Introduction

Asthma 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, airflow obstruction within the lung that is often reversible either spontaneously or with treatment ***(GINA, 2012).***

Asthma prevalence has increased very considerably in recent decades such that it is now one of the commonest chronic disorders in the world ***(Anandan et al., 2010).***

Wide variations exist in the symptom prevalence of children with asthma. While severe symptoms among children in less affluent countries are more common, there are more children with any symptoms of asthma in wealthy countries ***(Lai et al., 2009).***

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, 2012).***

Asthma continues to pose a challenge to public health, health care providers, and researchers, and the majority of children with asthma still suffer from exacerbations of symptoms ("attacks") ***(Akinbami et al., 2009).***

Carnitine is a naturally occurring amino acid-like compound, found in nearly all living cells, and plays an important role in β-oxidation of long chain fatty acids in mitochondria. It is a quaternary ammonium compound biosynthesized from the amino acids lysine and methionine. Its name is derived from the fact that it was first isolated from meat (carnus) in 1905. Carnitine occurs in two forms, known as D and L, which are mirror images (isomers) of each other. Only L carnitine is active in the body and is the form found in food ***(Rebouche et al., 2006).***

Carnitine is thus considered a "conditionally essential" nutrient since individuals' requirements might exceed dietary intake during specific disease states.These nutrients include taurine, lipoic acid, choline, and carnitine. They are normally synthesized by the mammalian organism, but may be required under special conditions, such as during long-term parenteral nutrition, by hemodialysis patients, or by premature infants ***(Alesci et al., 2004).***

Carnitine is found in the skeletal and cardiac muscle, kidney, liver and brain in addition to plasma. The lung also contains more than 40 different cell types, most of them involved in lipid metabolism. Pulmonary surfactant, a complex of 90% lipids and 10% lung specifi c apoproteins, is synthesized and secreted from type II cells ***(Andreeva et al., 2007).***

Since L Carnitine has an essential role in the transport of long-chain fatty acids through the mitochondrial membrane in order to ensure efficient β-oxidation of fatty acids, it is important for activation of pulmonary surfactant synthesis ***(Seliger et al., 2007).***

Carnitine deficiency leads to toxic accumulation of long chain fatty acids in the cytoplasm and of acyl CoA in the mitochondria. The accumulated saturated and monounsaturated fats may have different effects on airway inflammation ***(Huang and Pan, 2001).***

Aim Of The Work

The aim of this work is to evaluate serum carnitine levels in children with asthma.

Asthma

Definition:

Asthma 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, airflow obstruction within the lung that is often reversible either spontaneously or with treatment ***(GINA, 2012)***.

Epidemiology:

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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, 2012).***

Childhood asthma is the most common chronic disease among children in the United States. The debilitating effects of this condition are well documented and place a huge burden on millions of children and their families, especially in minority and medically underserved communities. Asthma continues to pose a challenge to public health, health care providers, and researchers, and the majority of children with asthma still suffer from exacerbations of symptoms ("attacks") ***(Akinbami et al., 2009).***

The overall rates of adverse outcomes attributable to asthma have remained relatively constant despite promising progress demonstrated by some innovative intervention efforts, large socioeconomic and ethnic disparities in asthma morbidity and mortality rates continue to widen, and the primary causes of asthma and the reasons for its historically high current prevalence remain elusive ***(Akinbami et al., 2009).***

However, a wide variation in prevalence rates has been documented: studies have revealed low prevalence rates (2%–4%) in Asian countries (especially China and India) and high rates (15%–20%) in the United Kingdom, Canada, Australia, New Zealand and other developed countries ***(Asher et al., 2006).***

Approximately 32.7 percent of all asthma hospital discharges in 2006 were in those under 15, however only 20.1% of the U.S. population was less than 15 years old ***(Centers for Disease Control and Prevention, 2006).***

In 2005, there were approximately 679,000 emergency room visits were due to asthma in those under 15 ***(Centers for Disease Control and Prevention, 2005).***

Approximately 500,000 annual hospitalizations (34.6% in individuals aged 18 y or younger) are due to asthma. In the United States, asthma prevalence, having increased from 1980 to 1996, showed a plateau at 9.1% of children (6.7 million) in 2007 ***(Akinbami et al., 2009).***

According to a study published in Egypt in 2010, the overall prevalence of asthma among children is 14.7% while that of physician-diagnosed asthma is 9.4% ***(Salama et al., 2010).***

Many factors may have contributed to the rise of the problem of bronchial asthma. Increasing air pollution, fast modernization, and widespread construction work are some of the reasons for asthma to thrive. The situation is complicated by poor access to medical services, high price of effective drugs, and poor health education among the affected population ***(Ramos et al., 2006).***

Pathophysiology:

