Assessment of Interleukin ١- β in controlled & uncontrolled Type ٢ Diabetic patients.

Thesis

Submitted for Partial Fulfillment of the master degree
Of ***Internal Medicine***

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Mark Nabil Bios Yacoub

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List of Abbreviations

AIDS : Acquired immune-defficiency syndrome
APCs : Antigen presenting cells
BAL : Broncho –alveolar lavage
BMI : Body mass index
BMI : Body mass index
BSF : Beta-cell stimulating factor
CCR٢ : Chemokine receptor-٢
CD : Cluster of differentiation
CIDP : Chronic Inflammatory Demyelinating Polyneuropathy
CVD : Cardivasular disease
CXCL : Chemokine ligand
DCs : Dendritic cells
DKA : Diabetic ketoacidosis
DM : Diabetes mellitus
DME : Diabetic macular edema
DNA : Deoxyribonucleic acid
ECM : Extracellular matrix
ER : Endoplasmic reticulum
ESKD : End-stage kidney disease
FAS : Type-II transmembrane protein that belongs to the tumor necrosis factor (TNF) family. Its binding with its receptor induces apoptosis.
G-CSF : Granulocyte colony stimulating factor
GMB : Glomerular basement membrane
HbA١C : Glycosylated hemoglobin
HHS : Hyperosmolar hyperglycemic state
HNF : Hepatocyte nuclear factor
IADPSG : International Association of Diabetes and Pregnancy Study Groups
IBD : Inflammatory Bowel Disease
IDDM : Insulin dependent DM
IFN-γ : Interferon Gamma
Ig : Immune globulin gamma

List of Abbreviations (cont.)

IL : Interleukin
IL-١ : Interleukin ١
IL-١R١ : Interleukin ١ receptors
IL-١Ra : Interleukin ١ receptor antagonist
IL-١β : Interleukin ١ Beta
IL-٦ : Interleukin ٦
IRMAs : Intra-retinal microvascular abnormalities
IRS : Insulin receptor substrate
Kd : Kilo-dalton
KO : Knockout
LAK : Lymphokine-activated killer cells
LPS : Lipopolysaccharides
MBP : Mannose-binding protein
M-CSF : Monocytes colony stimulating factor
MHC : Major histocompatibility complex
MIP : Macrophage inflammatory protein
MODY : Maturity-onset diabetes of the young
mRNA : Messenger ribo-nueclic acid
MS : Multiple sclerosis
MW : Molecular weight
NHL : Non-Hodgkin's lymphoma
NIDDM : Non Insulin dependent DM
NPDR : Non-proliferative diabetic retinopathy
PDR : Proliferative diabetic retinopathy
RA : Rheumatoid arthritis
SLE : Systemic Lupus Erythromatosis
SOCS : Suppressor of cytokine signaling
TGF : Tumor growth factor
TH : T- helper cells
TLR : Toll like receptors
TNF-α : Tumor Necrosis Factor
UVB : Ultra-violet beam
VEGF : vascular endothelial growth factor

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Introduction

Cytokines are small cell signaling protein molecules which encompass a large and diverse family. They consist of immunomodulating agents such as interleukins and inteferons. Virtually all nucleated cells, especially endothelial, epithelial cells and macrophages are potent producers of Interleukin ١ (IL-١), Interleukin ٦ (IL-٦) and Tumor Necrosis Factor (TNF-α) (١).

Type ٢ diabetes has been recognized as an immune mediated disease leading to impaired insulin signaling and selective destruction of insulin producing β-cells in which cytokines play an important role. Disturbance of anti-inflammatory response could be a critical component of the chronic inflammation resulting in type ٢ diabetes (٢).

Interleukin ١ (IL-١) family of cytokines has important roles in endocrinology and in the regulation of responses associated with inflammatory stress.Interleukin ١ (IL-١) family has a central role in regulation of immune and inflammatory responses. It regulates basic metabolic rate, blood glucose levels, blood pressure *etc*. Also it impairs insulin secretion and induces β-cell apoptosis leading to type ٢ diabetes.Interleukin ١ (IL-١) gene polymorphisms are type ٢ diabetes susceptibility indicators in different populations(٣).

The Interleukin ١ (IL-١) family consists of two pro-inflammatory cytokines, Interleukin ١ Alpha (IL-١α) and Interleukin ١ Beta (IL-١β), and a naturally occurring anti-inflammatory agent, the Interleukin ١ receptor antagonist (IL-١Ra or IL-١RN) (٤).

Interleukin ١ Beta (IL-١β) is a regulator of the body's inflammatory response and is produced after infection, injury, and antigenic challenge. It plays a role in various

diseases, including autoimmune diseases such as rheumatoid arthritis, inflammatory bowel diseases and type ١ diabetes, as well as in diseases associated with metabolic syndrome such as atherosclerosis, chronic heart failure and type ٢ diabetes(٥).

Interleukin ١ Beta (IL-١β) has been a known mediator of Beta-cell dysfunction and death and is potentiated by Tumor Necrosis Factor (TNF-α) and Interferon Gamma (IFN-g), both of which are present at high levels under conditions of insulin resistance. Indeed, Beta-cells are uniquely susceptible to Interleukin ١ Beta's effects as they express higher levels of Interleukin ١ receptors (IL-١R١) than any other cell type in the body (٦). & their subsequent activation resulting in direct promotion of apoptosis, as well as the inhibition of insulin signaling, which is critical for optimal Beta-cell function (٧).

In addition, Interleukin ١ Beta (IL-١β) signaling results in the production of pro-inflammatory mediators that act in a feed-forward autocrine/paracrine manner in Beta-cells and local innate immune cells to amplify these effects (٨).

Aim of work:

The aim of this work is to assess the role of interleukin ١B, in patients with type ٢ Diabetes Mellitus (controlled and uncontrolled) compared to healthy individuals.