Serum Concentration of the Interferon-γ-Inducible Chemokine IP-10 (CXCL10) in Type 1 Diabetic Children, Adolescences and Subjects at High Risk of Type 1 Diabetes

Thesis

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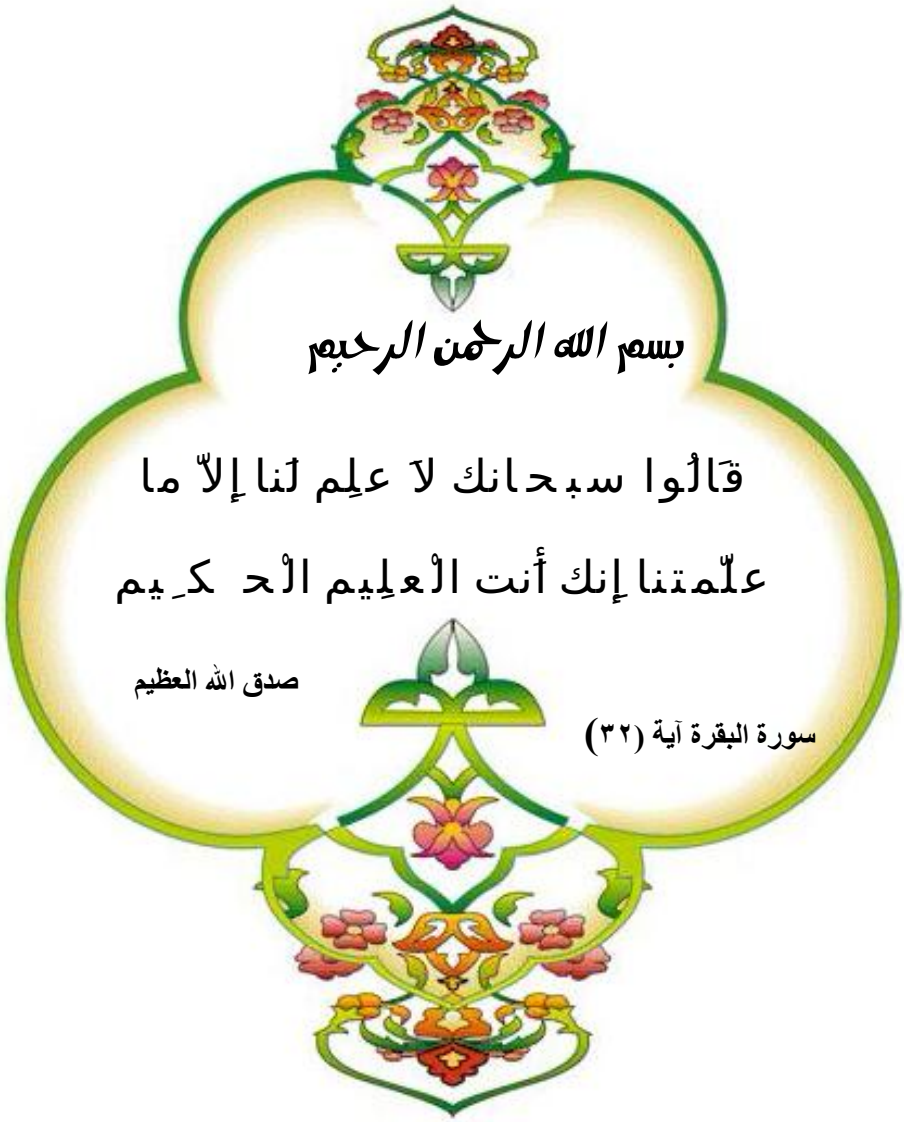

بسم الله الرحمن الرحيم

قَالُوا سبحانك لاَ علِم لَنا إلاّ ما

علّمتنا إنك أنت الْعلِيم الْحـ كـِيم

صدق الله العظيم

سورة البقرة آية (٣٢)

List of Contents

List of abbreviations

ACE : Angiotensin converting enzyme
ADA : American Diabetes Association
AER : Albumin excretion rate
AIA : anti-insulin antibodies
AKt : serine/threnine-specific protein kinase
ARB : ang iotensin II receptor blockers
bFGF : basic Fibroblast Growth Factor
BG : Blood glucose
BMI : Body mass index
CCR4 : C - chemokine receptor type 4
CHC : Chronic Liver Disease
CMP : Cow's milk proteins
CXCL10 : C-X-C motif chemokine 10
D.D : Disease duration
DBP : Diastolic Blood Pressure
DKA : Diabetic ketoacidosis
DM : Diabetes Mellitus
EAE : autoimmune encephalomyelitis
ELISA : Enzyme-linked immunosorbent assay
ERK : Extracellular signal-regulated Kinase
ESRD : End-stage renal disease
FPG : Fasting Plasma Glucose
GAD : Glutamic Acid Decarboxylase antibodies.
GD : Graves' disease
HbA1c : Glycated hemoglobin
HDL : high density lipoprotein
HIV : Human Immundeficiency Virus
HLA : Human leukocyte antigen.
HT : Hashimoto's thyroidites
HZFC : Human zona fasciculata cells
IA2 : Islet antigen 2
IAA : insulin autoantibodies
ICA : Islet Cell Antibody.
IDDM : Insulin-dependent (type 1) diabetes mellitus
IFN-γ : interferone- γ

