INTRODUCTION

Asthma is a chronic inflammatory disease of the airways, involving reversible airflow obstruction and characterized by symptoms such as coughing, breathlessness and wheezing. Both genetic and environmental factors, such as dietary intake, are believed to contribute to asthma development and progression ***(Wood et al., 2015).***

It has been postulated that the rise in the prevalence of asthma in western societies may be related to changed dietary habits since the 1950s—specifically, decreased intake of fruits, vegetables and fish. Another factor that may be important is that, as a result of recommendations to substitute saturated fatty acids with n‐6 fatty acids to reduce serum cholesterol concentrations, the current western diet is rich in n‐6 fatty acids. The biological mechanisms by which these dietary changes may affect asthma all seem to include airway inflammation ***(Tabak et al., 2006).***

Consumption of a westernized dietary pattern may promote a pro-inflammatory environment. Indeed, there are a number of studies that have shown that certain nutrients modify systemic inflammation. For example, high fat meals have been shown to lead to increased circulating IL6, TNFα and CRP ***(Wood et al., 2015).***

Other nutrients such as n-3 polyunsaturated fatty acids, fiber, moderate alcohol intake, vitamin E, vitamin C, β-carotene and magnesium also have been consistently associated with lower levels of systemic inflammation ***(Wood et al., 2015).***

Antioxidants are thought to reduce airway inflammation by protecting the airways against oxidants from both endogenous (activated inflammatory cells) and exogenous (cigarette smoke) sources. Fruits, vegetables, and whole grain products are rich in antioxidant vitamins (vitamin C, vitamin E, β - carotene) and other substances with antioxidant capacity (including phenolic acids and phytic acid in whole grains ***(Tabak et al., 2006).***

Fish oils are rich sources of n - 3 fatty acids. Both n - 6 and n - 3 fatty acids are precursors for the production of pro - inflammatory mediators called eicosanoids, including prostaglandins and leukotrienes. Increasing the intake of n - 3 fatty acids shifts the balance towards eicosanoids derived from n - 3 fatty acids, which are thought to be biologically less active.2 As a result, the present western diet may promote airway inflammation, a major characteristic of asthma ***(Tabak et al., 2006).***

There are few reports available in literature regarding the relationship of anemia with childhood asthma. Some are of the opinion that iron supplements significantly reduce the morbidity of upper respiratory tract infection (URTI) in

children. An increased incidence of anemia has been reported in chronic obstructive pulmonary disease (COPD).The increased incidence of asthmatic attacks in anemic children may be due to the following facts: Hemoglobin facilitates oxygen (O 2) and carbon dioxide transport. It carries and inactivates nitric oxide (NO) and also plays the role of a buffer. Hemoglobin in the blood is mainly responsible for stabilizing the oxygen pressure in the tissues. Qualitative and/or quantitative reduction in Hb may adversely affect the normal functions.

The dietary inflammatory index (DII) has recently been developed to provide an overall score for the inflammatory potential of the diet. The DII is based upon an extensive literature search incorporating cell culture, animal, and epidemiologic studies on the effect of diet on inflammation ***(Wood et al., 2015).***

The overall score is dependent on the whole diet, not just certain nutrients or foods. DII scoring is not dependent on population means or recommendations of intake; It is based on results published in the scientific literature. The DII is not limited to micronutrients and macronutrients, but also incorporates commonly consumed components of the diet including flavonoids, spices, and tea ***(Wood et al., 2015).***

Because oxidative stress and inflammation are features of many lung diseases, nutrients with anti-oxidant and anti-

inflammatory properties could be useful in prevention or treatment. Further work is needed to explore the possible relationship between the intake of B group vitamins, Vitamin E, n-3PUFAS and the development and progression of lung disease ***(Chambaneau et al., 2016).***

It was found that asthmatics within the subgroup of severe persistent asthma (according to the GINA criteria) have a different pattern of dietary intake as compared with healthy subjects which was associated with lower lung function and increased airway inflammation ***(Berthon et al., 2013).***

AIM OF THE WORK

The aim of the study is to assess the severity of asthma clinically regarding frequency of the attacks, hospital admissions and visits to the E.R after exposure to dietary modification and to assess the dietary inflammatory index in those patients.

The study will also assess the effect of the dietary modification on the pulmonary functions of those asthmatic patients via spirometry pulmonary functions and on systemic inflammatory marker. This study of dietary modification and iron supplementation for those asthmatic patients will be assessed over period of six months.

Chapter (1)

BRONCHIAL ASTHMA

Definition of Asthma:

The new definition of asthma: "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." ***(Reddel et al., 2015)***.

