Urinary Concentrations of Eosinophil-Derived Neurotoxin in Children with Atopic Dermatitis

Thesis

Submitted for Partial Fulfillment of Master Degree in Pediatrics

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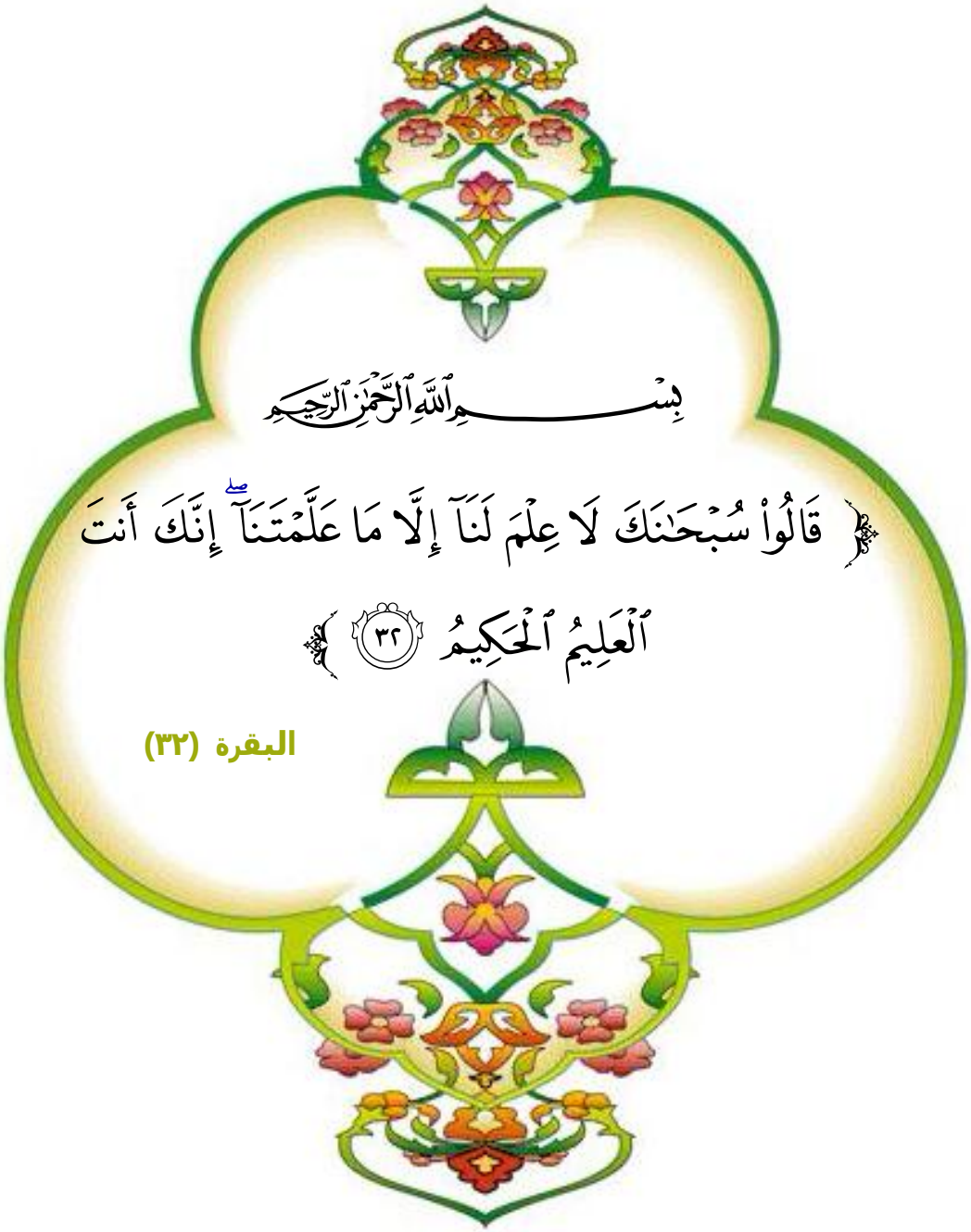
بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ
﴿ قَالُواْ سُبْحَٰنَكَ لَا عِلْمَ لَنَآ إِلَّا مَا عَلَّمْتَنَآ صلے إِنَّكَ أَنتَ
ٱلْعَلِيمُ ٱلْحَكِيمُ ٣٢ ﴾
البقرة (٣٢)

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*At first and foremost thanks to "**ALLAH**" who granted me the power to finish this work.*

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To my colleagues, my patients and to everyone who participated one way or another in this work, I owe my thanks and appreciation.