IgA : Immunoglobulin A
IL : interleukin.
INGAP : Islet neogensis associated protein
IP-10 : inducible protein 10.
ISPAD : International Society of Pediatric and Adolescents Diabetes
JNKs : Jun N –terminal Kinesis.
LCMV : Lymphocytic choriomeningitis virus
LDL : low-density lipoprotein
MAPK : mitogen-activated protein kinase
MC : Mesangial cells:
MHC : major histocompatibility complex.
MIP-1a : Macrophage Inflammatory Proteins-1a
MRBG : mean random blood glucose
mRNA : Messenger ribonucleic acid
NAD : Nicotinamide adenine dinucleotide
NK : Natural killer cell
NPH : neutral protamine Hagedorn
PF4 : Platelet Factor 4
PGN : Proliferative glomerulonephritis
PI3K : phosphoinositide 3-kinase
PKB : Protein Kinase B
RANTES : Regulated on Activation Normal T Cell Expressed and Secreted
ROC : Receiver operator characteristic
SBP : Systolic Blood Pressure
SD : Standard deviation
SDS : Standard Deviation Score
SMBG : Self monitoring of blood glucose
SPSS : Statistical package for social sciences
T1DM : Type 1 Diabetes Mellitus.
T2DM : Type 2 diabetes mellitus
Th1 : T helper 1 cell.
TLRs : Toll like Receptors.
TNF : tumor necrosis factor.
WHO : World Health Organization

List of Tables

List of Tables *(Cont...)*

List of Tables *(Cont...)*

List of Figures

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Introduction

Type 1 diabetes results from the autoimmune destruction of pancreatic B cells. Although the pathogenesis of the initiation and amplification of the autoimmune injury of B cells remains unknown, T-helper 1 (Th1) cells are suggested to be crucial ***(Atkinson and Eisenbarth, 2001).***

In type 1 (insulin-dependant) diabetes mellitus, the migration of immune effector cells (e.g. macrophages and T cells) from the blood stream into the pancreatic islet is necessary to exert their autoreactive potential and commence the local secretion of type 1 pro-inflammatory cytokines such as (IFN)-γ, interleukin (IL)-1B, IL-2, IL-12, IL-18 and tumor necrosis factor (TNF)-α ***(Rabinovitch, 1998).***

The entry of leukocytes into tissue compartment is primarily controlled by adhesion molecules and chemokines ***(Arimilli et al., 2001).***

Whilst the involvement of adhesion molecules in the patyhogensis of the disease ***(Martins et al., 1998)***, less is known about the possible contribution of chemokines.

Chemokines are chemotactic cytokines controlling the recruitment of leukocytes from the blood by regulating integrin adhesivness ***(Arimilli et al., 2001).***

Depending on the position of N-terminal cysteine residues, chemokines can be divided into four highly conserved families namely CXC, CX3C (α chemokines), and C and CC (B chemokines). It has been shown that the migration of CD4+ Th1 and CD4+ Th2 cells is governed by specific chemokines. For example, activated Th1 cells express the chemokines receptors CCR5 and CXCR3, wherever activated Th2 cells express CCR3, CCR4 and CCR8 ***(Armilli et al., 2001).***

The ligand for CXCR3 is CXCL 10, also termed IFN-γ-inducible protein-10 (IP-10). Increasing evidence suggests a role of this chemokine in immumoinflammatory diseases, including multiple sclerosis, autoimmune hepatitis and thyroiditis ***(Negayama et al., 2001).***

CXCL 10/IP-10, one of the CXC chemokine family, has mainly chemotactic activity for activated Th1 cells, Tc1 cells and NK cells expressing CXCR3, So that CXCL 10 is involved in pathogensis of various Th1-dominant autoimmune diseases; such as experimental autoimmune encephalomyelitis (EAE) and rheumatoid arthritis ***(Salomon et al., 2002).***

In human type 1 diabetes, ***Shimada et al. (2001)*** have reported elevated serum levels of CXCL 10, especially in the subgroup with recent onset.

Xin et al. (2007) reported that serum level of (IP 10) in children with type 1 diabetes mellitus is higher than those of control and gradually decrease with long diseased period.

Aim of the Work

The objective of this study is to assess serum concentration of IP-10 in groups of newly diagnosed and long-standing type 1 diabetic patients as well as in subjects at high risk and low risk of developing the disease, depending on whether they will be positive or negative for islet cell antibodies (ICA) and anti-glutamic acid decarboxylase (GAD) antibodies; to study the role of IP-10 in the pathogenesis of type 1 diabetes mellitus.