# Introduction

Asthma is a serious global health problem. People of all ages in countries throughout the world are affected by this chronic airway disorder. The prevalence of asthma is increasing in most countries, especially among children. Asthma is a significant burden, not only in terms of health care costs but also of lost productivity and reduced participation in family life ***(GINA, 2008).***

Obesity is a condition of excess body fat (adibosity), which is associated with adverse health states and risk of future diseases. Body mass index (BMI) is the most common measure used to define over weight and obesity in children. BMI is a hight –adjusted weight measure that is calculated from measured weight (in kg) divided by height in meters-squared ($kg/m^2$) ***(Whitlock et al., 2010).***

Asthma appears to be determined by multiple interacting genetic and environmental factors. Obesity is a particularly common co-morbidity that may adversely affect asthma inception, severity, and response to therapy. There is mounting evidence that childhood obesity is a risk factor for the development of asthma, including cross sectional ***(Wickens et al., 2005)*** and prospective studies ***(Castro-Rodriguez et al., 2001; Aiddedcsb, 2003)*** and recent studies have also suggested that obese asthmatics respond differently to standard therapies than

their non-obese counterparts ***(Carroll et al., 2006; Woolford et al., 2007).*** Moreover, the evidence that the proinflammatory environment created by excess adiposity may provide a mechanism leading to obese asthma in children and adolescents ***(Jensen, 2011).***

Mast cells are found to be more abundant in subcutaneous abdominal adipose tissue from obese humans than from non-obese humans ***(Liu et al., 2009)***. Tryptase is granule stored and released with other heparin - bound compounds when mast cells are activated therefor, total serum tryptase(ST) may be considered as a measure of mast cell activity، as a marker of the risk of severe allergic reactions and as a marker of recent allergic reactions ***(Schwartz et al., 2003).***

# Aim of the Study

The aim of this study is to evaluate serum tryptase in obese asthmatic children as an intermediate variable in the relationship between obesity (a body mass index, or (BMI), greater than or equal to 30 and asthma.

# Chapter 1
# Pediatric Asthma

## Definition of asthma:

It is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, air flow obstruction within the lung that is often reversible either spontaneously or with treatment ***(GINA, 2006).***

Asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm. Symptoms include wheezing, coughing, chest tightness, and shortness of breath ***(BTS, 2009).***

## Epidemiology

- *Prevalence:*

The prevalence of asthma has been increasing worldwide over the past several decades. In 2006, the National Health Interview Survey (NHIS) estimated that 16.1 million adults (7.3% of the population) and 6.8 million children (9.4% of the

population) in the United States had a diagnosis of asthma. The prevalence of asthma decreases with increasing age. There are important racial differences in the prevalence and morbidity of asthma. In 2005, Puerto Ricans had an asthma prevalence rate 125% higher than non-Hispanic whites and 80% higher than non-Hispanic blacks. Females had a 40% higher prevalence rate than males; however, boys under the age of 18 years old had a higher prevalence than girls ***(Eder et al., 2006).***

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 as seen in **(Figure 1)**. Its prevalence increases by 50% every decade ***(Braman, 2006).***

Allergic diseases and asthma affect an estimated 20% of the population in developed countries ***(Nauta et al., 2008).*** It affects about 300 million people worldwide, a total that is expected to rise by an additional 100 million mainly in children over the next 15-20years ***(Adcock et al., 2008).***

