INTRODUCTION

Asthma is a common and potentially serious chronic disease that impose a substantial burden on patients, their families and the community. Asthma causes symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time in their occurrence ***(GINA, 2014).***

Airway remodeling in asthma postulates that the alteration of the structure and function of airway constituents, including airway smooth muscle, epithelium, blood vessels, and mucus glands, might explain, at least in part, the progressive loss of lung function that is observed clinically. Inflammation driven by CD4+ lymphocytes and mediated by effector cells, particularly the eosinophil, appears to modulate the function of mesenchymal cells, including fibroblasts and myofibroblasts, changing the composition of the airway wall matrix. Changes in the airway epithelium might alter the function of the underlying smooth muscle and the composition of the matrix and could drive inflammation. Alterations in the structure and function of airway smooth muscle change the mechanical properties of the airway wall and might also affect the function of other airway constituents ***(Pascual and Peters, 2005).***

Airway remodeling may lead to irreversible airflow obstruction with increased morbidity and mortality. Despite

advances in the treatment of asthma the mechanisms underlying airway remodeling still poorly understood ***(Veraldi et al., 2009).***

Insulin-like growth factors (IGFs) are well known as key regulators of energy metabolism and growth ***(Pollak, 2008),*** The IGF system plays critical roles in somatic growth in an endocrine fashion (somatomedin hypothesis) as well as proliferation and differentiation of normal and malignant cells in a paracrine/autocrine fashion. IGFBP-3 is known to modulate the actions of IGF in circulation as well as the immediate extracellular environment. Interestingly, apart from the ability to inhibit or enhance IGF actions, IGFBP-3 also exhibits very clear, distinct biological effects independent of the IGF/IGF-I receptor axis ***(Brahim et al., 2008).***

The insulin-like growth factor binding protein 3 (IGFBP-3) is the major circulating IGF binding protein, its function is regulated by proteolytic cleavage ***(Dehghani et al., 2012).*** IGFBP-3 affects airway inflammation and airway hyperresponsiveness through IGFBP-3 receptor–mediated activation. It also enhances the IGF-I/hypoxia-inducible factor/vascular endothelial growth factor axis via IGF-I–dependent and/or IGF-I–independent mechanisms ***(Lee et al., 2014).***

AIM OF THE WORK

This study was designed with the aim to evaluate the level of insulin growth factor binding protein 3 (IGBP3) as a member of insulin like growth factor binding proteins that play a role in assessment of severity and airway remodeling in asthmatic children.

ASTHMA

Asthma is a heterogeneous disease, which usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and coughs that differ over time and in intensity, together with variable expiratory airflow limitation ***(GINA, 2015).***

Epidemiology

Asthma affects an estimated 300 million people worldwide it affects 5-10% of the population including 7 million children; it affects between 11 and 20% of all school age children. The prevalence of asthma among Egyptian children aged 3 - 15 years was estimated to be 8.2% ***(Abdallah et al., 2013; Lafta and Shamssain, 2016).***

Sex

Male sex is a risk factor for asthma in pre-pubertal children In the U.S. 15% percent of boys compared to 13% of girls have had asthma, Boys with asthma are more likely to grow out of their asthma during adolescence than girls. Female sex is a risk factor for persistent asthma ***(SING, 2014; Liu et al., 2016).***

Age

Asthma prognosis depends on age at first presentation, the earlier the onset of wheeze, the better the prognosis ***(SING, 2014; Myers et al., 2015).***

Prevalence of childhood asthma changes corresponding to age, wheeze in 6-7 year (2.4-37.6%) and 13-14 year old children (0.8-32.6%), (80% of all asthmatic patients report disease onset prior to 6 years of age) ***(Liu et al., 2016).***

In undeveloped countries the proportion of severe symptoms are much higher and are associated with more impaired asthma control than in wealthy countries ***(Moorman et al., 2011; To et al., 2012).***

Etiology and risk factor:

