

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

Thesis

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

By

Mark Nabil Bios Yacoub

M.B, B.CH

Faculty of Medicine – Ain-Shams University

Supervised by

Prof. Dr. Mohamad Saad Hamed

Professor of Internal Medicine& Endocrinology

Faculty of Medicine - Ain Shams University

Prof. Dr. Enas Mohamed Sabry

Assistant Professor of Internal Medicine& Endocrinology

Faculty of Medicine - Ain Shams University

Dr. Bassem Murad Mostafa

Lecturer of Internal Medicine and Endocrinology

Faculty of Medicine- Ain Shams University

**Faculty of Medicine
Ain Shams University**

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Acknowledgement

First of all, all gratitude is due to **Allah** almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.

Really I can hardly find the words to express my gratitude to **Prof. Dr. Mohamad Saad Hamed**, Professor of Internal Medicine & Endocrinology, Faculty of Medicine - Ain Shams University, for his supervision, continuous help, encouragement throughout this work and tremendous effort he has done in the meticulous revision of the whole work. It is a great honor to work under his guidance and supervision.

I would like also to express my sincere appreciation and gratitude to **Prof. Dr. Enas Mohamed Sabry**, Assistant Professor of Internal Medicine & Endocrinology, Faculty of Medicine - Ain Shams University, for his continuous directions and support throughout the whole work.

I cannot forget the great help of **Dr. Bassem Murad Mostafa**, Lecturer of Internal Medicine and Endocrinology, Faculty of Medicine- Ain Shams University for his invaluable efforts, tireless guidance and for his patience and support to get this work into light.

Last but not least, I dedicate this work to my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.



Mark Nabil Bios Yacoub

List of Contents

	Page
Acknowledgment	--
List of Abbreviations	i
List of Figures	ii
List of Tables	v
Introduction	\
Aim of The Work	ʃ
Review of Literature	ε
Chapter \ : Diabetes Mellitus	ε
Chapter ʃ : Interleukins	ʃ^
Chapter ʄ : Interleukin one (IL-\\β) & Insulin	
Resistance	ʃ^
Patients and Methods	^^
Results	9^
Discussion	1 ʃʃ
Summary and Conclusion	1 εʃ
Recommendations	1 ε ε
References	1 ε 5

Arabic Summary --

List of Abbreviations

AIDS	: Acquired immune-deficiency syndrome
APCs	: Antigen presenting cells
BAL	: Broncho –alveolar lavage
BMI	: Body mass index
BMI	: Body mass index
BSF	: Beta-cell stimulating factor
CCR γ	: Chemokine receptor- γ
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
HbA 1 C	: 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- γ	: Interleukin γ
IL- γ R γ	: Interleukin γ receptors
IL- γ Ra	: Interleukin γ receptor antagonist
IL- γ β	: Interleukin γ Beta
IL- η	: Interleukin η
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-nucleic 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 Erythematosus
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

List of Figures

Fig.	Title	Page
Review of literature		
١	Diagnosis of diabetes mellitus	١٥
٢	Clinical features of DR by fundus examination	٢٥
٣	Major key factors involved in the pathogenesis of diabetic retinopathy	٢٥
٤	Pathogenesis of type II diabetic nephropathy	٢٨
٥	Schematic diagram showing types of diabetic neuropathy	٣٣
٦	Antigen presentation by DCs to naive T cells and other factors	٣٩
٧	Insulin resistance damages Beta cells & leads to autoimmune insulinitis	٧١
٨	Stress Kinases mediate insulin resistance	٧٤
٩	Obesity results in recruitment of macrophages into adipose tissue,	٧٧
١٠	Mechanism of action of interleukin-١ receptor antagonist (IL-١Ra).	٨٣
Results		
١	Comparison between cases & controls regarding Body Mass Index (BMI) (Kg/m ^٢)	١٠٦
٢	Comparison between cases & controls regarding Fasting blood sugar & ٢ hours post prandial (mg\dl).	١٠٨
٣	Lipid profile among different studied groups (mg\dl).	١٠٩
٤	Fasting insulin among different studied groups (uIU/ml).	١١٠
٥	HOMA IR among different studied groups	١١١
٦	Interleukin ١β among different study groups	١١٢
٧	Correlation between IL ١β & fasting blood sugar (FBS) in recently uncontrolled diabetics	

Fig.	Title	Page
۸	Correlation between IL ۱β & ۲ hrs PP in recently uncontrolled diabetics	۱۱۴
۹	Correlation between IL ۱β & fasting blood sugar (FBS) in diabetics	۱۱۶
۱۰	Correlation between IL ۱β & ۲ hrs PP in diabetics	۱۱۶
۱۱	Correlation between IL ۱β & HBA۱C in diabetics	۱۱۷
۱۲	Correlation between IL ۱β & TG in diabetics	۱۱۷
۱۳	Correlation between IL ۱β & HDL in diabetics	۱۱۸
۱۴	Correlation between IL ۱β & HOMA IR in diabetics	۱۱۸
۱۵	Correlation between F. insulin & FBS in recently uncontrolled diabetics	۱۲۰
۱۶	Correlation between F.insulin& BMI in controlled diabetics	۱۲۰
۱۷	Correlation between F.insulin& FBS in controlled diabetics	۱۲۱
۱۸	Correlation between F.insulin& ۲ hrs PP in controlled diabetics	۱۲۱
۱۹	Correlation between F.insulin& HDL in controlled diabetics	۱۲۲
۲۰	Shows correlation of Fasting insulin with ۲ hrs PP blood sugar in diabetics	۱۲۳
۲۱	Shows correlation of Fasting insulin with triglycerides (TG) in diabetics	۱۲۳
۲۲	Correlation between HOMA IR & F.insulin in recently uncontrolled diabetics	۱۲۵
۲۳	Correlation between HOMA IR & F. insulin in controlled diabetics	۱۲۵
۲۴	Correlation between HOMA IR & BMI in controlled diabetics	۱۲۶

