INTRODUCTION

Asthma is an inflammatory disorder of the airway associated with airflow obstruction & bronchial hyper-responsiveness that varies in severity across the spectrum of the disease. Most patients with asthma are easily diagnosed, responding to standard treatment with a short-acting inhaled B2 agonists for symptom control and to long term therapy including inhaled glucocorticosteroids to control airway inflammation ***(NHBLI/WHO workshop, 2009).***

Asthma is a worldwide problem with an estimated 300 million affected individuals. Nonetheless, based on the application of standardized methods to measure the prevalence of asthma and wheezing illness in children and adults, it appears that the global prevalence of asthma ranges from 1% to 18% of the population in different countries So, it is important to assess accurately the impact of such a wide spread illness and its treatment regarding efficacy and safety ***(GINA, 2014).***

The Global Initiative for Asthma (GINA) guidelines **in 2014** classified features suggesting asthma in children ≥5 years into 5 steps, according to clinical features before treatment, as well as by daily medication regimen and the response to treatment ***(GINA, 2014).***

Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of

persistent asthma. Studies demonstrated their efficacy in reducing asthma symptoms, improving quality of life, improving lung function, decreasing airway hyper responsiveness, controlling airway inflammation, reducing frequency and severity of exacerbations and reducing asthma mortality, and when they are discontinued deterioration of clinical control follows within weeks to months in proportion of patients ***(GINA, 2017).***

A potential safety concern of inhaled corticosteroids ICS use for systemic adverse events in children is growth and adrenal gland suppression, which may limit appropriate ICS use by physicians and individuals and, thus, the attainable therapeutic benefits. Such effects, however, are potentially transient, affording no effect on finally attained adult height ***(Agertoft and Pedersen, 2000).***

In a chohart systemic review in 2002 Jones and his colleagues found that low to moderate doses of ICS did not affect bone mineral density BMD or risk of fractures in adults. However, it is not possible to extrapolate finding from adults to children **(Markku, 2010).**

Persistent uncontrolled asthma may lead to growth restriction. In addition, bone mineral density may be affected by chronic illness and corticosteroid intake ***(William Kelly et al., 2003).***

Case control studies, have identified increased risk of fractures with high doses of ICS ***(Hubbard et al., 2002; Suissa et al., 2003).*** Therefore, there have been some concern that the use of ICS as long term asthma maintenance therapy in children have a determinant effect on bone mineral density(BMD) and risk of fractures ***(Markku et al., 2010).***

Long term use of ICS may be associated also with adverse effects such as cataract, osteoporosis, fractures & reduction in growth velocity in children. Concerns surrounding these potential harms may have a negative effect on ICS adherence thus exposing patients to poorer asthma control & potentially higher risk of needing oral corticosteroids ***(Yoon Loke et al., 2016).***

Aim of the Work

To assess the effect of long term inhalation of corticosteroids for asthma control in children on fat distribution and bone density.

Chapter 1
BRONCHIAL ASTHMA

Definition

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation ***(GINA, 2017).***

Epidemiology and risk factors:-

Asthma is a common, chronic respiratory disease affecting 1-18 % of the population in different countries. Asthma is characterized by variable symptoms of wheeze, shortness of breath, chest tightness and/or cough, and by variable expiratory airflow limitation. Both symptoms & airflow limitation characteristically vary over time & in intensity. These variations are often triggered by factors such as exercise, allergen or irritant exposure, change in weather, or viral respiratory infections ***(GINA, 2016).***

Asthma is usually associated with airway hyper-responsiveness to direct or indirect stimuli, and with chronic airway inflammation. These features usually persist, even when symptoms are absent or lung function is normal, but may normalize with treatment ***(GINA, 2016).***

Worldwide, 300 million people have asthma. The prevalence being much higher in developed countries (e.g., United States, Great Britain, Australia, and New Zealand) than the developing countries ***(Mintz, 2004)***.

