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

Thesis

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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

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

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

N	Number
Neuro.D1	Neurogenic differentiation
ng	Nanogram
NS	Non significant
OGGT	Oral glucose tolerance test
S	Significant
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SDS	Standard Deviation Score
Sig	Significance
SMBG	Self-monitoring of blood glucose
SPSS	Statistical Package for the Social Sciences
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TNF α	Tumor necrosis factor alpha
UAE	Urinary albumin execration
VSMCs	Vascular smooth muscle cells
WHO	World Health Organization
Wt	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 1diabetic 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 1included 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 ±40.9 ng/ml) was significantly higher than controls (33.5 ±7.5 ng/ml), ($p<0.001$).Also, it was higher in diabetics with microvascular complications, than diabetics without microvascular complications (104.2 ±45.7 ng/ml) and (52±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 1diabetic 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.

Introduction

Diabetes 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 abbreviationYKL-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.