Amal EL Awady EL Deep

DEDICATION

To

My Mother

My Father

and my Sister

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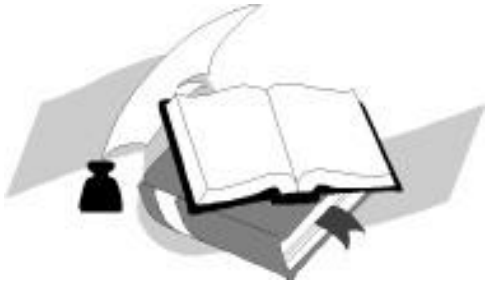
List of Abbreviations

AAEDS	Allergic IgE associated atopic dermatitis/eczema syndrome
ACD	Allergic contact dermatitis
AD	Atopic dermatitis
AEC	Absolute eosinophilic count
AEDS	Atopic eczema/dermatitis syndrome
APC	Antigen presenting cell
BLN	Bi lobed nuclus
CBC	Complete blood count
CCR	Chemokine receptor
CD	Cluster of differentiation
CML	Chronic myeloid leukamia
COX	Cyclo oxygenase
CRTH2	Chemoattractant receptor homologous molecule expressed on Th2 cells
DC	Dentritic cell
DNA	Deoxy ribonucleic acid
ECP	Eosinophil cationic protein
EDN	Eosinophil derived neurotoxin
EPO	Eosinophil peroxidase
EPX	Eosinophil protein X
FPR	Formyl peptide receptor
GM-CSF	Granulocyte macrophage colony stimulating factor
HIV	Human immunodeficiency virus
HLA	Human leucocytic antigen
ICAM	Intercellular adhesion molecule

IDEC	Inflammatory dendritic epidermal cell
IFN-γ	Interferon gamma
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interlukin
ILTs	Ig like transcripts
IQR	Interquartile range
ITIM	Immunoreceptor tyrosine –based inhibitory motif
LB	Lipid bodies
LC	Langerhans cells
LFA	Leucocyte function-associated antigen
LO	Lipo oxygenase
LPL	Lysophospholipase
LTR	Leukotriene receptor
MBP	Major basic protein
MIP	Macrophage inflammation protein
MPDs	Myeloproliferative disorders
mRNA	Messenger ribonucleic acid
NAAEDS	Non allergic IgE associated atopic dermatitis/eczema syndrome
Obj	Objective
PAF	Platelet-activating factor
PGE2	Prostaglandin E2
PMD	Piecemeal degranulation
P. ovale	Pityrasis ovale
RANTES	Regulated upon activation normal T-cell expressed and secreted

RSV	Respiratory synctial virus
SCORAD	Scoring atopic dermatitis index
SD	Standard deviation
SG	Small granules
SIT	Specific immunotherapy
SNAP	Soluble N-ethylmaleimide –sensitive factor attachment protein
SNARE	SNAP receptor
TGF-β	Transforming growth factor-β
Th cells	T helper cells
TNF	Tumor necrosis factor
TNF-NGF	Tumour necrosis factor-nerve growth factor
T Regs	T regulatory cells
TSLP	Thymic stromal lymphopoietin
VCAM-1	Vascular cell adhesion molecular-1

INTRODUCTION
AND
AIM OF THE WORK



Introduction

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease that is characterized by cutaneous hyperactivity to environmental triggers that are innocuous to non-atopic individuals ***(Leung et al., 2004).*** AD is often the first step in the atopic march resulting in asthma and allergic rhinitis ***(Leung and Bieber, 2003).*** There are at least 13 scoring systems and indices for assessment of disease severity in children with AD ***(Chairman and Williams, 2000)***. Problems with inter and intrapersonal variability become an unavoidable issue when using subjective clinical indices to assess the severity of AD. Thus, it would be useful for clinicians to have objective laboratory markers that correlate with clinical aspects of AD to assess the disease severity to manage it properly ***(Leung et al., 2004).***

Eosinophils have a unique contribution in initiating inflammatory and adaptive responses, due to their bidirectional interactions with dendritic cells and T cells, as well as their large panel of secreted cytokines and soluble mediators ***(Blanchard and Rothenberg, 2009).*** Eosinophils play an effector role in AD because they migrate from blood into lesional skin of AD and release cytotoxic mediators such as cytotoxic proteins (eosinophil cationic protein and eosinophil

protein X) ***(Nassenstein et al., 2003),*** lipid mediators, oxygen metabolites and cytokines ***(Barouch et al., 2000).***

Understanding the complex pathophysiology of allergic diseases has been a main challenge of clinical and experimental research for many years. During allergic inflammation, a bidirectional regulation of neuronal stimulation and allergic inflammation has been prospected. Neuromediators (neurotrophins and neuropeptides) represent the key factor of this process, working on either immune or structural cells and exerting neuroimmunomodulatory functions ***(Nockher and Renz, 2006).*** Eosinophils are potentially able to express cell surface receptors for all neurotrophins ***(Nassenstein et al., 2003)***. When eosinophils were cultured in the presence of neurotrophins, an antiapoptotic effect of neurotrophins was observed ***(Braun et al., 1999).***

The eosinophil-derived neurotoxin (EDN, also known as eosinophil protein-X) is best-known as one of the four major proteins found in the large specific granules of human eosinophilic leukocytes. Although it was named for its discovery and initial characterization as a neurotoxin, it is also expressed constitutively in human liver tissue and its expression can be induced in macrophages by proinflammatory stimuli. EDN and its divergent orthologs in rodents have ribonuclease activity, and are members of the extensive RNase A superfamily, although the relationship between the

characterized physiologic functions and enzymatic activity remains poorly understood. Recent explorations into potential physiologic functions for EDN have provided us with some insights into its role in antiviral host defense, as a chemoattractant for human dendritic cells, and most recently, as an endogenous ligand for toll-like receptor ***(Rosenberg ,2008).***