Family history of atopy

Asthma often runs in families, and identical twins are more likely to both be asthmatic than are non-identical twins. A family history of atopy is the most clearly defined risk factor for atopy and asthma in children. The strongest association is with maternal atopy ***(GINA, 2014).***

Epigenetics

Chemical modification of DNA and histone proteins that can be passed down to offspring could have a role in translating environmental interactions into changes in expression of

specific disease-related genes indicating a contribution from both genetic and non-genetic factors. Genes controlling factors involved in airway development and repair, including remodeling ***(Michel et al., 2010; GINA, 2014).***

Genetics

Genetic approaches in diseases such as asthma can predict risk for development or progression On the past decade, genome wide association studies (GWASs) report about 30 GWASs in different populations in the investigation of chromosomal regions that are linked to asthma and atopy, or related phenotypes ***(Orlandi et al., 2014; Chung et al., 2014).***

More than 100 genetic loci have been linked to asthma, few have consistently been linked to asthma such as ILL33, IL1RL1, IL18R1 and TSLB which are involved in epithelial cells danger signal pathway and elevated levels of IgE identified near HLA-DQB1(located on chromosome 5Q), and there are genes which are associated with asthmatics response to treatment such as variation in gene encoding the beta2-adrenoreceptorwhich is responsible of the response of short acting beta2 agonists) ***(Ito et al., 2006; Moffatt et al., 2010; Daley et al., 2012 and Levin et al., 2013).***

Environment

Adding of environmental to genetic factors in early life show how the immune system develops and responds to environmental exposures, respiratory microbes, inhaled

allergens, and toxins which can injure the lower airways leading the disease process to the lungs (figure 1) ***(Havstad et al., 2012; Pawankar et al., 2012 and Liu et al., 2016).***

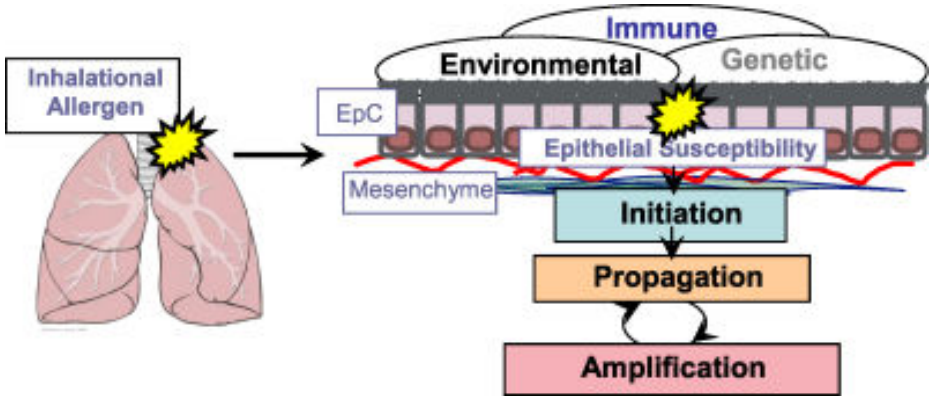

Figure (1): Asthma complex of genetic susceptibility and environmental influences ***(Murdosh et al., 2010).***

Obesity

Some changes in lifestyle and exposures may help to explain increases in asthma prevalence. There is recognized association between asthma and obesity, which has been abroved as a risk factor for asthma ***(Farah and Salome, 2012).***

Obesity leads to release of pro-inflammatory cytokines from adipose tissue, and mechanical changes that alter lung function ***(Sideleva et al., 2012).***

Viral infection in children

There is growing evidence that respiratory viruses resulting in severe and prolonged inflammation, lung

pathology, morbidity, and mortality as viral pathogens that target the respiratory system typically evoke well-defined and unique innate immune responses, which trigger specialized adaptive immune responses ***(Shibata et al., 2014).***

