

# **YKL-40 in Relation to Microvascular Complications in Type 1 Diabetic Children and Adolescents**

Thesis

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By

**Mohamed Fouad Abd El Samee Mohamed**

M.B. BCh. – 2004

Faculty Of Medicine – Cairo University, Fayoum Branch

**Under Supervision of**

**Prof. Dr. Randa Mahmoud Asaad Sayed Matter**

Professor of Pediatrics

Faculty of Medicine – Ain Shams University

**Prof. Dr. Abeer El Sayed Ali Shehab**

Professor of Clinical Pathology

Faculty of Medicine – Ain Shams University

**Dr. Nevine Gamal Andrawes**

Assistant professor of Pediatrics

Faculty of Medicine – Ain Shams University

**Faculty of Medicine  
Ain Shams University  
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## **DEDICATION**

Love and devotion are the sources  
of life

***My Dear mother, the greatest  
person in my whole life,***

***My beloved sincere sister and  
brothers***

I dedicate my work and my whole  
life to you

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# LIST OF ABBREVIATIONS

<b>Abbreviation</b>	<b>The Full Term</b>
<b>ADA</b>	American diabetes association
<b>AIA</b>	Anti-insulin antibody
<b>ANOVA</b>	Analysis of variance
<b>APCs</b>	Antigen presenting cells
<b>BG</b>	Blood glucose
<b>BMI</b>	Body mass index
<b>BP</b>	Blood pressure
<b>CAD</b>	Coronary artery disease
<b>CHI3L1</b>	chitinase-3-like-1
<b>CRP</b>	C- reactive protein
<b>DBP</b>	Diastolic blood pressure
<b>DCCT</b>	Diabetes control and complications trial
<b>DKA</b>	Diabetic keto-acidosis
<b>dL</b>	Diciliter
<b>DM</b>	Diabetes mellitus
<b>DNA</b>	Deoxyribo nucleic acid
<b>DN</b>	Diabetic nephropathy
<b>EDTA</b>	Ethylene diamine tetra-acetic acid
<b>ELISA</b>	Enzyme linked immunosorbent assay
<b>ESRD</b>	End- stage renal disease
<b>FBG</b>	Fasting blood glucose
<b>FPG</b>	Fasting plasma glucose
<b>FT1DM</b>	Fulminant type 1 diabetes mellitus
<b>g</b>	Gram

<b>G</b>	Gravitational force
<b>GADA</b>	Glutamic acid decarboxylase autoantibody
<b>GDM</b>	Gestational diabetes mellitus
<b>HbA1c</b>	Glycated hemoglobin
<b>HDL</b>	High density lipoprotein
<b>HLA</b>	Human leukocyte antigen
<b>HNF</b>	Hepatocyte nuclear factor
<b>HS</b>	Highly significant
<b>hsCRP</b>	high sensitive C-reactive protein
<b>Ht</b>	Height
<b>HRP</b>	Horseradish Peroxidase
<b>IAA</b>	Insulin auto antibody
<b>ICA</b>	Islet cell antibodies
<b>IDDM</b>	Insulin dependent diabetes mellitus
<b>IFG</b>	Impaired fasting glucose
<b>IgG</b>	Immunoglobulin G
<b>IGT</b>	Impaired glucose tolerance
<b>IL</b>	Interleukin
<b>INF</b>	Interferon
<b>INGAP</b>	Islet neogenesis associated protein
<b>LDL</b>	Low density lipoprotein
<b>MCP-1</b>	monocyte chemoattractant protein-1
<b>mg</b>	milligram
<b>MHC</b>	Major histocompatibility complex
<b>mL</b>	milliliter
<b>MODY</b>	Maturity onset diabetes of youth
<b>mRNA</b>	Messenger ribonucleic acid

<b>N</b>	Number
<b>Neuro.D1</b>	Neurogenic differentiation
<b>ng</b>	Nanogram
<b>NS</b>	Non significant
<b>OGGT</b>	Oral glucose tolerance test
<b>S</b>	Significant
<b>SBP</b>	Systolic blood pressure
<b>SC</b>	Subcutaneous
<b>SD</b>	Standard deviation
<b>SDS</b>	Standard Deviation Score
<b>Sig</b>	Significance
<b>SMBG</b>	Self-monitoring of blood glucose
<b>SPSS</b>	Statistical Package for the Social Sciences
<b>T1DM</b>	Type 1 diabetes mellitus
<b>T2DM</b>	Type 2 diabetes mellitus
<b>TNF <math>\alpha</math></b>	Tumor necrosis factor alpha
<b>UAE</b>	Urinary albumin excretion
<b>VSMCs</b>	Vascular smooth muscle cells
<b>WHO</b>	World Health Organization
<b>Wt</b>	Weight

## ABSTRACT

**Background:** Type 1 diabetes mellitus (T1DM) is the most common chronic disease in childhood. It has long-term microvascular complications, which include nephropathy, retinopathy and neuropathy. YKL-40 is a marker of inflammation and endothelial dysfunction, both of which play important roles in the progression of diabetic microvascular complications. Little information has been obtained about serum YKL-40 levels in type 1 diabetic patients.

