

**Serum Concentration of the Interferon- $\gamma$ -  
Inducible Chemokine IP-10 (CXCL10) in Type 1  
Diabetic Children, Adolescents and Subjects at  
High Risk of Type 1 Diabetes**

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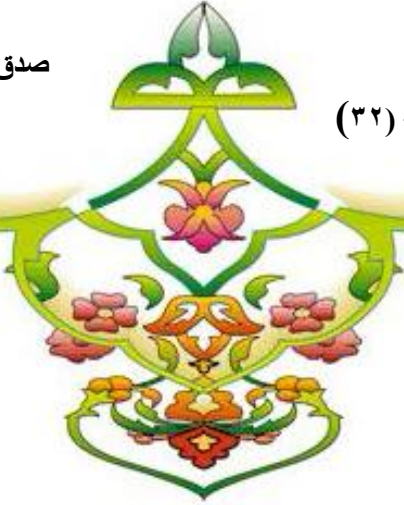
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## **List of abbreviations**

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

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

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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)- $\gamma$ , interleukin (IL)-1B, IL-2, IL-12, IL-18 and tumor necrosis factor (TNF)- $\alpha$  (*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 pathogenesis 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 adhesiveness (*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 ( $\alpha$  chemokines), and C and CC (B chemokines). It has been shown that the migration of CD4<sup>+</sup> Th1 and CD4<sup>+</sup> Th2 cells is governed by specific chemokines. For example, activated Th1 cells express the chemokines receptors CCR5 and CXCR3, whereas activated Th2 cells express CCR3, CCR4 and CCR8 (*Armilli et al., 2001*).

The ligand for CXCR3 is CXCL 10, also termed IFN- $\gamma$ -inducible protein-10 (IP-10). Increasing evidence suggests a role of this chemokine in immunoinflammatory 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 pathogenesis 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.