Asthma Burden:

I. Prevalence and Epidemiology:

a. **Internationally**:

The prevalence of asthma in different countries varies widely, but the disparity is narrowing due to rising prevalence in low and middle income countries and plateauing in high income countries ***(World Allergy Organization (WAO), 2013).***

An Estimated 300 million people worldwide suffer from asthma, with 250,000 annual deaths attributed to the disease. It is estimated that the number of people with asthma will grow by more than 100 million by 2025.Workplace conditions, such as exposure to fumes, gases or dust, are responsible for 11% of asthma cases worldwide. About 70% of asthmatics also have

allergies ***(World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases, 2007).***

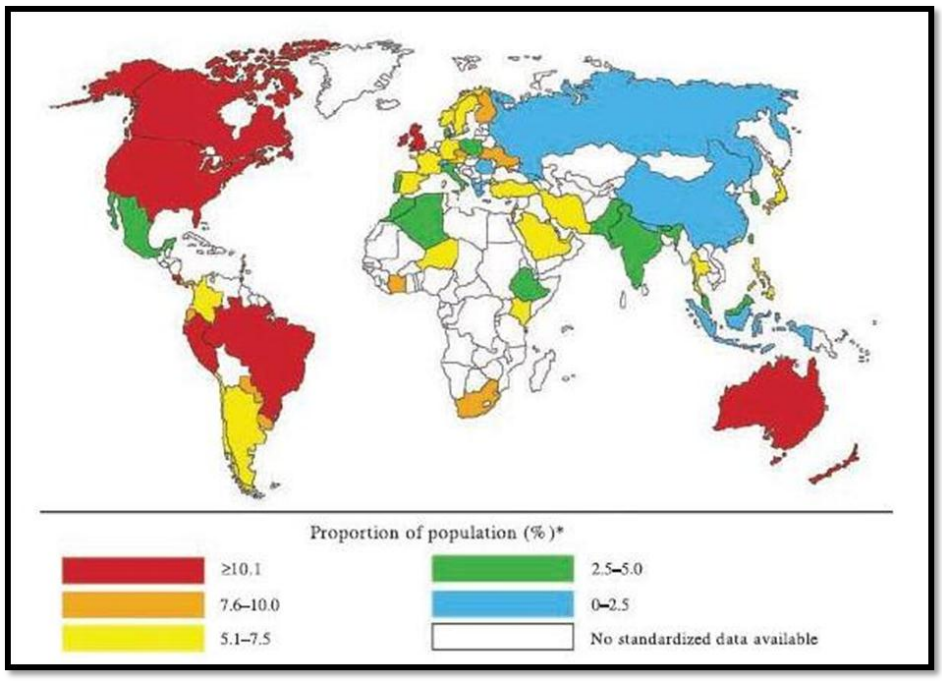

Figure (1): Map shows asthma prevelance world wide in 2004 ***(GINA, 2012).***

b. Egypt:

The Prevalence and socioeconomics of asthma and allergic rhinitis were assessed in northern Africa including Egypt that among 11-15 yrs old schoolchildren in Cairo, the overall prevalence of wheezing in the last year was 14.7% and of physician-diagnosed asthma was 9.4%. This study clearly shows that allergic rhino-conjunctivitis and asthma symptoms are much more prevalent among those from poorer backgrounds. Asthma is relatively common, and probably

undiagnosed and untreated, particularly among children from less wealthy families in Cairo ***(Georgy et al., 2006).***

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).***

In Egypt, one in four children with asthma is unable to attend school regularly because of poor asthma control ***(GINA, 2008)***.

II. Prognosis:

Children with mild asthma who are asymptomatic between attacks are likely to improve and be symptom-free later in life ***(Moorman et al., 2007).***

Asthma has the tendency to remit during puberty, with a somewhat earlier remission in girls ***(National Heart, Lung, and Blood Institute, 2009).***

Etiology of Asthma:

The development of bronchial asthma is associated with several external factors (environmental and occupational) and individual (genetic and psychological) factors, and depends on the interaction between these external factors and genetic predisposition to the development of bronchial hyperresponsiveness and atopy i.e., genetic predisposition to

the overproduction of immunoglobulin E(IgE) specific to common environmental antigens ***(GINA, 2011).***