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

Bronchoconstriction: 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 (bronchoconstriction) occurs quickly to narrow the airways in response to exposure to a variety of stimuli including allergens or irritants. Allergen-induced acute bronchoconstriction results from an IgE-dependent release of mediators from mast cells that includes histamine, tryptase leukotrienes, and prostaglandins that directly contract airway smooth muscle ***(Busse and Lemanske, 2001).***

Airway edema: As the disease becomes more persistent and inflammation more progressive, other factors further limit airflow. These include edema, inflammation, mucus hypersecretion and the formation of inspissated mucus plugs, as well as structural changes including hypertrophy and hyperplasia of the airway smooth muscle ***(Holgate and Polosa, 2006).***

Airway hyperresponsiveness: Airway hyperresponsiveness an exaggerated bronchoconstrictor response to a wide variety of stimuli is a major, but not necessarily unique, feature of asthma. The degree to which airway hyperresponsiveness can be defined by contractile responses to challenges with methacholine correlates with the clinical severity of asthma ***(Expert Panel Report 3, 2007).***

The mechanisms influencing airway hyperresponsiveness are multiple and include inflammation, dysfunctional neuro regulation, and structural changes, as inflammation appears to be a major factor in determining the degree of airway hyperresponsiveness. Treatment directed toward reducing inflammation can reduce airway hyperresponsiveness and improve asthma control ***(Expert Panel Report 3, 2007).***

Airway remodeling: Airway remodelling and asthma Airway remodelling refers to structural changes in the bronchial wall causing reduced lung function ***(Durrani et al., 2011)*** in asthmatic patients. These structural changes are diagnosed by histology and are characterised by epithelial damage, thickening of reticular basement membrane and, subepithelial fibrosis, as well as mucus gland and airway smooth muscle hypertrophy and hyperplasia. Remodelling is found in the majority of school age children with problematic severe asthma and the progressive loss of lung function found in these patients is probably caused by remodelling ***(Fitzpatrick and Teague, 2011).***

In some persons who have asthma, airflow limitation may be only partially reversible. Permanent structural changes can occur in the airway; these are associated with a progressive loss of lung function that is not prevented by or fully reversible by current therapy. Airway remodeling involves an activation of many of the structural cells, with consequent permanent changes in the airway that increase airflow obstruction and airway responsiveness and render the patient less responsive to therapy ***(Holgate and Polosa, 2006).***

Regulation of the repair and remodeling process is not well established, but both the process of repair and its regulation are likely to be key events in explaining the persistent nature of the disease and limitations to a therapeutic response ***(Expert Panel Report 3, 2007).***

Development of airway inflammation

Airway inflammation is one of the pathophysiological characteristics of asthma, which is mediated through infiltration of inflammatory cells, including mast cells, and eosinophilic and neutrophilic granulocytes in the airwaywall. This cell infiltration subsequently leads to bronchial hyperresponsiveness (BHR) and, in the case of chronic inflammation, persistent changes of the airways, i.e. airway remodelling ***(Bossley et al., 2012).***

- ***Inflammation***

The level of symptoms and markers of inflammation do not always correlate; some children might have persistent symptoms without any inflammatory cells on histology, whereas other children might have no symptoms between exacerbations but still have increased markers of airway inflammation ***(Chung et al., 2011).***

The aetiology of airway inflammation in asthmatic children varies depending on age. Whereas viral infections, including rhinovirus and respiratory syncytial virus, are linked to obstructive bronchitis in infancy and early childhood, and considered by some to be a combined risk factor with allergen sensitisation ***(Holt et al., 2012).***

Inflammation has a central role in the pathophysiology of asthma. As noted in the definition of asthma, airway inflammation involves an interaction of many cell types and multiple mediators with the airways that eventually results in the characteristic pathophysiological features of the disease: bronchial inflammation and airflow limitation that result in recurrent episodes of cough, wheeze, and shortness of breath. The processes by which these interactive events occur and lead to clinical asthma are still under investigation ***(Expert Panel Report, 2007).***

Moreover, although distinct phenotypes of asthma exist (e.g., intermittent, persistent, exercise-associated, aspirin-sensitive, or severe asthma), airway inflammation remains a consistent pattern. The pattern of airway inflammation in asthma, however, does not necessarily vary depending upon disease severity, persistence, and duration of disease. The cellular profile and the response of the structural cells in asthma are quite consistent ***(Expert Panel Report, 2007).***

- ***Inflammatory Cells:***

Lymphocytes: An increased understanding of the development and regulation of airway inflammation in asthma followed the discovery and description of subpopulations of lymphocytes, T helper 1 cells and T helper 2 cells (Th1 and Th2), with distinct inflammatory mediator profiles and effects on airway function. After the discovery of these distinct lymphocyte

subpopulations in animal models of allergic inflammation, evidence emerged that, in human asthma, a shift, or predilection, toward the Th2-cytokine profile resulted in the eosinophilic inflammation characteristic of asthma ***(Cohn et al., 2004).***