In Egypt, the prevalence of asthma among school aged children was found to be 8.2% ***(Abu Gahel et al., 2008)*** while, ***(El-Shafy et al., 2006)*** found that the prevalence of childhood asthma in Cairo metropolitan was 16.8%.

Risk factors:

A) Age:

Although the highest asthma incidence rates are in early childhood, rates may by biased upwards by the labeling of wheezing during infections as asthma. Based upon the International study of asthma and Allergies in childhood (ISAAC) questionnaire, the 0-7 years incidence for childhood asthma is around 11% and 0-10 years is around 15% ***(Roel et al., 2005)***.

B) Prenatal risk factors

Risk factors in the prenatal period are multifactorial. Assessment is complicated by the variety of wheezing conditions that may occur in infancy and childhood, only some of which evolve to classical asthma.

Prenatal tobacco smoke

Prenatal maternal smoking has been consistently associated with early childhood wheezing, and there is a dose-response relation between exposure and decreased airway caliber in early life ***(Lau et al., 2002).*** Studies have also shown a clear prenatal effect of smoking which is increased when combined with postnatal smoke exposure ***(Lodrup Carlsen, 2002).***

C) Sex:

Sex affects the development of asthma in a time-dependent manner studies showed that boys have more asthma than girls (8.2 % versus 5.7%), but after puberty in adolescence and adulthood, more women have asthma than men ***(Milwaukee, 2002)***.

D) Race:

Although asthma is a problem among all races, blacks have more asthma attacks and are more likely to be hospitalized for asthma attacks and to die from asthma ***(NIH-NHLBI, 2004).***

E) Genetics:

Family and twin studies have indicated that genetics plays an important role in the development of asthma and allergy ***(Willemsen et al., 2008).***

Also **Van Beijsterveldt and Boomsma, in 2007**, proved that there is a significant increase in asthma, hey fever and eczema in parents, siblings and grandparents of asthmatics.

F) <u>Diet and nutrition</u>

Observational studies examining prenatal nutrient levels or dietary interventions and the subsequent development of atopic disease have focused on foods with anti-inflammatory properties (e.g., omega-3 fatty acids) and antioxidants such as vitamin E and zinc. Several studies have demonstrated that higher intake of fish or fish oil during pregnancy is associated with lower risk of atopic disease (specifically eczema and atopic wheeze) up to age 6 years ***(Romieu et al., 2007).***

Also some studies reported an inverse relation of maternal vitamin D levels with wheeze in early life, but no relation with atopy or symptoms in later life ***(Devereux et al., 2007).***

G) <u>Breastfeeding</u>

The influence of breastfeeding on the risk of childhood atopy and asthma remains controversial. Some studies have shown protection, whereas others have reported higher rates of allergy and asthma among breastfed children ***(Gdalevich et al., 2001 and Kull et al., 2004).***

A meta-analysis and several individual studies showed that exclusive breastfeeding for at least 3 months was associated with lower rates of asthma between 2 and 5 years of age, with the greatest effect occurring among those with a parental history of atopy ***(Kull et al.,2004).***

H) <u>Obesity as a risk factor:</u>

It has been suggested that lifestyle changes related to obesity (e.g. Changes in diet and decrease in physical activity) are associated with asthma ***(Platis-Mils et al., 2005).*** There is some evidence of a correlation between higher body mass index (BMI) and greater risk of developing asthma ***(Wickens et al., 2005).***

Asthma is more common in obese than non-obese patients. ICS are the mainstay of treatment in obese patients although their response maybe reduced. Weight reduction should be included in the treatment plan for obese patients with asthma . Weight loss improves asthma control, lung function, health status and reduces medication needs in obese patients ***(GINA, 2017).***

I) Environmental Factors:

A) **(Factors that influence the susceptibility to the development of asthma, in predisposed individuals):**

(1) Allergens.

- Indoor: Domestic mites, furred animals (dogs, cats, mice). Cockroach, fungi, molds, yeasts.
- Outdoor: Pollens, fungi, molds, yeasts.