Respiratory viruses, as influenza and respiratory syncytial virus (RSV), cause serious damage to airway epithelium and increase the exposure of inflammatory and antigen-presenting cells to allergens and other irritants ***(Loisel et al., 2016 and Redding et al., 2006).***

Comorbidities of Childhood Bronchial Asthma:

A. Sinusitis

The upper and lower airways share the same physiology and histomorphology so there is relationship between rhino-sinusitis and asthma, which can occur in both directions ***(Ilmarinen et al., 2015).***

Evidence suggests that (Human rhinovirus C) illness during infancy is a significant risk factor for the development of wheezing in preschool children and a frequent trigger of wheezing illnesses in children with asthma ***(Bizzintino et al., 2011 and Saglani, 2013).***

Chronic rhino-sinusitis causes more severe asthma especially in patient with nasal polyps ***(GINA, 2015 and Bachert et al., 2015).***

B. Gastroesophageal reflux disease:

Gastro-esophageal reflux disease (GERD) produce airway hyper-responsiveness, lung function decrease and exaggerate asthma symptom, there are three potential mechanisms by which esophageal acid affect asthma: increased vagal tone, increase bronchial reactivity, and micro aspiration of gastric contents into the upper airway which damages epithelial cells causing an inflammatory response ***(Amarasiri et al., 2013 and Gaude, 2009).***

Respiratory symptoms in asthmatics are increased among patients with GE reflux. The prevalence varies from 30 to 90 percent, and GE reflux is common among asthmatic patients ***(Naika and Vaezi, 2015).***

C. Exercise-induced asthma

Exercise-induced asthma (EIA), defined as a condition in which exercise or vigorous physical activity triggers acute bronchospasm in persons with heightened airway reactivity ***(Kurti et al., 2016).***

A child with asthma symptoms that are triggered during exercise only may have intermittent asthma. However, symptoms increased during exercise indicate that the child may have persistent asthma ***(Hallstrand, 2012).***

Pathophysiology of asthmatic airways:

Asthma is an inflammatory disorder of the airways (figure 2), which involves multiple inflammatory cells and mediators ***(GINA, 2015).***

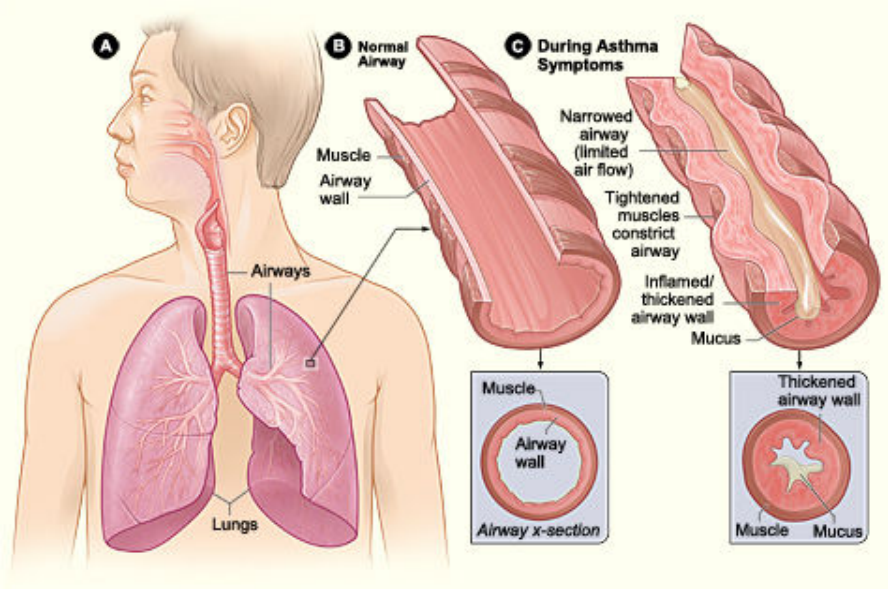

Figure (2): Pathophysiology of asthmatic airway ***(NIH, 2016).***

Airway Inflammation

Triggers act on airway afferent nerves (which release their own peptide mediators and stimulate reflex release of the bronchoconstriction acetylcholine) and airway epithelial cells to initiate responses in multiple cell types that contribute to the mucous metaplasia and airway smooth muscle contraction that characterize asthma (figure 3) ***(Erle et al., 2014).***