**Aim:** To assess serum YKL-40 in relation to microvascular complications in type 1 diabetic children and adolescents.

**Patients & Methods:** The study included 50 children and adolescents with type 1 DM, regularly attending the Diabetic Clinic, Children's Hospital, Ain Shams University, with disease duration of 5 years or more. Type 1 diabetic patients were divided into two groups: group 1 included 20 diabetics with microvascular complications, and group 2 included 30 diabetics without microvascular complications. Thirty healthy age and sex matched subjects served as control. The study group were subjected to history taking and clinico-laboratory evaluation including ; age at study entry, sex, weight, height, BMI, diabetes duration, total cholesterol, HDL-cholesterol, LDL-cholesterol, HbA1c, microalbuminuria, fundoscopy and neurological examination. Also, serum YKL-40 was performed, using quantitative enzyme immunoassay technique.

**Results:** Mean Serum YKL-40 among diabetics ( $72.9 \pm 40.9$  ng/ml) was significantly higher than controls ( $33.5 \pm 7.5$  ng/ml), ( $p < 0.001$ ). Also, it was higher in diabetics with microvascular complications, than diabetics without microvascular complications ( $104.2 \pm 45.7$  ng/ml) and ( $52 \pm 17.9$  ng/ml) respectively, ( $p < 0.001$ ). Serum YKL-40 had a significant correlation to patients' age, duration of diabetes, HbA1c, level of microalbuminuria, total cholesterol, triglycerides and HDL-cholesterol. Meanwhile, no correlation was found between serum YKL-40 and weight, height, BMI, systolic BP, diastolic BP, LDL-cholesterol, retinopathy or neuropathy.

**Conclusion:** YKL-40 levels were significantly higher in type 1 diabetic patients with microvascular complications and associated with increased levels of microalbuminuria. Thus, YKL-40 levels can be a tool to assess the risk of diabetic microangiopathy in the early stage in type 1 diabetic patients.

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## **Introduction**

**D**iabetes mellitus is a complex, chronic illness requiring continuous medical care with multifactorial risk reduction strategies beyond glycemic control (*ADA, 2008*). The chronic hyperglycemia of diabetes has metabolic, vascular and neuropathic components that are interrelated; making DM a major health problem with long-term microvascular complications (*Rossing et al., 2005*). They include nephropathy, retinopathy and neuropathy (*ISPAD, 2009*). Microvascular complications are challenging health problems which affect both quality of life and life expectancy in diabetics (*Donaghue et al., 2005; Schram et al., 2005 and Cho et al., 2006*). Therefore, it is important to identify some predictors of diabetic complications in their early stage. Despite exhausting efforts, no markers to predict the prognosis in early stage of diabetes have been identified yet (*Sakamoto et al., 2013*).

Chronic low-grade inflammation and endothelial dysfunction were associated with the occurrence and progression of diabetic microangiopathy including nephropathy (*Schram et al., 2005 and Lin et al., 2008*) retinopathy (*Klein et al., 2009*) in type 1 diabetics.

YKL-40 (chitinase-3-like-1 [CHI3L1], human cartilage glycoprotein-39), is a heparin-, chitin-, and collagen-binding lectin produced by immunologically active cells such as macrophages and neutrophils (*Volck et al., 1998 and Johansen et al., 2006*), also by vascular smooth muscle and endothelial cells, arthritic chondrocytes, cancer cells, and embryonic and fetal cells (*Hakala et al., 1993; Shackelton et al., 1995; Nishikawa and Millis, 2003 and Johansen et al., 2006*). It is a highly conserved mammalian chitinase-like protein (*Hakala et al., 1993; Johansen et al., 2006 and Bussink et al., 2007*). The abbreviation YKL-40 is based on the

one letter code for the first three Nterminal amino acids, tyrosine (Y), lysine (K) and leucine(L) and the apparent molecular weight of YKL-40 (*Hauschka et al ., 1986*).The knowledge about the physiological function and the mechanisms by which YKL-40 mediates its effects is still scarce, but many studies have suggested that YKL-40 has a role in inflammation and remodeling of the extra-cellular matrix (*Johansen et al., 2007 and Ringsholt et al., 2007*). Currently, YKL-40 is known to stimulate growth of fibroblast cells, exert antiapoptosis, and function in angiogenesis and may take part in the innate immune response (*Malinda et al., 1999; Recklies et al., 2002; Ling and Recklies, 2004 and Dickey, 2007*).Important link was demonstrated between YKL-40 and diseases characterized by inflammation or increased tissue remodeling or with cancer (*Johansen et al., 2006 and Johansen et al., 2007*), asthma (*Chupp et al., 2007*), hypertension (*Ma et al., 2012*), insulin resistance (*Kyrgios et al., 2012*), and atherosclerosis ( *Kucur et al., 2007; Michelsen et al., 2010 and Gong et al., 2014*). It may be a potential biomarker and therapeutic target for the related diseases .YKL-40 plays an important role in the pathogenesis of diabetic microangiopathy via intermediating low-grade inflammation and endothelial dysfunction (*Sakamoto et al., 2013*). Also, it was elevated in type 2 diabetics (*Nielsen et al., 2008 and Rondbjerg et al., 2011*) and demonstrated a significant positive association with albuminuria (*Yasuda et al., 2011*). However, little information has been obtained about YKL-40 levels in type 1 diabetics (*Rathcke et al., 2009*).

## **Aim of the work**

To assess serum YKL-40 in relation to microvascular complications in type 1 diabetic children and adolescents.