INTRODUCTION

Asthma places a huge burden both on individuals and society as a whole. Approximately 300 million people worldwide currently have asthma, with estimates suggesting that asthma prevalence increases globally by 50% every decade. Although from the perspective of both the patient and society, the cost to control asthma seems high, the cost of not treating asthma correctly is even higher. As clinical manifestations of asthma can be controlled with appropriate treatment, there should be no more than occasional flare ups and severe exacerbations should be rare ***(GINA, 2012).***

In the last years, it has been recognized that in addition to the classical role of vitamin D in calcium and bone homeostasis, Vitamin D modulates a variety of processes and regulatory systems including host defense, inflammation, immunity, and repair. Several lung diseases, all inflammatory in nature, may be related to activities of Vitamin D including asthma ***(Herrc et al., 2011).***

Vitamin D deficiency has been blamed as one causes of increased asthma prevalence in the last decades ***(Litonjua and Weiss, 2007).***

Vitamin D plays important role in pathogenesis of asthma as it has potent immunomodulatory effect acting on the cells of the innate immunity. It also reduce the risk of respiratory viral infections which are important initiators of asthma exacerbations ***(Abd-Elmonem et al., 2013).***

Children with asthma appear to be at increased risk of vitamin D insufficiency. Epidemiologic data suggest that low serum vitamin D in children with asthma is associated with more symptoms, exacerbations, reduced lung function, increased medication usage and severe disease ***(Gupta et al., 2012).***

Additionally ***Chinellato et al. (2011)*** stated that lower levels of vitamin D are associated with reduced lung function and increased reactivity to exercise.

AIM OF THE WORK

The aim of this study was to evaluate vitamin D serum level in relation to bronchial asthma severity in children.

Chapter One

BRONCHIAL ASTHMA

Introduction:

Asthma is a disease that defined by its typical clinical, physiological and pathological characteristics. The major feature of clinical history is episodic shortness of breath, cough and wheezing particularly at night or during exercise. The characteristic physiological feature of asthma is variable airway obstruction and its measure bronchial hyper-responsiveness. The main pathological findings are airway inflammation and structural airway changes namely airway remodeling ***(Manuyakorn, 2014).***

Definition of Bronchial Asthma:

Asthma is a chronic airway inflammatory disease with functional and structural changes, leading to bronchial hyperresponsiveness and airflow obstruction ***(Manuyakorn, 2014),*** which may be completely or partially reversed with or without specific therapy. In susceptible individuals, airway inflammation may cause recurrent or persistent bronchospasm, which causes symptoms including wheezing, breathlessness, chest tightness, and cough, particularly at night or after exercise ***(Sharma, 2013).***

Although the cause of childhood asthma has not been determined, contemporary research implicates a combination of environmental exposures and inherent biological and genetic vulnerabilities ***(Liu et al., 2007).***

Epidemiology OF Bronchial Asthma:

Asthma affects an estimated 300 million individuals worldwide. Evidence shows that the prevalence of asthma is increasing, especially in children. Annually, the World Health Organization (WHO) has estimated that 15 million disability-adjusted life-years are lost and 250,000 asthma deaths are reported worldwide ***(GINA, 2010).***

Rates vary between countries with prevalences between 1 and 18%. It is more common in developed than developing countries. Within developed countries it is more common in those who are economically disadvantaged while in contrast in developing countries it is more common in the affluent ***(GINA, 2011).***

One thus sees lower rates in Asia, Eastern Europe and Africa ***(Murry and Nadel, 2010).*** Low and middle income countries make up more than 80% of the mortality ***(WHO, 2007).***

Approximately 479,000 annual hospitalizations (34.6% in individuals aged 18 y or younger) are due to asthma. The cost of illness related to asthma is around $6.2 billion. Each year, an estimated 1.9 million people (47.8% in individuals aged 18 y or younger) require treatment in the emergency department. Among children and adolescents aged 5-17 years, asthma accounts for a loss of 10 million school days and costs caretakers $726.1 million because of work absence ***(National Centre for Health Statics "CDC", 2012).***

In 2007, 9.6 million children (13.1%) had been diagnosed with asthma in their lifetimes. Of this group, 70% had asthma currently, and 3.8 million children (5.2%), nearly 60% of those with current asthma, had experienced at least one asthma attack in the prior year. Boys (14% vs 10% girls) and children in poor families (16% vs 10% not poor) are more likely to have asthma ***(Liu et al., 2011).***

In Egypt asthma has been estimated to affect up to 8.2% of Egyptian children ***(El-Henfy et al., 1994)***. In ***(2009) Zedan et al*** found that the prevalence of asthma among school children in the Nile Delta region was 7.7%.

In Cairo, the overall prevalence of wheezing during 2008 was 14.7% and of physician-diagnosed asthma was 9.4% ***(Georgy et al., 2006).***

Also ***Ali et al. (2010)*** found that asthma prevalence was higher in 6-10 years old students (13%) compared to 11-15 years old students (10%), and the incidence of asthma is higher in urban students(14%) compared to rural students (7.1%).