Cells contribute to airway Inflammation include mast cells, eosinophil, epithelial cells, macrophages, and activated T lymphocytes, all of these can fill and obstruct the airways and induce epithelial damage and desquamation. Mast cells have long been considered a key effector cell of asthma pathogenesis (Figures 3&4); as they are located in both the airway epithelium and deeper layers of the mucosa ***(Murdoch and Lloyd, 2010 and Liu et al., 2016).***

T lymphocytes play an important role in the regulation of airway inflammation through the release of numerous cytokines, Airway inflammation in asthma may represent a loss of normal balance between:Th1 and Th2, Th1 cells produce interleukin (IL)-2 and interferon-α (IFN-α), which are critical in cellular defense mechanisms. Th2, in contrast, generates a family of cytokines (interleukin-4 [IL-4], IL-5, IL-6, IL-9, and IL-13) that mediate allergic inflammation (figure3) ***(Gauvreau et al., 2011 and Erle et al., 2014).***

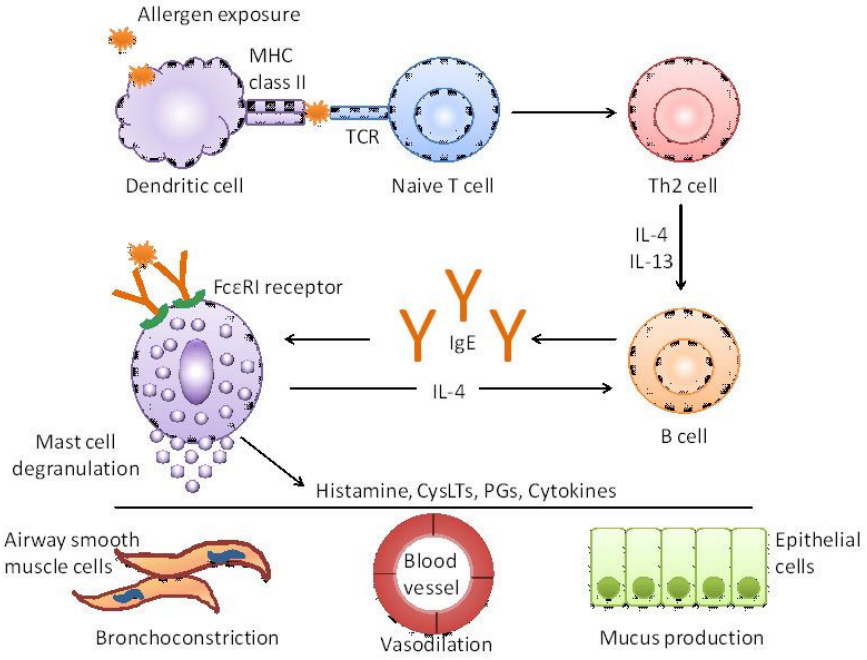

Figure (3): Pathogenesis of asthma ***(Pundir, 2013).***

Airway hyper-responsiveness:

Airway hyper-responsiveness is a characteristic functional abnormality of asthma ***(GINA 2015).*** The mechanisms of airway hyper-responsiveness include the following: ***(GINA, 2015).***

- Excessive contraction of smooth muscle.
- Uncoupling of airway contraction.
- Thickening of the airway wall.
- Sensory nerves sensitization by inflammation.

