB</b>	: Exercise-induced bronchospasm
<b>ESR</b>	: Erythrocyte sedimentation rate
<b>ETS</b>	: Environmental tobacco smoke
<b>F</b>	: Female
<b>FEF25-75%</b>	: Forced expiratory flow rate over 25-75% part of FVC
<b>FEV1</b>	: Forced expiratory volume in first second
<b>FGF2</b>	: Fibroblast growth factor -2
<b>FP</b>	: Fluticasone propionate
<b>FVC</b>	: Forced vital capacity
<b>GAGs</b>	: Glycosaminoglycans
<b>GINA</b>	: Global Initiative for Asthma
<b>GPRA</b>	: G-protein related receptore for asthma
<b>H.S.</b>	: Highly significant
<b>Hb</b>	: Hemoglobin
<b>HDM</b>	: House dust mites

## List of Abbreviation (Cont.)

<b>HFA</b>	: Hydro Fluoro Alkane
<b>HSCR</b>	: Highly Sensitive C-reactive protein
<b>ICS</b>	: Inhaled Corticosteroid
<b>IgE</b>	: Immunoglobulin E
<b>IL</b>	: Interleukin
<b>IU</b>	: International unit
<b>Kg</b>	: Kilogram
<b>L</b>	: Liter
<b>LABA</b>	: Long Acting B2 Agonist
<b>LTRA</b>	: Leukotriene receptor antagonists
<b>M</b>	: Molar
<b>M</b>	: Male
<b>MDI</b>	: Meter-dose inhaler
<b>µg</b>	: Microgram
<b>µL</b>	: Microliter
<b>µmol</b>	: Micromole
<b>Mg</b>	: Milligram
<b>ml</b>	: Milliliter
<b>Mmol</b>	: Millimole
<b>n.</b>	: Number
<b>NA</b>	: Not approved
<b>N.S.</b>	: Non significant
<b>NAEPP</b>	: National Asthma Education and Prevention Program
<b>NHLBI</b>	: National Heart, Lung, and Blood Institute
<b>NK</b>	: Natural killer
<b>Nm</b>	: Nanomole
<b>NO</b>	: Nitric oxide
<b>O<sub>3</sub></b>	: Ozone
<b>PEFR</b>	: Peak Expiratory Flow Rate
<b>PFTs</b>	: Pulmonary function tests
<b>PGs</b>	: Proteoglycans
<b>PHF11</b>	: Plant homeodomain zinc finger protein 11

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### List of Abbreviation (Cont.)

<b>R</b>	: Correlation coefficient
<b>RBC</b>	: Red Blood Cells
<b>Rpm</b>	: Revolutions per minute
<b>RSV</b>	: Respiratory syncytial virus
<b>SABA</b>	: Short Acting B2 Agonist
<b>SD</b>	: Standard deviation
<b>Sig.</b>	: Significance
<b>SLIT</b>	: Sublingual immunotherapy
<b>SO<sub>2</sub></b>	: Sulphur dioxide
<b>SPINK5</b>	: Serine protease inhibitor Kazal type 5
<b>SPSS</b>	: Statistical package for social science
<b>T.L.C</b>	: Total leucocytic count
<b>Th1</b>	: T helper type 1
<b>Th2</b>	: T helper type 2
<b>TNF</b>	: Tumor necrosis factor
<b>UK</b>	: United Kingdom
<b>USA</b>	: United State of America
<b>VC</b>	: Vital capacity
<b>WHO</b>	: World Health Organization

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## **INTRODUCTION**

Bronchial asthma is " a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning" (*NAEPP, 2010*).

There has been a sharp increase in the global prevalence, morbidity, mortality and economic burden associated with asthma over the last 40 years particularly in children. Approximately 300 million people worldwide currently have asthma, and its prevalence increase by 50% every decade. Pediatric asthma is a leading cause of hospital stay and school absences (*GINA, 2006*).

In recent years, there has been a worldwide increase in number of children with asthma, this trend has been linked to environmental factors including air pollution but indoor triggers can also play just as much of a role as outdoor triggers in bringing an asthmatic attack (*Allen and Blaiwas, 2009*).

Inhaled corticosteroids (ICS) are considered the corner stone of chronic asthma management as they reduce symptoms and frequency of asthma exacerbation and improve lung function (*Merkus et al., 2004*). Poor adherence to inhaled

corticosteroids (ICS) may contribute to the rise in asthma morbidity (*Scott et al., 2011*).

Glycosaminoglycans (GAGs) are long straight chain polysaccharides composed of repeated disaccharide units which occur in free form or attached to a protein core to form proteoglycans. Proteoglycans are important structural and functional components of the extracellular matrix (ECM) and basement membrane (*Priftis et al., 2006*).

Increase the extracellular matrix (ECM) deposition in the airway wall contributes to the airway remodeling in asthmatics (*Vignola et al., 2003*). The term "remodling" describes the structural alterations that occur in the lung of asthmatic patients, even before a clear clinical diagnosis, due to prolonged chronic inflammation within the airways (*Pohunck et al., 2005*).

Endobronchial biopsies obtained from patients with mild asthma showed that proteoglycans deposition was significantly increases in asthmatics as compared with that in control subjects (*Priftis et al., 2006*). Short-term treatment with high doses of inhaled fluticasone propionate (FP) can significantly reduce not only inflammatory cells but also the vascular component of airway remodeling and basement membrane thickening, suggesting a potential reversibility of both inflammatory and structural changes in asthma (*Chetta et al., 2003*).

## **AIM OF THE WORK**

The aim of this work is to evaluate the urinary glycosaminoglycans (GAGs) as an objective marker for response to anti-inflammatory treatment of asthmatic children on inhaled corticosteroids (ICS).