Also ***Abdallah et al. (2012)*** found that the prevalence of questionnaire – diagnosed asthma was 6.2% in Assiut district. This rate is less than what has been previously estimated in Cairo in 2006. This may be due to the different geographical, social and environmental factors between these two localities.

Approximately 5-8% of all black children have asthma at some time. The prevalence in Hispanic children is reported to be as high as 15%. In blacks, the death rate is consistently higher than in whites ***(Sharma, 2013).***

Asthma predominantly occurs in boys in childhood, with a male-to-female ratio of 2:1 until puberty, when the male-to-female ratio becomes 1:1. Asthma prevalence is greater in females after puberty, and the majority of adult-onset cases diagnosed in persons older than 40 years occur in females. Boys are more likely than girls to experience a decrease in symptoms by late adolescence ***(Morris, 2013).***

In most children, asthma develops before age 5 years, and, in more than half, asthma develops before age 3 years ***(Morris, 2013).***

Mortality and morbidity associated with asthma

Globally, morbidity and mortality associated with asthma have increased over the last 2 decades. This increase is attributed to increasing urbanization. Despite advancements in the understanding of asthma and the development of new therapeutic strategies, the morbidity and mortality rates due to asthma definitely increased from 1980-1995 ***(Sharma, 2013).***

According to report of ***Centers for Disease Control and Prevention (CDC) (2012):*** 1 in 11 children have asthma, 1 in 5 children with asthma went to an emergency department for asthma related care.

Prognosis

The prognosis for asthma is generally good, especially for children with mild disease ***(Sergal et al., 2009).*** Of asthma diagnosed during childhood, half of cases will no longer carry the diagnosis after a decade ***(Elward et al., 2010).***

Eitiology of Bronchial 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. The former include host factors (which are primarily genetic) and the latter are usually environmental factors**.** However, the mechanisms that influence the development and expression of asthma are complex and interactive. For example, genes likely interact both with other genes and with environmental factors to determine asthma susceptibility ***(Ober, 2005).***

A- Host factors

1. Genetics of asthma and atopy

Genetic risk factors likely play acentral role in asthma development. Twin studies support a strong genetic component to asthma (especially childhood asthma) with heritability estimates suggesting that 48–79% of asthma risk is attributable to genetic risk factors ***(Pinto et al., 2008).***

Many regions of the genome have been found to have linkage with the phenotypes of asthma and atopy. Over 70 variants in candidate genes have been reported to be associated

with these phenotypes. The main regions these variants have been found are on chromosomes 2q, 5q, 6p, 11q, 12q, 16q and 17q ***(Blumenthal, 2005).***

Genome-wide association studies (GWASs) have emerged as a powerful approach for identifying novel candidate genes for common, complex diseases ***(Hancock et al., 2009).***

Case-control and family-based association studies have mostly confirmed a link between a novel gene-ADAM33- and asthma. Its restricted expression to mesenchymal cells as well as its association with bronchial hyper-responsiveness and accelerated decline in lung function overtime point strongly to its involvement in the structural airways components of asthma, such as remodeling ***(Holgate et al., 2006).***

Table (1): Factors influencing the development and expression of asthma

Host factors
Genetic , e.g.,
• Genes predisposing to atopy
• Genes predisposing to airway hyper-responsiveness
Obesity
Sex
Environmental factors
Allergens
• Indoor: domestic mites, furred animals (dogs, cats, mice) cockroach allergen, fungi, molds, yeasts
• Outdoor: pollens, fungi, molds, yeast
Infections (predominantly viral)
Occupational sensitizers
Tobacoo smoke
• Passive smoking
• Active smoking
Outdoor/indoor air pollution
Diet

(GINA, 2012)

Atopy:

Over years, major advances have occurred in understanding of the role of atopy in asthma ***(LeSouef, 2009).***

Atopy is defined as a tendency to produce immunoglobulin (IgE) antibobies in response to exposure to allergen, leading to symptoms of asthma, rhino-conjunctivites, and eczema or food allergy. Allergy is defined as a hypersensitivity reaction initiated by specific immunological mechanisms ***(Johansson et al., 2001).***

The order of appearance of atopic diseases seems to Follow a certain pattern referred to as "the atopic march" ***(Johansson et al., 2004).*** The most common manifestations of atopy during the first years are gastrointestinal and eczema symptoms, often related to food allergens, while asthma and rhinitis develop later along with aero-allergen sensitization ***(Juntti, 2008).***

Improved diagnostic classification of atopic diseases based on genotypic variants that identify subsets of atopy (eg, aspirin-sensitive patients with asthma) could help direct pharmacologic interventions by identifying individuals who would be more likely to respond to a particular treatment (eg, leukotriene receptor antagonists) ***(Blumenthal, 2005).***

2. Obesity

Obesity has also been shown to be risk factor for asthma, certain mediators such as leptins (proteins mainly synthesized by adipose tissues, which regulate immune functions) may affect airway function and increase the likelihoods of asthma development ***(Beuther et al., 2006).***