(2) Infections (predominantly Viral).

(3) Occupational Sensitizers.

(4) Tobacco smoke:

- Passive smoking.
- Active smoking.

(5) Outdoor /indoor Air Pollution.

(6) Diet.

B) **Factors that precipitate asthma exacerbation and/or cause symptoms to persist**:

- Indoor and outdoor allergens.
- Respiratory infections.
- Exercise and hyperventilation.
- Weather changes.
- Sulfur dioxide.
- Foods, additives, drugs.
- Extreme emotional expression.
- Tobacco smoke (passive and active).
- Irritants such as paint fumes.

(Padmaja Subbarao et al., 2009)

Pathophysiology;

Asthma is a chronic inflammatory lung disease involving complex interactions between numerous cell types and mediators that result in airway reactivity and airflow limitation ***(Dweik et al., 2001).***

The pathophysiology is complex and involves the following components; airway inflammation, intermittent airflow obstruction, and bronchial hyper-responsiveness ***(Comhair, Erzurum, 2010).***

I) <u>Airway narrowing in asthma</u>:

Airway smooth muscles contraction in response to bronchoconstrictor mediators is the predominant mechanism of airway narrowing and is largely reversed by bronchodilators. Airway edema is due to increased microvascular leakage in response to inflammatory mediators, which may be particularly important during acute exacerbations. Airway thickening due to structural changes, often termed "remodeling" may be important in more severe disease and is not fully reversible by current therapy. Mucus hypersecretion may lead to luminal occlusion "mucus plugging" and is a product of increased mucus secretion and inflammatory exudates ***(Hirst et al., 2004)***.

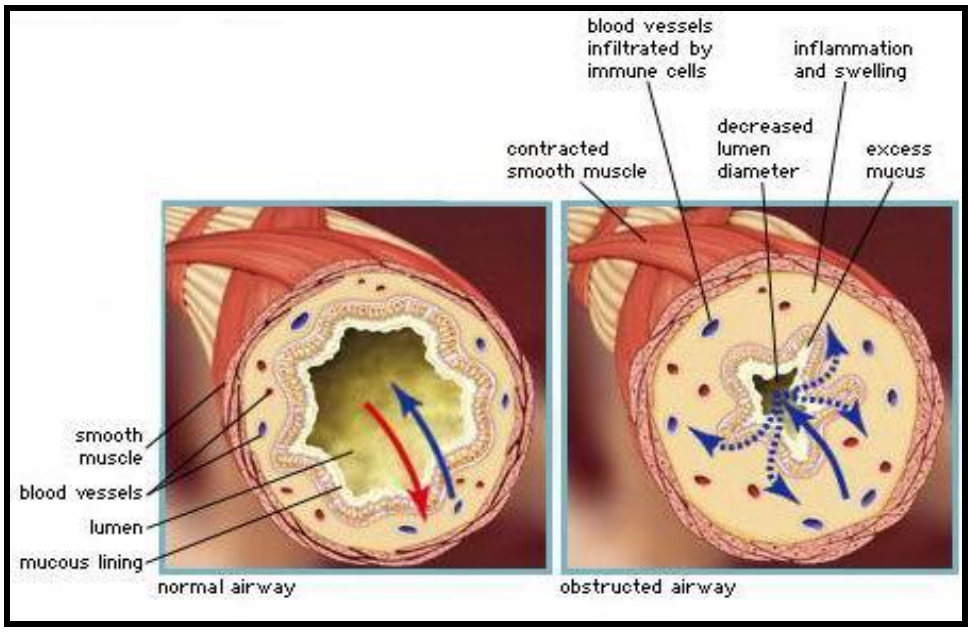

Figure (1): Airway narrowing in asthma Airway narrowing in asthma ***(Black, 2004).***

