Introduction

Asthma is a serious global health problem. People of all ages in countries throughout the world are affected by this chronic airway disorder that, when uncontrolled, can place severe limits on daily life and is sometimes fatal. 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. Although there was a little change in the overall prevalence of current wheeze, the percentage of children reported to have had asthma increased significantly, possibly reflecting greater awareness of this condition and/or a change in diagnostic practice ***(GINA, 2011)***.

Asthma is a chronic inflammatory pulmonary disease related to increased oxidative stress ***(Vignola et al., 1998)***. The association between chronic inflammation and oxidative stress is well documented. Elevated levels of reactive oxygen species, such as hydroxyl radicals, superoxides, and peroxides in inflammatory conditions have been reported previously ***(Grisham et al., 2000)***.

Endothelial dysfunction is a systemic pathological state of the endothelium and can be broadly defined as an imbalance between vasodilating and vasoconstricting substances produced by (or acting on) the endothelium ***(Taddei and Webb, 2005).***

Endothelial dysfunction in the extrapulmonary circulation has been linked to cardiovascular disease. Recent investigations have revealed that in the airway circulation, cigarette smoking, chronic obstructive pulmonary disease (COPD), and asthma are also accompanied by endothelial dysfunction ***(Wanner and Mendes, 2010).***

Some studies documented that asthma itself could be a risk factor for stroke and heart disease ***(Iribarren et al., 2004).***

Aim of The Study

This current study aimed at assessment of endothelial function parameters namely Flow Mediated Dilatation (FMD),Flow Mediated Resistive Index (FMRI), and Circulating Endothelial Cells count (CEC) in asthmatic children of various functional and clinical severity and correlating the studied endothelial function parameters with the level of disease control and severity.

Bronchial Asthma

Definition:

Asthma is a chronic inflammatory disorder of the airways. It is characterized by:

- Airway inflammatory cells, including esinophils, macrophages, mast cells, epithelial cells, and activated lymphocytes that release various cytokines, adhesion molecules, and other mediators.

Inflammation resulting in an acute, subacute or chronic process that alters airway tone, modulates vascular permeability, activates neurons, increases secretion of mucus, and alters airway structure reversibly or permanently.

Airway hyperresponsiveness in response to allergens, environmental irritants, viral infections, and exercise.

Airflow obstruction caused by acute bronchial constriction, edema, mucus plugs, and frequently permanent remodeling.

(Sveum et al., 2012)

Epidemiology:

A. **Across the world:**

Asthma and allergies are world-wide common chronic diseases with high prevalences among children and young people and large variation between and within countries and cities ***(Mallol et al., 2013)***.

A worldwide rapid increase in the number of asthma sufferers is particularly acute in the Gulf States, health professionals in the Middle East and North Africa (MENA) region have drawn the attention to the scale of the problem.

Saudi Arabia took the lead, with a rate of 24% of the population suffering. In a previous research, Qatar and Kuwait came next, with a rate of 19.8% and 16.8% respectively, followed by 13% in the United Arab Emirates. Oman had the lowest prevalence among the Gulf Cooperation Council with a rate of just more than 10%.

(Al Ghobain et al., 2012)

One of the main reasons for the rise of asthma prevalence is the rapid spread of urbanization, especially in the Gulf States, however, another reason for the increased prevalence of asthma in the region may be related to better diagnosis, adding that many cases in the past used to be mislabeled as an "allergy" ***(Al-Ghazawy, 2013)***.

B. **In Egypt:**

The prevalence of asthma in Egyptian school children ranged from 10.9% to 18.7% with a mean of 15%. The asthma prevalence is more evident in urban areas as 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)***.

Etiology of asthma:

The development of bronchial asthma is associated with several external (environmental and occupational) and individual (genetic and psychosocial) factors, and depends on the interaction between these external factors and genetic predisposition to the development of bronchial hyperresponsiveness and atopy; **Fig (1)** i.e., genetic predisposition to the overproduction of immunoglobulin E (IgE) specific to common environmental antigens ***(GINA,2011)***.