In addition, generation of Th2 cytokines (e.g., IL-4, IL-5, and IL-13) could also explain the overproduction of IgE, presence of eosinophils, and development of airway hyperresponsiveness. There also may be a reduction in a subgroup of lymphocytes, regulatory T cells, which normally inhibit Th2 cells, as well as an increase in natural killer (NK) cells that release large amounts of Th1 and Th2 cytokines ***(Akbari et al., 2006).***

T lymphocytes, along with other airway resident cells, also can determine the development and degree of airway remodeling. Although it is an over simplification of a complex process to describe asthma as a Th2 disease, recognizing the importance of n families of cytokines and chemokines has advanced our understanding of the development of airway inflammation ***(Zimmermann et al., 2003).***

Mast cells: Activation of mucosal mast cells releases bronchoconstrictor mediators (histamine, cysteinylleukotrienes, prostaglandin D2) ***(Galli et al., 2005).***

Although allergen activation occurs through high-affinity IgE receptors and is likely the most relevant reaction, sensitized mast cells also may be activated by osmotic stimuli to account

for exercise-induced bronchospasm (EIB). Increased numbers of mast cells in airway smooth muscle may be linked to airway hyperresponsiveness ***(Brightling et al., 2002).***

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

These cells contain inflammatory enzymes, generate leukotrienes, and express a wide variety of pro-inflammatory cytokines. Increases in eosinophils often correlate with greater asthma severity. In addition, numerous studies show that treating asthma with corticosteroids reduces circulating and airway eosinophils in parallel with clinical improvement ***(Expert Panel Report, 2007).***

However, the role and contribution of eosinophils to asthma is undergoing a reevaluation based on studies with an anti-IL-5 treatment that has significantly reduced eosinophils but did not affect asthma control. Therefore, although the eosinophil may not be the only primary effector cell in asthma, it likely has a distinct role in different phases of the disease ***(Leckie et al., 2000).***

Neutrophils: Neutrophils are increased in the airways and sputum of persons who have severe asthma, during acute exacerbations, and in the presence of smoking. Their pathophysiological role remains uncertain; they may be a determinant of a lack of response to corticosteroid treatment ***(Expert Panel Report, 2007).***

The regulation of neutrophil recruitment, activation, and alteration in lung function is still under study, but leukotriene B4 may contribute to these processes ***(Wenzel, 2006).***

Dendritic cells: These cells function as key antigen-presenting cells that interact with allergens from the airway surface and then migrate to regional lymph nodes to interact with regulatory cells and ultimately to stimulate Th2 cell production from naïve T cells ***(Kuipers and Lambrecht, 2004).***

Macrophages: Macrophages are the most numerous cells in the airways and also can be activated by allergens through low-affinity IgE receptors to release inflammatory mediators and cytokines that amplify the inflammatory response ***(Peters, 2004).***

Epithelial cells: Airway epithelium is another airway lining cell critically involved in asthma ***(Polito and Proud, 1998)***.

The generation of inflammatory mediators, recruitment and activation of inflammatory cells, and infection by respiratory viruses can cause epithelial cells to produce more inflammatory mediators or to injure the epithelium itself. The repair process, following injury to the epithelium, may be abnormal in asthma, thus furthering the obstructive lesions that occur in asthma. Inflammatory Mediators Chemokines are important in recruitment of inflammatory cells into the airways and are mainly expressed in airway epithelial cells ***(Zimmermann et al., 2003).***

New insights in the pathogenesis of asthma suggest that lymphocytes play a role. Airway inflammation in asthma may represent a loss of normal balance between two "opposing" populations of T helper (Th) lymphocytes. Two types of Th lymphocytes have been characterized: Th1 and Th2. Th1 cells produce interleukin (IL)-2 and interferon-α (IFN-α), which are critical in cellular defense mechanisms in response to infection. Th2, in contrast, generates a family of cytokines (interleukin-4 [IL-4], IL-5, IL-6, IL-9, and IL-13) that can mediate allergic inflammation ***(Eder et al., 2006).***

The term "hygiene hypothesis" of asthma illustrates how this cytokine imbalance may explain some of the dramatic increases in asthma prevalence in Westernized countries. This hypothesis is based on the concept that the immune system of the newborn is skewed toward Th2 cytokine generation (mediators of allergic inflammation). Over time, environmental stimuli such as infections activate Th1 responses and bring the Th1/Th2 relationship to an appropriate balance ***(Anderson and Watson, 2001).***

Evidence suggests that the prevalence of asthma is reduced in children who experience some events as certain infections (Mycobacterium tuberculosis, measles, or hepatitis A), rural living ,Exposure to other children (e.g. presence of older siblings and early enrollment in childcare, less frequent use of antibiotics, including in the first week of life and early introduction of fish in the diet, furthermore, the absence of these lifestyle events is associated with the persistence of a Th2 cytokine pattern ***(Goksör et al., 2011).***