Relationship between Serum Level Indoleamine 2, 3-Dioxygenase (IDO) and Level of Asthma Control in Patients with Allergic Bronchial Asthma

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Submitted by

Ahmad Talat Faheem Yehia

M.B.B.Ch. Ain Shams University

Supervised by

Prof. Dr. Maged Mohamed Refaat
Professor of Internal Medicine, Allergy and Clinical Immunology
Faculty of Medicine, Ain Shams University

Dr. Asmaa Saber Moustafa
Lecturer of Internal Medicine, Allergy and Clinical Immunology
Faculty of Medicine, Ain Shams University

Dr. Osama Mohamed Abdel Latif
Lecturer of Internal Medicine, Allergy and Clinical Immunology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
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بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ ورَسُولُهُ والْمُؤْمِنُونَ

صدق الله العظيم

سورة التوبة آية (105)

*I humbly submit my sincere gratitude to Almighty **God**, our creator; all praise is due to Allah, the Lord of the Worlds, the Beneficent, the Merciful, master of the Day of Judgment. Thee do we serve and Thee do we beseech for help.*

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Ahmad Talat Faheem Yehia

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List of Abbreviations

3-OH-KYN	: 3-hydroxy-kynurenine.
APC	: Antigen-presenting cells.
BMI	: Body Mass Index.
CCL	: Chemokines Ligand.
COPD	: Chronic Obstructive Lung Disease.
CpG	: Cytosine-Guanine.
CSF	: Colony Stimulating Factor.
DCs	: Dendritic cells.
EIA	: Exercise Induced Asthma.
FceR	: Fc-epsilon receptors.
FEV1	: Forced Expiratory Volume in 1 second.
FGF	: Fibroblast Growth Factor.
FVC	: Forced Vital Capacity.
GINA	: Global Initiative For Asthma.
ICAM	: Intercellular Adhesion Molecule 1.
ICS	: Inhaled Corticosteroids.
IDO	: Indoleamine 2,3-dioxygenase.
IFN	: Interferon.
IgE	: Immunoglobulin E.
IL	: Interleukins.
KYN	: Kynurenine.
LABA	: Long Acting Beta-2 Agonists.

List of Abbreviations (Cont.)

LCs	: Langerhans Cells.
MBP	: Major basic protein.
ODN	: Oligodeoxynucleotides.
PG	: Prostaglandins.
PUFA	: Polyunsaturated Fatty Acids.
ROS	: Reactive Oxygen Species.
RSV	: Respiratory Syncytial Virus.
SA	: Symptomatic Atopic individual.
SABA	: Short Acting Beta-2 Agonists.
SIT	: Systemic allergen Immunotherapy.
TDO	: Tryptophan 2,3-dioxygenase.
TGF	: Transforming Growth Factor.
TH	: T helper cells.
TNF	: Tumor Necrosis Factor.
TRP	: Tryptophan.
TXA	: Thromboxane.
VCAM	: Vascular cell adhesion molecule.
VEGF	: Vascular Endothelial Growth Factor.
WHO	: World Health Organization.

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Introduction

Bronchial asthma is a disease with multifactor etiology ***(Ito et al., 2006)***. The mutual correlations among the groups of factors predisposing to the development of the disease and the prevalence of asthma are complex in character ***(Masoli et al., 2004).***

The hereditary component of asthma is determined polygenetically ***(Pietras et al., 2011)***. The environmental component is implied significantly by neuroimmune reactions occurring at the molecular level. It should be emphasized that bronchial asthma is a disorder whose primary cause can probably be traced in the disturbed immunoregulatory mechanisms at the lymphocyte level, with secondary overproduction of IgE class antibodies and allergic inflammatory condition ***(Pietras et al., 2011).***

Tryptophan catabolism-dependent mechanisms exert relevant immunoregulatory activities ***(Chen et al., 2009).*** Tryptophan is an essential amino acid that is metabolized through two different biosynthetic pathways: the generation of the neurotransmitter serotonin and the formation of kynurenine derivatives ***(Huber et al.1984).*** This latter pathway is initiated by cleavage of the indole-ring by the enzymes tryptophan pyrrolase (tryptophan 2,3-dioxygenase, TDO) or indoleamine 2,3-dioxygenase (IDO). TDO resides primarily in the liver and is regulated by tryptophan and steroid hormones ***(Von Bubnoff and Bieber, 2012).***

IDO is the predominant extrahepatic enzyme and can be found in several cells, including macrophages, microglia, and dendritic cells, and is preferentially induced by Th1-type cytokine interferon (IFN)–γ. IFN-γ is able to induce both the gene expression and enzymatic activity of IDO ***(Masoli et al., 2004).***

The IDO pathway has been found to contribute substantially to the control of allergic inflammation.

Traditionally recognized for its immunomodulatory role in infection, pregnancy, autoimmunity and neoplasia, current data suggest that a normal induction of IDO activity, which decreases serum tryptophan (trp) levels and increases the levels of trp metabolites, controls the allergic inflammation ***(Pietras et al., 2011).***

Aim of the Study

The aim of this study is to determine the relationship between serum level IDO and the level of asthma control in atopic patients with allergic bronchial asthma.