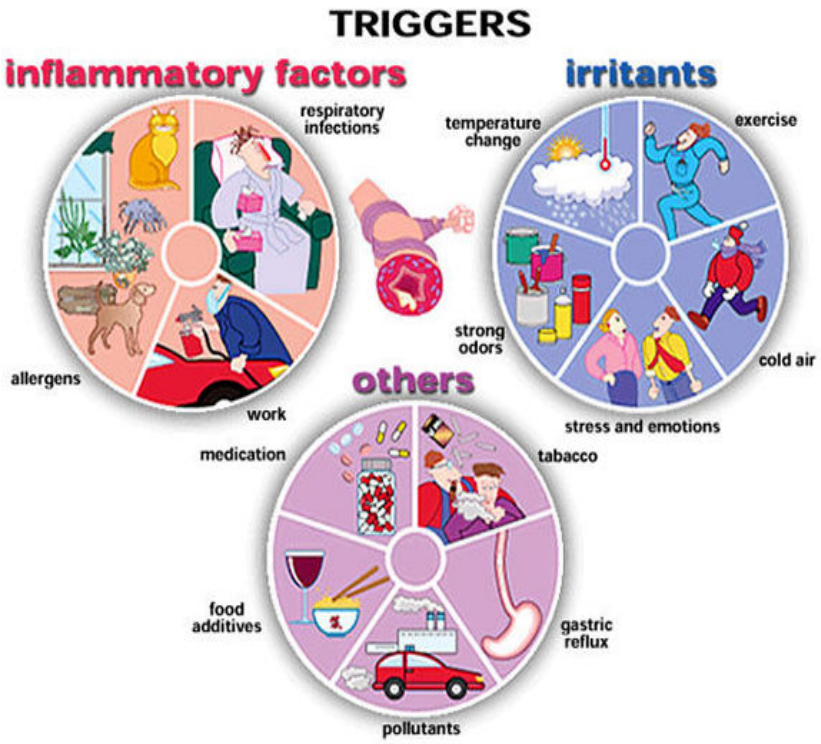

Figure (1): Triggers of asthma

(www. immunoehealth.com).

Genetics of asthma:

Several candidate genes, have been associated with different asthma phenotypes; **Fig (2)**. Typically, the individual impact of these various genes on phenotypic manifestations of the disease is small; however, large effects can arise from the synergistic action of multiple genes in an environmental context.

Gene	Chromosome	Function and pathway	Common variants
GSTM1	1p13.3	Environmental and oxidative stress — detoxification	+/null
FLG	1q21.3	Epithelial barrier integrity	Arg510X, 2282del4
IL10	1q31-q32	Immunoregulation	–1082A/G, –571C/A
CTLA4	2q33	T-cell-response inhibition and immunoregulation	–318C/T, 49A/G
IL13	5q31	T_H2 effector functions	–1112C/T, Arg130Gln
IL4	5q31.1	T_H2 differentiation and IgE induction	–589C/T, +33C/T
CD14	5q31.1	Innate immunity — microbial recognition	–1721G/A, –260C/T
SPINK5	5q32	Epithelial serine protease inhibitor	Glu420Lys
ADRB2	5q31-q32	Bronchial smooth-muscle relaxation	Arg16Gly, Gln27Glu
HAVCR1	5q33.2	T-cell-response regulation — HAV receptor	5383_5397del
LTC4S	5q35	Cysteinyl leukotriene biosynthesis — inflammation	–444A/C
LTA	6p21.3	Inflammation	NcoI (intron 1)
TNF	6p21.3	Inflammation	–308G/A, –857C/T
HLA-DRB1	6p21	Antigen presentation	Multi-SNP alleles
HLA-DQB1	6p21	Antigen presentation	Multi-SNP alleles
HLA-DPB1	6p21	Antigen presentation	Multi-SNP alleles
GPRA	7p14.3	Regulation of cell growth and neural mechanisms	Haplotypes
NAT2	8p22	Detoxification of drugs and carcinogens	Slow acetylation SNPs
FCER1B	11q13	High-affinity Fc receptor for IgE	Ile181Leu, Gly237Glu
CC16	11q12.3-q13.1	Epithelium-derived anti-inflammatory protein	38A/G
GSTP1	11q13	Environmental and oxidative stress — detoxification	Ile105Val
IL18	11q22.2-q22.3	Induction of IFNγ and TNF	–656T/G, –137G/C
STAT6	12q13	IL-4 and IL-13 signalling	2964G/A, (GT)n exon 1
NOS1	12q24.2-q24.31	Nitric oxide synthesis — cell–cell communication	3391C/T, 5266C/T
CMA1	14q11.2	Mast-cell chymotryptic serine protease	*Bst*XI, –1903G/A
IL4R	16p12.1-p12.2	α-chain of the IL-4 and IL-13 receptors	Ile50Val, Glu551Arg
CCL11	17q21.1-q21.2	Epithelium-derived eosinophil chemoattractant	Ala23Thr, –1328G/A
CCL5	17q11.2-q12	Monocyte, T-cell and eosinophil chemoattractant	–403A/G, –28C/G
ACE	17q23.3	Inactivation of inflammatory mediators	In/del
TBXA2R	19p13.3	Smooth-muscle contraction, inflammation	924T/C, 795T/C
TGFB1	19q13.1	Immunoregulation, cell proliferation	–509C/T
ADAM33	20p13	Cell–cell and cell–matrix interactions	Multiple SNPs
GSTT1	22q11.23	Environmental and oxidative stress — detoxification	A/null