Fig.	Title	Page
٢٥	Correlation between HOMA IR & FBS in controlled diabetics	١٢٦
٢٦	Correlation between HOMA IR & ٢ hrs PP in controlled diabetics	١٢٧
٢٧	Correlation between HOMA IR & HBA١C in controlled diabetics	١٢٧
٢٨	Correlation between HOMA IR & TG in controlled diabetics	١٢٨
٢٩	Correlation between HOMA IR & HDL in controlled diabetics	١٢٨
٣٠	Correlation between HOMA IR & F. insulin in diabetics	١٢٩
٣١	Correlation between HOMA IR & FBS in diabetics	١٣٠
٣٢	Correlation between HOMA IR & ٢ hrs PP blood sugar in diabetics	١٣٠
٣٣	Correlation between HOMA IR & cholesterol level in diabetics	١٣١
٣٤	Correlation between HOMA IR & HBA١C in diabetics	١٣١
٣٥	Correlation between HOMA IR & triglycerides level (TG) in diabetics.	١٣٢
٣٦	Correlation between HOMA IR & high density lipoproteins level (HDL) in diabetics	١٣٢

List of Tables

Fig.	Title	Page
Review of literature		
I	Prevelence of diabetes in ٢٠١١ and ٢٠٣٠	٥
II	Etiological classification of diabetes mellitus	٧
III	Comparison between Type I and Type I diabetes mellitus	١١
IV	Criteria for the diagnosis of diabetes mellitus	١٦
V	Clinical manifestations of autonomic diabetic neuropathy	٣٣
Results		
١	Descriptive data of studied cases and controls	١٠٣
٢	Descriptive data of diabetic cases and non diabetics (controls).	١٠٤
٣	Comparison between cases & controls regarding age (yrs).	١٠٥
٤	Comparison between cases & controls regarding Body mass index (BMI) (kg\m ^٢).	١٠٥
٥	Comparison between cases & controls regarding Blood pressure	١٠٦
٦	Comparison between cases & controls regarding Fasting blood sugar & ٢ hours post prandial (mg\dl).	١٠٧
٧	Comparison between cases & controls regarding Lipid profile among different study groups (mg\dl).	١٠٨
٨	Comparison between cases & controls regarding fasting insulin among the studied groups (uIU/ml).	١١٠
٩	Comparison between cases & controls regarding HOMA IR.	١١١
١٠	Comparison between cases & controls regarding Interleukin ١β (pg/ml).	١١٢

Fig.	Title	Page
١١	Correlation between IL ١ β and all other parameters in the ٧ studied groups using Pearson correlation test.	١١٣
١٢	Correlation of Interleukin one Beta (IL ١ β) with other data by using Pearson correlation test in diabetic population as a whole (group ١ plus group ٢)	١١٥
١٣	Correlation between Fasting insulin and all other parameters in the ٧ studied groups using Pearson correlation test.	١١٩
١٤	Correlation between Fasting insulin and all other parameters in the diabetics population using Pearson correlation test	١٢٢
١٥	Correlation between HOMA IR and all other parameters in the ٧ studied groups using Pearson correlation test	١٢٤
١٦	Correlation between HOMA IR and all other parameters in the diabetics group using Pearson correlation test	١٢٩

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Lecturer of Internal Medicine and Endocrinology

Faculty of Medicine- Ain Shams University

**Faculty of Medicine
Ain Shams University**

٢٠١٥

Introduction

Cytokines are small cell signaling protein molecules which encompass a large and diverse family. They consist of immunomodulating agents such as interleukins and interferons. Virtually all nucleated cells, especially endothelial, epithelial cells and macrophages are potent producers of Interleukin 1 (IL-1), Interleukin 6 (IL-6) and Tumor Necrosis Factor (TNF- α) (1).

Type 2 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 2 diabetes (2).

Interleukin 1 (IL-1) family of cytokines has important roles in endocrinology and in the regulation of responses associated with inflammatory stress. Interleukin 1 (IL-1) 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 2 diabetes. Interleukin 1 (IL-1) gene polymorphisms are type 2 diabetes susceptibility indicators in different populations (3).

The Interleukin 1 (IL-1) family consists of two pro-inflammatory cytokines, Interleukin 1 Alpha (IL-1 α) and Interleukin 1 Beta (IL-1 β), and a naturally occurring anti-inflammatory agent, the Interleukin 1 receptor antagonist (IL-1Ra or IL-1RN) (4).

Interleukin 1 Beta (IL-1 β) 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 1 diabetes, as well as in diseases associated with metabolic syndrome such as atherosclerosis, chronic heart failure and type 2 diabetes(°).

Interleukin 1 Beta (IL-1 β) has been a known mediator of Beta-cell dysfunction and death and is potentiated by Tumor Necrosis Factor (TNF- α) and Interferon Gamma (IFN- γ), both of which are present at high levels under conditions of insulin resistance. Indeed, Beta-cells are uniquely susceptible to Interleukin 1 Beta's effects as they express higher levels of Interleukin 1 receptors (IL-1R1) than any other cell type in the body (¶). & 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 (¥).

In addition, Interleukin 1 Beta (IL-1 β) 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 (^).

Aim of work:

The aim of this work is to assess the role of interleukin 1B, in patients with type 2 Diabetes Mellitus (controlled and uncontrolled) compared to healthy individuals.