3. Sex

Sex affects the development of asthma in a time-dependent manner. Until age 13–14 years, the incidence and prevalence of asthma are greater among boys than among girls. Studies through puberty have shown a greater incidence of asthma among adolescent and young adult females and a greater proportion of males with remission of asthma ***(DeMarco et al., 2000).*** Before age 12, boys have more severe asthma than girls, with higher rates of admission to hospital. In contrast, adult females have more severe asthma than males, with more hospital admissions ***(Trawick et al., 2001 and Chen et al., 2003).***

Most authors have attributed these changes in prevalence and severity to events of puberty although mechanisms for differences between the sexes have not been established ***(Subbarao et al., 2009).***

B- Environmental factors:

1. Indoor and outdoor allergens:

- ***Indoor allergens:***

Common indoor allergens include house dust mite, cockroach, animal dander, and certain molds. In genetically susceptible children, exposure to these indoor allergens during the critical postnatal period may lead to sensitization in early childhood. Consistent evidence indicates that children

sensitized to common indoor allergens are at several-fold higher risk of asthma and allergy. Due to conflicting evidence from prospective studies, some doubt remains regarding a direct and dose–response relationship between exposure and development of asthma. However, in recent years, evidence has accumulated that exposure to indoor allergen causes asthma and allergy, but this effect may depend on dose and type of allergen as well as the underlying genetic susceptibility of the child ***(Hasan, 2010).***

- ***Outdoor allergens:***

Airborne allergens in the outdoor environment are associated primarily with pollen grains and mold spores and usually induce seasonal symptoms. Exposure varies according to geographic location, season, and weather conditions ***(Scott and Peyton, 2007).***

Fungi are ubiquitous in outdoor air, and their concentration, aerodynamic diameters and taxonomic composition have potentially important implications for human health. Although exposure to fungal allergens is considered a strong risk factor for asthma prevalence and severity ***(Yamamoto et al., 2012).***

However, the relationship between allergen exposure and sensitization in children is not straightforward. It depends on the allergen, the dose and the time of exposure ***(Huss et al., 2001).***

2. Viral respiratory infections

Viral respiratory infections (VRIs) have been related to the onset of recurrent wheezing illness and asthma in infants and are probably the most frequent cause of exacerbations of established disease in children ***(Cantani, 2008).*** During infancy, a number of viruses have been associated with the inception of the asthmatic phenotype. Respiratory syncytial virus (RSV) and parainfluenza virus produce a pattern of symptoms including bronchiolitis that parallel many features of childhood asthma ***(Gern and Busse, 2002).***

A number of long-term retrospective studies of children admitted to the hospital with documented RSV have shown that approximately 40% will continue to wheeze or have asthma into later childhood ***(Sigurs et al., 2000).***

A "hygiene hypothesis" of asthma suggests that exposure to infections early in life influences the development of a child's immune system along a non allergic pathway, leading to a reduced risk of asthma and other allergic diseases ***(DeMeer et al., 2005).***

3. Occupational asthma

Work exposures are a significant contributor to the burden of asthma and, therefore, there is great scientific interest in work-related asthma. Although the majority of cases probably represent work-aggravated asthma, in a relevant proportion of cases, asthma is actually caused by one or more agents present in the workplace ***(Quirce and Sastre, 2011).***

4 -Second hand smoking:

Secondhand smoke can trigger asthma episodes and increase the severity of attacks. Secondhand smoke is also a risk factor for new cases of asthma in preschool aged children who have not already exhibited asthma symptoms. Scientists believe that secondhand smoke irritates the chronically inflamed bronchial passages of children with asthma ***(American Lung Association, 2013).***

Prenatal maternal smoking has been consistently associated with early childhood wheezing. Studies have shown a clear prenatal effect of smoking; this effect is increased when combined with postnatal smoke exposure ***(Subbarao et al., 2009).***

5. Indoor and outdoor air pollutants

Children raised in a polluted environment have diminished lung function, but the relationship of this loss function to the development of asthma is not known ***(GINA, 2010).***

Outbreaks of asthma exacerbations have been shown to occur in relationship of increased levels of air pollution, and this may be related to a general increase in the level of pollutants or to specific allergens to which individuals are sensitized ***(Frideman and Zeiger, 2005).*** However, the role of pollutants in the development of asthma is less well defined.

Similar associations have been observed in relation to indoor pollutants, e.g., smoke and fumes from gas and biomass fuels used for heating and cooling, molds and cockroach infestations ***(GINA, 2010).***

6. Diet

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 and Willers et al., 2007).***

Similarly, higher prenatal vitamin E and zinc levels have been associated with lower risk of development of wheeze up to age 5 years ***(Litonjua et al., 2006).***

However, no protective effect against the development of atopic disease in infants has been shown for maternal diets that excluded certain foods (e.g., cow's milk, eggs) during pregnancy ***(Subbarao et al., 2009).***

Other studies have shown that breastfeeding might have a protective effect against asthma in the first 3 years of life ***(Elliott et al., 2008).***