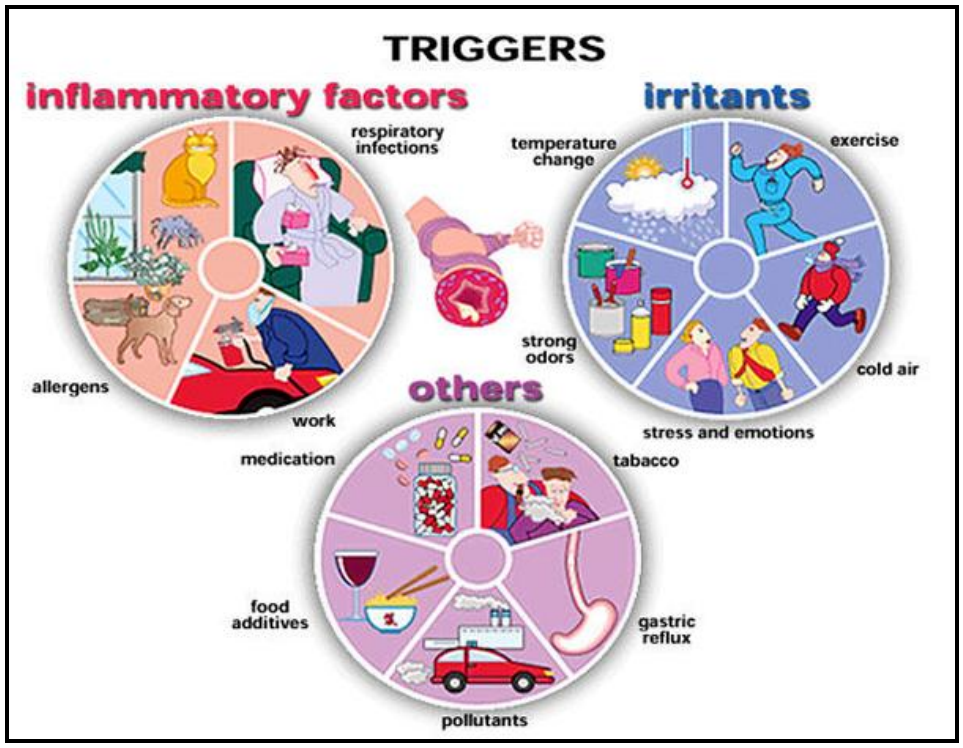

Figure (2): Triggers of Asthma ***(www.immunoehealth.com).***

Pathophysiology of Bronchial Asthma:

Interactions between environmental and genetic factors result in airway inflammation, which limits airflow and leads to functional and structural changes in the airways in the form of bronchospasm, mucosal edema, and mucus plugs. The pathophysiology of asthma is complex and involves the following components:

- Airway inflammation.

- Intermittent airflow obstruction.
- Bronchial hyperresponsiveness.

(Michael, 2013)

1) Airway inflammation

Airway inflammation in allergic asthma is an allergic cascade. Inhaled allergens are taken up and processed by antigen presenting cells (APCs). These APCs then migrate to draining lymph nodes where the processed allergen is presented to allergen specific T and B cells. Activation of T helper (Th) cells by APCs leads to the production of cytokines that regulate the isotope switch of B cells in their production of immunoglobulin E (IgE) ***(Akdis and Akdis, 2007).***

Once synthesized, IgE antibodies circulate in the blood before binding to the high affinity IgE receptor that is present on mast cells in tissue or in peripheral blood basophils. After re-exposure, allergens cross-link to mast cell bound IgE, thus causing the activation of membrane and cytosolic pathways, which subsequently trigger the release of preformed mediators, synthesis of prostaglandins (PGs) and leukotrienes (LTs), and the transcription of cytokines by mast cells ***(Bloemen et al., 2007).***

Airway inflammation in asthma may represent a loss of normal balance between two "opposing" populations of Th

lymphocytes**.** Two types of Th lymphocytes have been characterized: Th1 and Th2. Th1 cells produce interleukin (IL)-2 and IFN-α, which are critical in cellular defense mechanisms in response to infection. Th2, in contrast, generates a family of cytokines (IL-4, IL-5, IL-6, IL-9, and IL-13) that can mediate allergic inflammation ***(Gauvreau et al., 2011).***

CD80 and CD86 expression on T-lymphocytes and monocytes have been implicated as co stimulatory factors in provocation of airway inflammation ***(Fouda et al., 2008).***