II) <u>Airway hyper – responsiveness:-</u>

Airway Hyper-responsiveness is the characteristic functional abnormality of asthma, it results in airway narrowing in response to a stimulus that would be innocuous in a normal person, in turn this airway narrowing leads to variable airflow limitation and intermittent symptoms. Airway hyper responsiveness is reversible with therapy ***(Wang et al., 2003 and Black, 2004).***

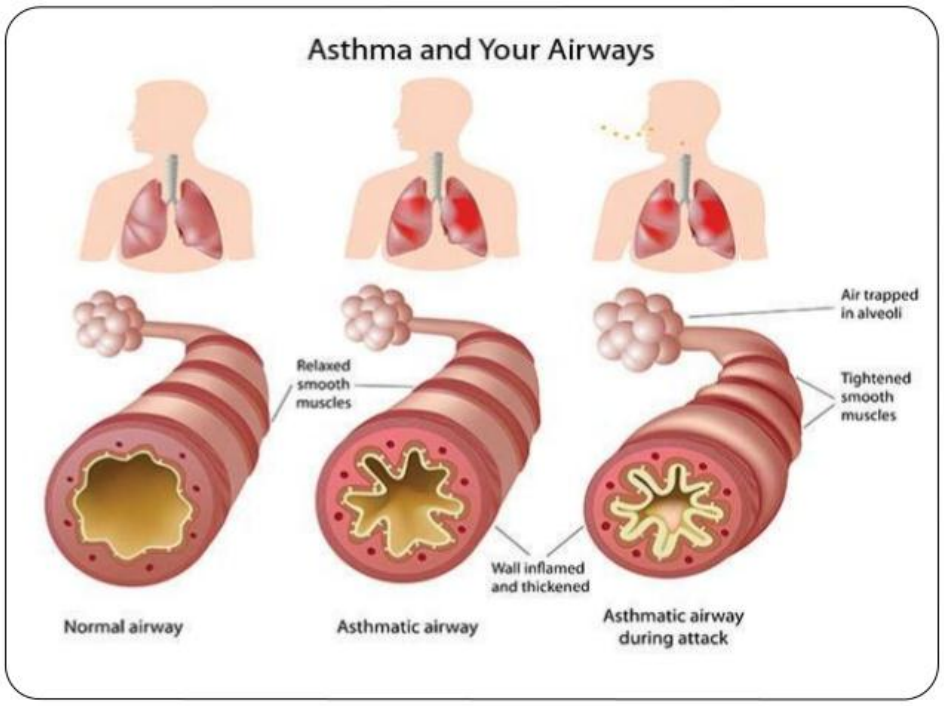

Figure (2): Asthma and Your Airways ***(Illi et al., 2006)***.

III) <u>Airway inflammation in asthma</u>:

The airway inflammation in asthma is persistent even though symptoms are episodic, and the relationship between the severity of asthma and the intensity of inflammation is not clearly established. The inflammation affects all airways including in most patients the upper respiratory tract and nose but its physiological effects are most pronounced in medium – sized bronchi ***(Cohn et al., 2004)***.