Airway narrowing:

Airway narrowing is the final common pathway leading to symptoms and physiological changes in asthma, itself likely to be an additional stimulus for remodeling ***(GINA, 2015).***

Histopathology of asthmatic airways:

Asthmatic airway epithelium typically shows sloughing of 1.ciliated columnar cells, 2.and squamous cell metaplasia, 3.and an increased thickness of the subepithelial basement membrane with goblet cell metaplasia (GCM) which is due to the proliferation of pre-existing goblet cells and trans differentiation of ciliated and Clara cells to goblet cells (figure 4) ***(Abonia et al., 2011 and Lambrcht et al., 2012).***

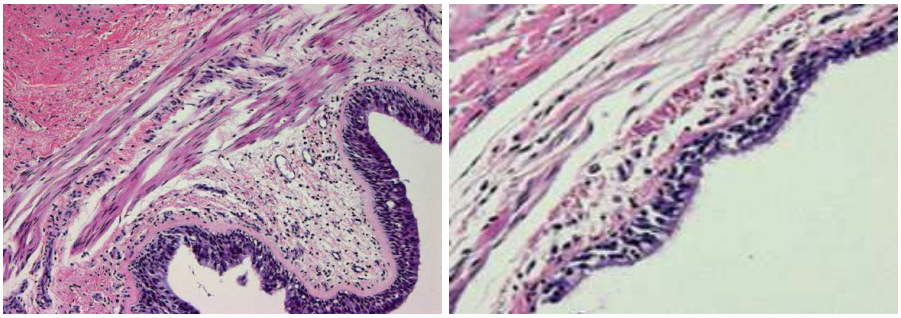

Figure (4): Histology of airway tissue section ***(Costa et al., 2014).***

The basement membrane consists of a superficial layer (the basal lamina) and a deeper layer (the lamina reticularis, or RBM), thickening is restricted to the RBM ***(Wenzel et al., 2012 and Dober et al., 2015).***

Goblet cells produce mucin glycoproteins being predominant in asthmatic airways in response to Type 2 cytokines ***(Salem et al., 2014 and Dober et al., 2015).***

Although mucus is critical for host defense, pathological mucus production is an important factor in asthma morbidity and mortality, mucus plugs obstruct movement of gas due to increased mucin production and secretion as well as changes in mucin cross-linking, mucus gel hydration, and mucus clearance ***(Grainge et al., 2011 and Erle et al., 2014).***

It is believed that large airway smooth muscle thickening in asthma is a consequence of both hypertrophy and hyperplasia of airway smooth muscle cells both of which correlate with asthma severity, but not with age or duration of disease ***(James et al., 2012 and Dober et al., 2015).***

Hypertrophy and hyperplasia of airway smooth muscle (ASM) cells increase the ability of the ASM to shorten ***(James et al., 2012 and Wenzel et al., 2012).***

Airway remodeling:

Airway remodeling is a complex and dynamic process that is believed to be the result of chronic asthma ***(Murdosh et al., 2010 and Holgat ST et al., 2013).***

Remodeling occurs in patients with all forms of asthma but allergic severe asthmatics patients has more prominent remodeling

features compared with non-allergic patients, despite of having better lung function ***(Elliot et al., 2014 and Szefler et al., 2014).***

Today it is assumed that eosinophils causes airway wall remodeling in asthma ***(Brannan et al., 2012 and Leclere et al., 2012).***

Remodeling response arising from injury and repair of airway and failure of treatment efficacy such as inhaled corticosteroids, with persistence of bronchial hyperresponsiveness (BHR), and the progressive decline in pulmonary function ***(Manuyakorn et al., 2013 and Salem et al., 2014).***

In airway remodeling all elements of the airway wall are involved (Figure 5), and remodeled airway wall thickness is substantially increased compared to normal airways ***(Manuyakorn et al., 2013).***

In remodeling; the physiological effects of extracellular matrix accumulation are predicted to result in an exaggerated degree of narrowing for a given amount of airway smooth muscle (ASM) contraction. Airway wall thickness is due to an increase in airway smooth muscle (ASM) mass and mucous glands ***(To et al., 2012).***