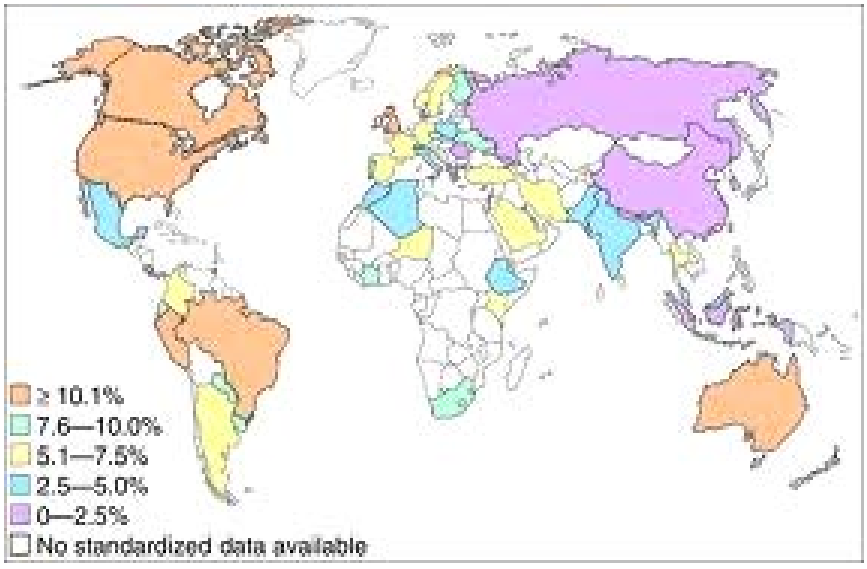


**Figure (1):** World wide prevalence of clinical asthma ***(Braman, 2006)***

- ***Prevalence of asthma in Egypt:***

Among 11and 15 years old school children in Cairo the overall prevalence of wheezing in the year 2005 was 14.7% and of physician-diagnosed asthma was 9.4% ***(Georgy et al., 2006).***

A large epidemiological study was conducted on school children aged 6-15 years. The study was conducted on the following governorates which are representative of Cairo and most of the Nile delta regions: Cairo metropolitan who represents Cairo governorate and adjacent areas of Giza and Kalioubia, Sharkia, Dakahlia and El- Behira governorates. The result of the study showed that asthma prevalence in the studied governorate was: 16.8% in Cairo metropolitan, 10.9% in Sharkia, 14.1% in Dakahlia and 18.7% in El-Behira governorate. So the prevalence of asthma in Egyptian school children ranged from 10.9 to 18.7% with a mean of 15.1% .

From the results of this study we can conclude that asthma prevalence is increasing in Egyptian children during the last few years. The increase in asthma prevalence is more evident in urban areas compared to rural areas. Exposure to environmental tobacco smoke, air pollution and bad housing conditions are important determinants of asthma and may explain the trend of increased asthma in Egyptian school children ***(Deraz et al., 2008).***

The overall prevalence of asthma was 7.7 % (8% in urban and 7% in rural areas) ***(Zedan et al., 2009).***

According to the WHO estimations asthma deaths outnumbered more than 250,000 persons per year all-over the world ***(GINA, 2009).***

- *Pathophysiology*

***Early asthmatic responses*** occur via IgE-induced mediator release from mast cells within minutes of exposure and last for 20-30 minutes ***(Sharma and Gupta, 2011)***.

***Late asthmatic response***s occur 4-12 hours after antigen exposure and result in more severe symptoms that can last for hours and contribute to the duration and severity of the disease. Inflammatory cell infiltration and inflammatory mediators play a role in the late asthmatic response. Allergens can be foods, household inhalants (eg, animal allergens, molds, fungi, roach allergens, dust mites), or seasonal outdoor allergens (eg, mold spores, pollens, grass, trees) ***(Sharma and Gupta, 2011).***

Airflow limitation in asthma is recurrent and caused by a variety of changes in the airway. These include:

1. Bronchoconstriction
2. Inflammatory Cells.
3. Inflammatory Mediators.
4. Airway remodeling.

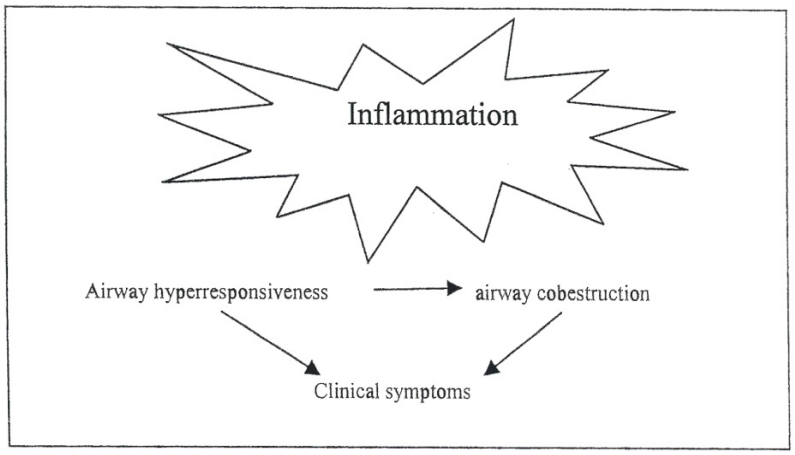


**Figure (2):** The interplay and interaction between airway inflammation and the clinical symptoms and pathophysiology of asthma ***(o'byern and parameswaran, 2006).***