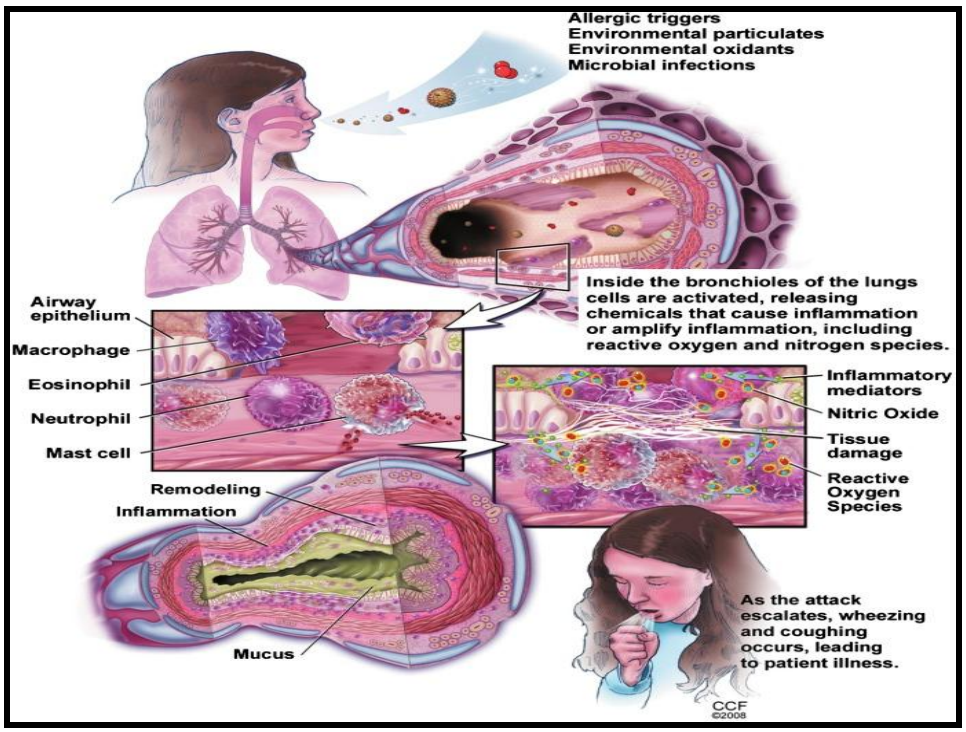

Figure (3): Airway inflammation in asthma ***(Comhair, Erzurum, 2010).***

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 T cell receptor in variant natural killer T cells and T helper 2 lymphocytes (Th_2), which release mediators that contribute to symptoms. Structural cells of the airways also produce inflammatory mediators, and contribute to the persistence of inflammation in various ways ***(Akbari et al., 2006).***

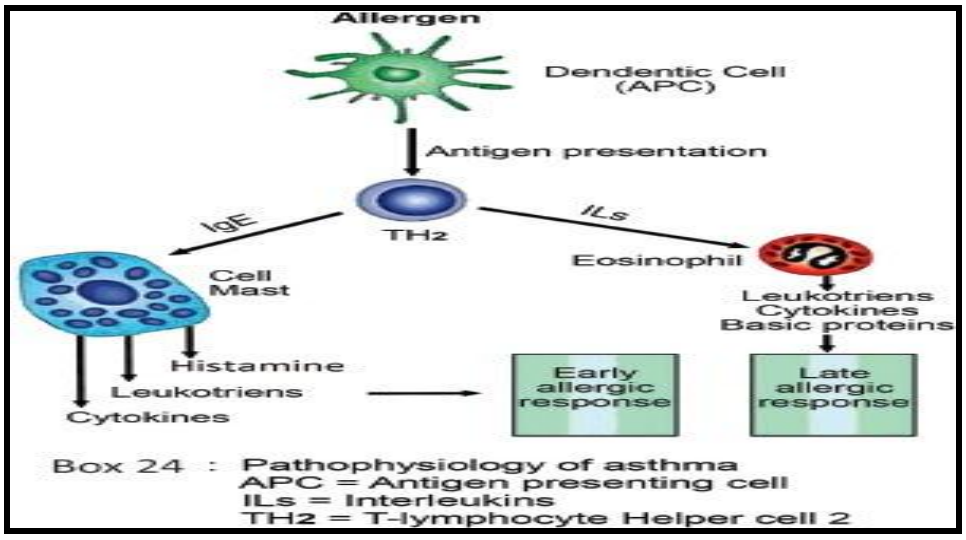

Figure (4): Inflammatory cells ***(The Saudi Initiative for Asthma, 2016 update).***

Inflammatory mediators:

Over 100 different mediators such as (Chemokines, Cysteinyl leukotrienes, Cytokines, Histamine, Prostaglandin D_2) are now recognized to be involved in asthma and mediate the complex inflammatory response in the airways ***(Ricciardolo et al, 2004).***