Figure (2): Susceptibility genes for asthma and asthma-related traits ***(Donata, 2008).***

More than 30 genes have been identified as candidates for susceptibility to the development of asthma, and are divided into 4 broad groups:

- Those associated with innate immunity and immunoregulation (e.g. toll-like receptor [TLR]-2, TLR-4, TLR-6, TLR-10, interleukin [IL]-10, and transforming growth factor-beta [TGF-β].
- Those associated with atopy and T-helper type 2 (Th2) cell differentiation and function (e.g. IL-4 receptor [IL-4R] and IL-5 receptor [IL-5R].
- Those associated with epithelial biology and immunity of mucous membranes.
- Those associated with pulmonary function and bronchial remodeling (e.g. ADisintegrin and Metalloprotease (ADAM-33)

(Vercelli, 2008)

Risk factors for asthma:

Factors that influence the risk of asthma can be divided into those that cause the development of asthma and those that trigger asthma symptoms, some do both; **Fig (3)**. The former include host factors (which are primarily genetic) and the latter are usually environmental factors ***(Busse and Lemanske, 2001)***.

Recently, the role of pulmonary microbiotic had emerged as a risk factor for developing allergic disease mainly asthma ***(Fouda, 2012)***.

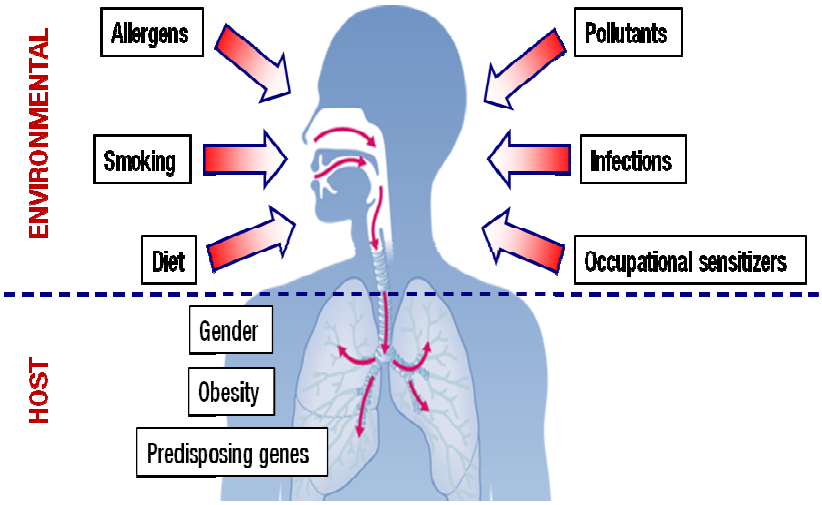

Figure (3): Risk factors of asthma
(www.alvesco.com)

Pathophysiology:

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; **Fig(4)**. The pathophysiology of asthma is complex and involves the following components:

- Airway inflammation.
- Intermittent airflow obstruction.
- Bronchial hyperresponsiveness.

(Michael, 2013)