Bronchial Asthma

Introduction:

Between 100 and 150 million people around the globe, roughly the equivalent of the population of the Russian Federation, suffer from asthma and this number is rising. World-wide, deaths from this condition have reached over 180,000 annually ***(WHO,2014).***

The major contribution to understanding asthma in the nineteenth century was made by Henry Hyde Salter (1823–1871). Salter provided a comprehensive classification of the stimuli associated with acute episodes and their proposed mechanisms. Provocations that operated directly on the air passages were called "extrinsic" and examples included exercise, cold air, laughing, coughing, sneezing, chemical and mechanical irritants and animal and vegetable emanations. Salter also realized that external stimuli were not the cause of the condition and that something else must be operating. Salter believed asthma to involve both neural and vascular mechanisms (***McFadden, 2004).***

Between 1870 and 1910, the importance of environmental influences on homeostasis was gaining notice and the potential pathogenesis of asthma was about to take a new form. By 1906, the concepts of hypersensitivity, allergy, and anaphylaxis were announced (***McFadden, 2004).***

Asthma:

Asthma is defined by the global and initiative for asthma management and prevention GINA as chronic inflammatory disorder affecting the air ways, 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

particularly at night or in the early morning ***(GINA, 2012).***

These episodes are usually associated with widespread, but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment. Asthma attacks are episodic but chronic inflammation is always present (***GINA, 2012)***.

Epidemiology:

Asthma is one of the leading chronic diseases in the world, with about 150 million people estimated to have the condition ***(WHO , 2014).***

Prevalence in Egypt:

A study in the Egyptian journal of bronchology estimated that the overall prevalence of asthma was 7.7% (***Zedan et al., 2009).***

Gender:

Asthma has a higher prevalence in boys than in girls before puberty and a higher prevalence in women than in men in adulthood. Owing to the complexity of the disease, no single straight forward mechanism can explain the gender differences found in asthma. It is still unclear why male predominance of asthma reverses after puberty; however, it is likely that hormonal changes contribute to genetic susceptibility (***Teresa et al., 2012).***

Mortality and Morbidity of Asthma:

It is estimated that asthma accounts for about 250 000 annual deaths worldwide. There are large differences between countries, and the rate of asthma deaths does not parallel prevalence (Fig. 1). Mortality seems to be high in countries where access to essential drugs is low and because delay of

obtaining help during fatal attacks (***Teresa et al., 2012).***

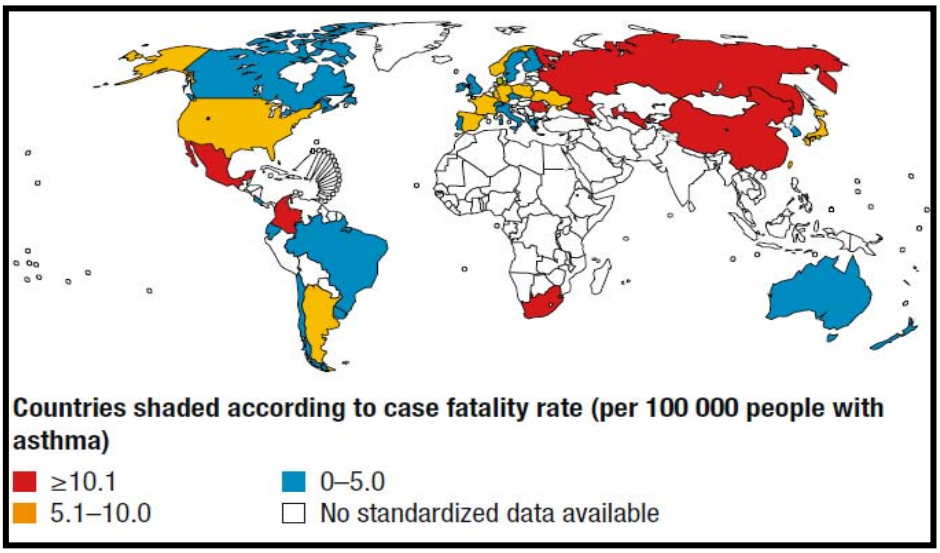

Fig. (1): Mortality and Morbidity of Asthma ***(Teresa et al., 2012).***

Pathogenesis of asthma:

Mechanisms of Asthma:-

Asthma is an inflammatory disorder of the airways, which involves several inflammatory cells and multiple mediators that result in characteristic pathophysiological changes (***GINA, 2012).***

Inflammatory Cells:

Many different inflammatory cells are involved in asthma, although the precise role of each cell type is not yet certain. It is evident that no single inflammatory cell is able to account for the complex pathophysiology of allergic disease, but some cells predominate in asthmatic inflammation (***Barnes, 2002).***

Inflammatory Mediators:-

Over 100 different mediators are now recognized to be involved in asthma and mediate the complex inflammatory response in the airways (Table1) ***(Barnes, 2002)***.

Table 1: Summary of mediators released by the various cell types that are involved in the early and late asthmatic reaction.

Cell source	Released mediators
Induction phase	
T cells	Cytokines (IL-4, IL-5, IL-9, IL-13)
Early asthmatic reaction	
Mast cells	Histamine; proteases (tryptase, chymase, carboxypeptidase); proteoglycans (heparin, chondroitinsulphate E); prostaglandins (PGD2); leukotrienes, cytokines (TNF-α, IL-3, IL-4, IL-5, IL-6, IL-8, IL-16, (CSF); chemokines (CCL2, CCL3, CCL11)
Basophils	Histamine; leukotrienes (cys-LTs: LTC4, LTD4, LTE4); cytokines (IL-4, IL-13)
Late asthmatic reaction	
Eosinophils	MBP; leukotrienes (cys-LTs: LTC4, LTD4, LTE4); cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, IL-11, IL-12, TNF- α, TGF- α, TGF-β, GM-CSF); chemokines (CCL3, CCL5)
Neutrophils	Leukotrienes (LTA4, LTB4); TXA2; cytokines (IL-1 β, IL-6, TNF- α, TGF- β); chemokine (CXCL8); proteases (elastase, collagenase, gelatinase B); microbicidal products (lactoferrin, myeloperoxidase, lysozyme); reactive oxygen intermediates (superoxide, hydrogen peroxide); NO
T cells	Cytokines (IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, GM-CSF); chemokines (CCL1,