Table (1): Inflammatory cells in asthmatic airways ***(GINA, 2012)***

Mast cells: Activated mucosal mast cells release bronchoconstrictor mediators (histamine, cysteinyl leukotrienes, prostaglandin D2). These cells arc activated by allergens through high-affinity IgE receptors, as well as by osmotic stimuli (accounting for exercise-induced bronchoconstriction. increased mast cell numbers in airway smooth muscle may be linked to airway hyperresponsiveness.
Eosinophils, present in increased number in the airways, release basic proteins that may damage airway epithelial cells. They may also have a role in the release of growth factors and airway remodeling.
T lymphocytes, present in increased number in the airways, release specific cytokines including IL-4, IL-5, IL-9, and IL-13, which orchestrates eosinophilic inflammation and IgE Production by B lymphocytes. An increase in Th2 cell activity may be due in part to a reduction in regulatory T cells that normally inhibit Th2 cells. There may also be an increase in NK T cells, Which release large amounts of T helper 1 (Th 1) and Th 2 cytokines.
Dendritic cells sample allergens from the airway surface and migrate to regional lymph nodes, where they interact with regulatory T cells and ultimately stimulate production of Th2 cells from native T cells,

Macrophages are increased in number 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.

Neutrophil number 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 even be due to glucocorticosteroid therapy.

Table (2): Key mediators of asthma ***(GINA, 2012)***

Chemokines are important in the recruitment of inflammatory cells into the airways and are mainly expressed in airway epithelia cells. Eotaxin is relatively selective for eosionphils, whereas thymus and activation-regulated chemokines (TARC and macrophage-derived chemokines (MDC) recruit Th2 cells.

Cysteinyl leukotrienes are potent bronchoconstrictors and pro inflammatory mediators mainly derived from mast cells and eosinophils. They are the only mediator whose inhibition has been associated with an improvement in lung function am asthma symptoms.

Cytokines orchestrate the inflammatory response in asthma id determine its severity. Key cytokines include IL-1B and TNF-alpha, which amplify the inflammatory response, and GM-CSF, which prolongs eosinophil survival in the airways. Th2-derived cytokines include IL-5, which is required for eosinophil differentiation and survival; IL-4which is important for Th2 cell differentiation; and IL-3, needed for IgE formation.

Histamine is released from mast cells and contributes to bronchoconstriction and to the inflammatory response.

Nitric oxide (NO), a potent vasodilator, is produced predominantly from the action of inducible nitric oxide synthase in airway epithelial cells. Exhaled NO is increasingly being used to monitor the effectiveness of asthma treatment because of its reported association with the presence of inflammation in asthma.

Prostaglandin D2 is a bronchoconstrictor derived predominantly from mast cells and is involved in Th2 cell recruitment of the airways.

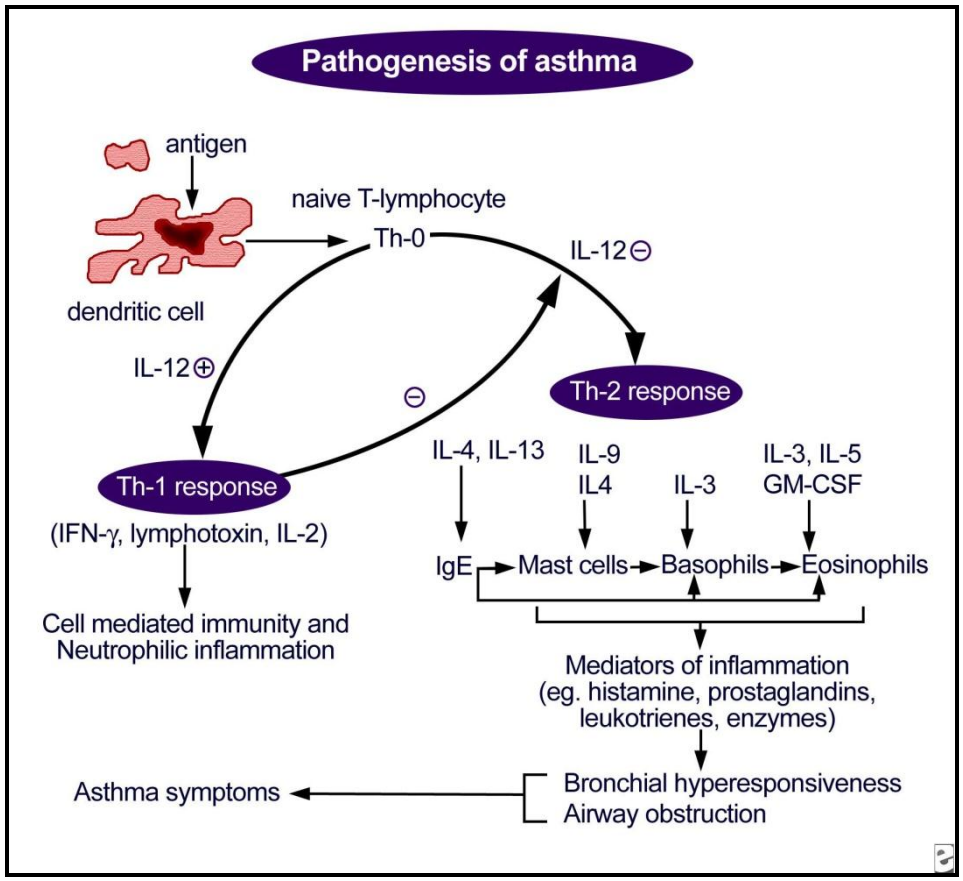

Figure (3): Pathogenesis of asthma (www.medscape.com)