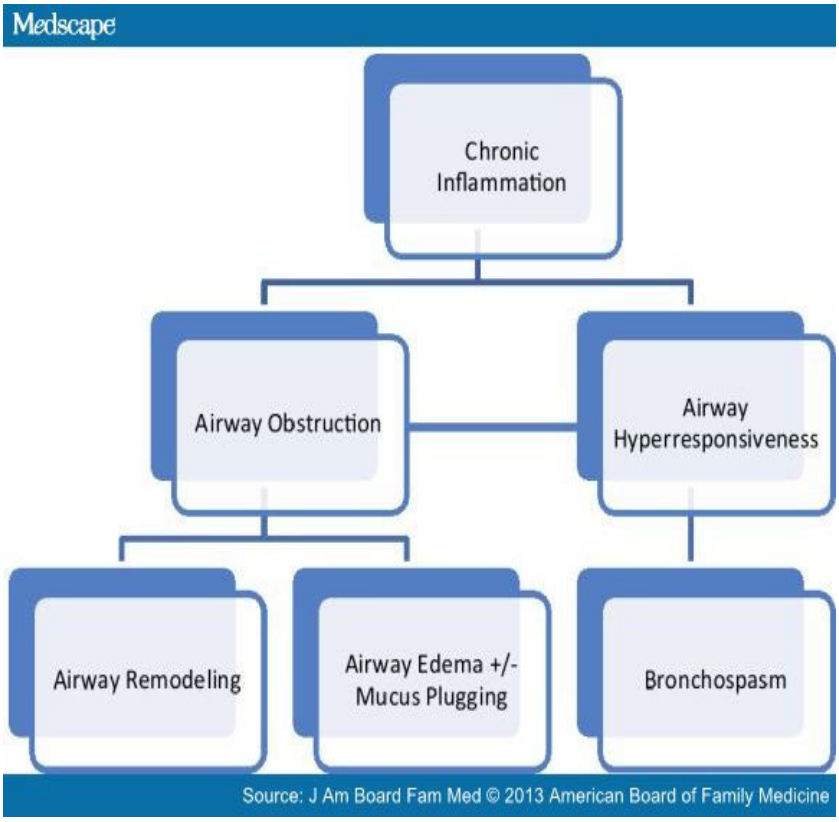

Figure (4): Pathophysiology of asthma

(www. medscape.com)

1) Airway inflammation:

Bronchial inflammation is the most important pathophysiological mechanism of asthma and is the result of complex interactions between inflammatory cells, inflammatory mediators, and structural airway cells. Atopic individuals, who have a genetically determined predisposition to produce large amounts of IgE antibodies specific to environmental allergens/inhalants. The binding of the allergen to IgE on the

membranes of mast cells in the mucosa and submucosa leads to degranulation and activation of these cells, which release preformed mediators such as histamine and platelet-activating factor (PAF) from their granular stores, as well as newly formed mediators produced from arachidonic acid released by cell membranes, such as prostaglandins and leukotrienes. The immediate effects of these substances are vasodilation and vascular extravasation, subsequent swelling of the bronchial wall, mucus hypersecretion, and bronchoconstriction, which are responsible for the clinical manifestations of asthma crises; **Fig (5)** (dyspnea, cough with viscous secretion, wheezing, and tightness of the chest) ***(GINA, 2011)***.