## 1) Bronchoconstriction

In asthma, the dominant physiological event leading to clinical symptoms is airway narrowing and a subsequent interference with airflow. In acute exacerbations of asthma, bronchial smooth muscle contraction occurs quickly to narrow the airways in response to exposure to a variety of stimuli including allergens ***(Busse and Lemanske, 2001).***

## 2) Inflammatory cells:

The characteristic pattern of inflammation found in allergic diseases is seen in asthma, with activated mast cells, increased numbers of activated eosinophils, and increased numbers of Th2 cells, which release mediators that contribute to symptoms. Structural cells of the air ways also produce inflammatory mediators, and contribute to the persistence of inflammation in various ways ***(Umetsu et al., 2003).***

### A-Inflammatory cells in asthmatic airways:

***I -Mast cells****:*

The activated mucosal mast cells release broncho-constrictor mediators (histamine, cysteinyl leukotrienes, prostaglandin D2) ***(Galli et al., 2005).***

Two types of mast cells are found in humans. The cells subtypes are distinguished primarily by their tissue location and biochemical characteristics ***(Bochner and Schleimer, 2001).***

Chronic mast cell activation contributes to the pathophysiology of many diverse diseases through the synthesis and release of numerous pro-inflammatory mediators and cytokines ***(Bradding et al., 2006*).**

There is the immediate release of preformed mediators including histamine and tryptase. In some mast cells, TNFα and vascular endothelial growth factor (VEGF) may also be among

the preformed mediators. This is followed by the synthesis of leukotrienes and cytokines which all contribute to the inflammatory process ***(Galli et al., 2005).***

Mast cells also synthesize and secrete a large number of pro-inflammatory cytokines (including IL-4, IL-5, and IL-13), which regulate both IgE synthesis and the development of eosinophilic inflammation ***(Bradding et al., 2006).***

***II -Eosinophils:***

Increased numbers of eosinophils exist in the airways of most, but not all, persons who have asthma ***(Williams, 2004).***

Eosinophils are considered as characteristic feature of allergic inflammation. The biology of eosinophils is well designed to cause airway inflammation, enhancement of AHR, and airflow obstruction. Eosinophils are recruited to the airway in asthmatic subjects by families of cytokines, and chemokines (e.g. IL-5)) ***(Lemanske and Busse, 2010).***

Increased eosinophils in the airways release basic proteins that may damage airway epithelial cells. They also have a role in the release of growth factors and airway remodeling ***(Kay et al., 2004).***

Eosinophils are a major cellular source of TGF-β mRNA in asthmatic airways which is an important modulator of fibrosis in asthma ***(Aceves and Broide, 2008).***

***III-T lymphocytes:***

An increased understanding of the development and regulation of airway inflammation in asthma followed the discovery and description of subpopulations of lymphocytes, Th1 and Th2, with distinct inflammatory mediator profiles and effects on airway function ***(Busse and Lemanske, 2001).***

T-cells are thought to be a prominent source of cytokines in the asthmatic inflammatory response. In asthma an increase in activated T- cells are observed in the air way ***(Umetsu et al., 2003).***

The study of T-cells and their relationship to inflammation led to the discovery of helper CD4+. T-cell subsets called Th1 and Th2 cells. These subsets are distinguishable on the basis of their pattern of cytokine production. Th1 cells are noted for the secretion of IL-12 and interferon γ (INF- γ), whereas Th2 cells secrets IL-4, IL-5, and IL-13 ***(Busse and Lemanske, 2001).***

Several subtypes of regulatory or suppressive T-cells have been described that can prevent activation of effectors T cells in vitro and in vivo in animal models ***(Robinson, 2005).***

These cells are noted to have an immunosuppressive function for both Th1 and Th2 cells and are thought to be important in generating and maintaining tolerance to antigen ***(Umetsu et al., 2003).***

An increase in Th2 cell activity may be due in part to a reduction in regulatory T cells that normally inhibit Th2 cell ***(Akbari et al., 2006).***

***IV-Macrophages:***

Macrophages are increased in the airways and may be activated by allergens through low-affinity IgE receptors to release inflammatory mediators and cytokines that amplify the inflammatory response ***(Peters-Golden, 2004).***