2) Airway hyperresponsivness:

Airway hyperresponsivness, the characteristic functional abnormality of asthma, results in airway narrowing in a patient with asthma in response to a stimulus that would be innocuous in a normal person. In turn, this airway narrowing lead to variable airflow limitation and intermittent symptoms. Airway hyperresponsivness is linked to both inflammation and repair of the airways and is partially reversible with therapy. Its mechanisms are incompletely understood ***(GINA, 2012).***

3) Airflow Obstruction:

Airflow obstruction can be caused by a variety of changes, including acute bronchoconstriction, airway edema, chronic mucous plug formation, and airway remodeling.

Airway remodeling is associated with structural changes due to long-standing inflammation and may profoundly affect the extent of reversibility of airway obstruction. Airway obstruction causes increased resistance to airflow and decreased expiratory flow rates. These changes lead to a decreased ability to expel air and may result in hyperinflation. The resulting overdistention helps maintain airway patency, thereby improving expiratory flow; however, it also alters pulmonary mechanics and increases the work of breathing; Fig (4) ***(Michael, 2013).***

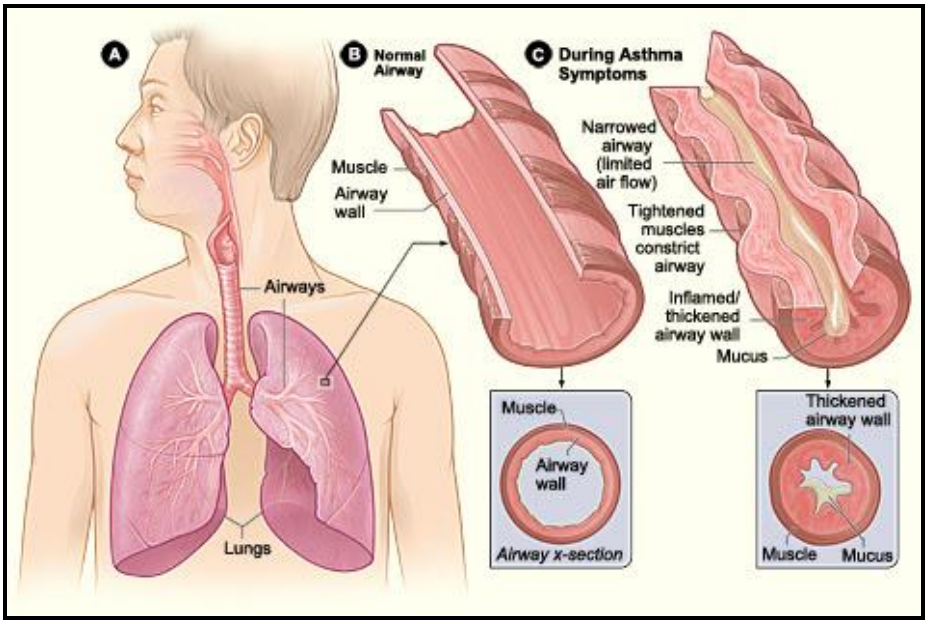

Figure (4): Bronchial hyperresponsiveness and airway narrowing (www.wikimedia.org).

Diagnosis of Asthma:

Criteria for making the diagnosis of asthma *(GINA, 2017*)

1. A history of variable respiratory symptoms

Typical symptoms are wheeze, shortness of breath, chest tightness, and cough

- People with asthma generally have more than one of these symptoms
- The symptoms occur variably over time and vary in intensity
- The symptoms often occur or are worse at night or on waking
- Symptoms are often triggered by exercise, laughter, allergens or cold air
- Symptoms often occur with or worsen with viral infections

2. Evidence of variable expiratory airflow limitation

- At least once during the diagnostic process when FEV1 is low, document that the FEV1/FVC ratio is reduced. The FEV1/FVC ratio is normally more than 0.75–0.80 in adults, and more than 0.90 in children.