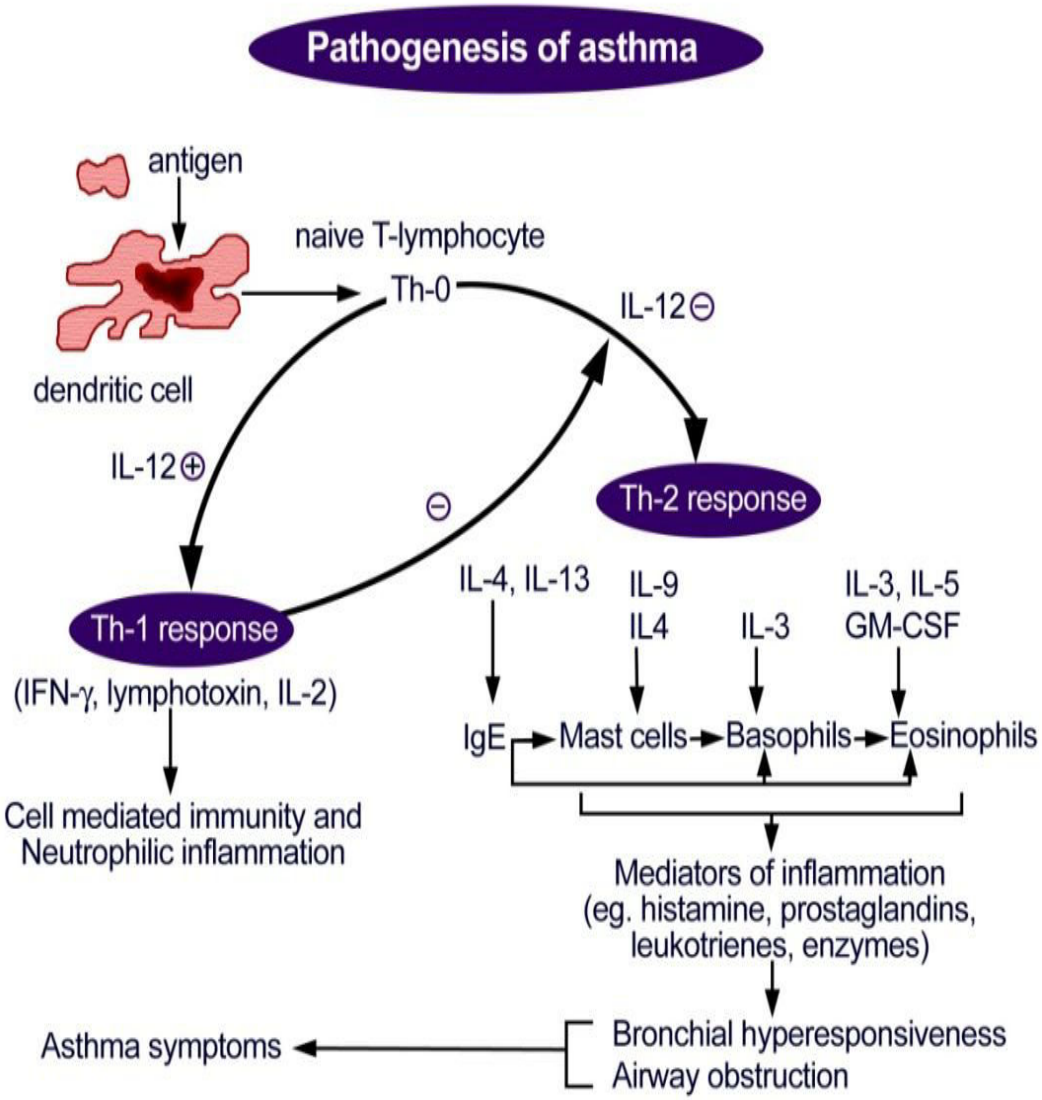

Figure (5): Pathogenesis of asthma
(www.medscape.com)

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; **Fig. (6)** ***(GINA, 2012)***.

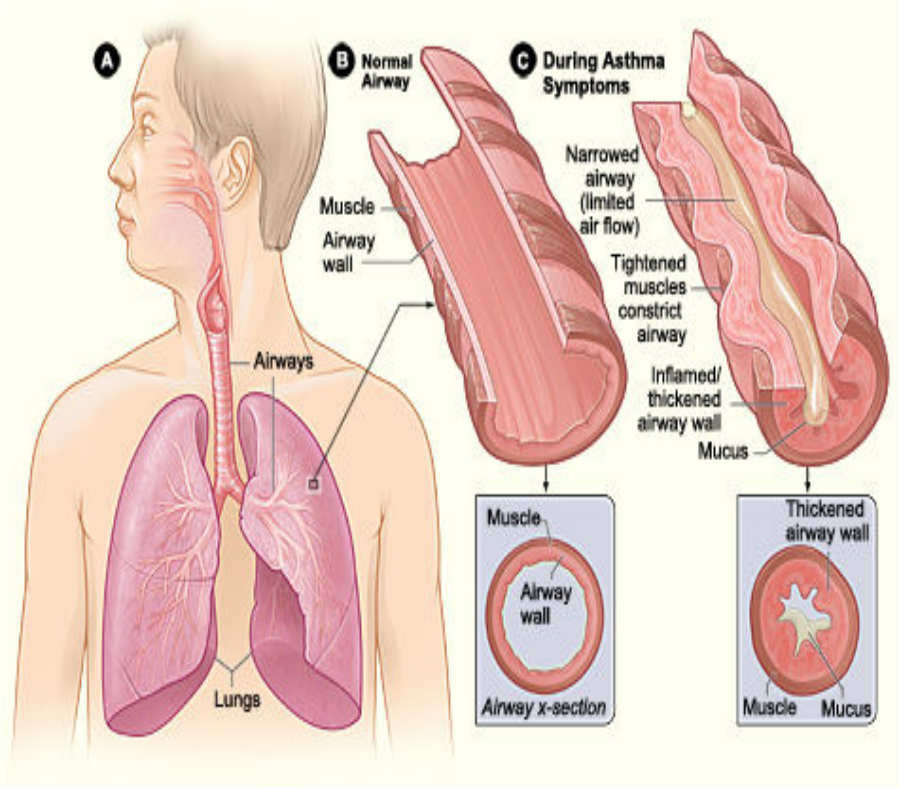

Figure (6): Bronchial hyperresponsiveness and airway narrowing. (***www.wikimedia.org)***

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 (7)**

(Michael, 2013)