There are also suggestions that alveolar macrophages can suppress allergic inflammation in the airway by the secretion of Th1 cytokines, including IL-12, IL-18, and INF- γ ***(Mathur and Busse, 2008).***

In vitro studies revealed that alveolar macrophages can respond to antigen through IgE to release leukotrienes, prostaglandin D2 (PGD2), superoxid anion, lysosomal enzymes, and platelet activating factors, thromboxane, and histamine- releasing factor ***(Hamid et al., 2003).***

***V-Neutrophils:***

Neutrophilic numbers are increased in the airways and sputum of patients with severe asthma and in smoking asthmatics, but the pathophysiological role of these cells is uncertain and their increase may be even be due to glucocorticosteroid therapy failure ***(Wenzel, 2003).***

Neutrophils, in contrast to eosinophils, are natural residents of the lungs, particularly the lung parenchyma. Airway neutrophilia can be observed in response to viral infections, during nocturnal exacerbations of asthma, and in bronchoalveolar lavage fluid of allergic asthmatics 4 hours, but not 24 hours, after inhaled allergen challenge ***(Sampson, 2000).***

**B- Airway structural cells involved in the pathogenesis of asthma:**

***I-Airway epithelial cells and goblet cells:***

Sense the environment of air way epithelial cells, express multiple inflammatory proteins in asthma, and release cytokines, chemokines, and lipid mediators so viruses and air pollutants interact with epithelial cells ***(Chung, 2000).***

Epithelial cells are capable of producing endothelines, which are a family of three related peptides with potent bronchoconstrictor activity. Some of the stimuli for endothelin secretion include IL-1, IL-6, IL-8, TGF-β and TNF-α. Endothelin secretion is inhibited by INF-γ and glucocorticoid treatment ***(Thompson et al., 2005).***

In asthma, goblet cell hyperplasia and increased mucus production are typically observed, the increased numbers of goblet cells are derived from the proliferation and differentiation of epithelial cells in asthma several cytokine signaling pathways, including IL-9and IL-13, induce goblet cell hyperplasia ***(Roger, 2003).***

***II-Airway smooth muscle cells:***

Airway smooth muscle is not only a target of the asthma response (by undergoing contraction to produce airflow obstruction) but also contributes to it (via the production of its own pro-inflammatory mediators). As a consequence of airway inflammation and the generation of growth factors, the airway smooth muscle cells can undergo proliferation, activation, contraction, and hypertrophy. Events that can influence airway dysfunction of asthma ***(Lazaar and Panettieri, 2005).***

***III-Endothelial cells:***

Endothelial cells of the bronchial circulation play a role in recruiting inflammatory cells from the circulation into the air way ***(Groneberg et al., 2004).***

The vascular endothelium, in addition to contributing to the passive barrier and also taking part in airway remodeling, seems to be involved in asthma pathogenesis and in the inflammatory processes associated in its sever forms ***(Persson et al., 2005).***

***IV-Fibroblasts and Myofibroblasts:***

Fibroblasts and myofibroblasts produce connective tissue components, such as collagens and proteoglycans that are involved in airwayremodeling ***(Antonio et al., 2003).***

***V-Airway nerves:***

Airway nerves are also involved. Cholinergic nerves may be activated by reflex triggers in the airway and caused bronchoconstriction and mucus secretion. Sensory nerves which may be sensitized by inflammatory stimuli including neutrophils, causing reflex changes and symptoms such as cough and chest tightness, and may be release inflammatory neuro-peptides ***(Groneberg et al., 2004)***

**3) Inflammatory Mediators In asthma:**

Chronic airway inflammation is one of the main features of asthma. Release of mediators from infiltrating cells in the airway mucosa has been proposed to contribute directly or indirectly to changes in airway structure and function. The airway smooth muscle has been recognized as a rich source of pro-inflammatory cytokines and growth factors ***(McCabe and Sharman, 2003).***

Inflammatory cells, such as activated eosinophils and neutrophils are associated with increased levels of IL-5, IL-8 and of pro-inflammatory mediators ***(Mathur and Busse, 2008).***

Activated T-lymphocytes produce interleukins IL-4, IL-5 and IL-13. The cross linkage of two IgE molecules by allergen causes mast cells to degranulate releasing histamine, leukotrienes, and other mediators that cause the airway inflammation. IL-5 activates the recruitment and activation of eosinophils ***(Fireman, 2003).***