Plasma Orosomucoid in Correlation to Carotid Intima Media Thickness in Type I Diabetes Mellitus Patients

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Dedication

This work is dedicated to …

My beloved father, to whom I owe everything I ever did in my life and will achieve.

My mother for always being there for me

My brothers for their support

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List of Abbreviations

Abb.	Meaning
AGP	Acid glycoprotein
AIA	Anti-insulin antibody
ANOVA	Analysis of variance
APCs	Antigen presenting cells
APPs	Acute phase proteins
AUC	Area under curve
BG	Blood glucose
BMI	Body mass index
CCA	Common carotid artery
CIMT	Carotid intima media thickness
CRP	C-reactive protein
CT	Computed tomography
CVD	Cardiovascular diseases
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic keotacidosis
DM	Diabetes mellitus
DN	Diabetic nephropathy
ECA	External carotid artery
ECG	Echocardiogram
EDIC	Epidemiology of diabetes intervention and complication
EDTA	Ethylenediamine tetracetic acid
ELiSA	enzyme linked immunosorbent assay
ESRD	Endstage renal diseases
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
FT1DM	Fulminant type 1 diabetes mellitus
GADA	Glutamic acid decraboxylase autoantibody
H2	Hertz
HbA1c	Glycated hemoglobin
HDL	High density lipoprotein

List of Abbreviations (cont...)

Abb.	Meaning
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HNF-4	Hepatocyte nuclear factor
IAA	Insulin antibody
ICA	Internal carotid artery
ICA	Islet cell antibody
IDDM	Insulin dependent diabetes mellitus
IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
IMT	Intima media thickness
INGAP	Islet neogenesis associated protein
KCNJII	Inward-rectifier potassium ion channel gene
LDL	Low density lipoprotein
LPS	Lipopolysaccharide
MHC	Major histocompatibility complex
MODY	Maturity onset diabetes of the young
mRNA	Messenger ribonucleic acid
NDS	neuropathy disability score
Neuro.D1	Neurogenic differentiation
NGSP	National Glycohemoglobin Standardization Program
NKT	Natural killer T cell
OGTT	Oral glucose tolerance test
ORM	Orosomucoid
PAI	Plasminogen activator inhibitor
ROC	Receiver operating characteristic
SD	Standard deviation
SMBG	Self monitoring blood glucose
T1DM	Type 1 diabetes mellitus
TNF	Tumor necrosis factors
UAE	Urinary albumin execration

ABSTRACT

Background*:* Diabetes mellitus is a risk factor for atherosclerosis as a macrovascular complication and the major cause of morbidity and mortality in these patients*.*

Objective*:* to determine the level of plasma orosomucoid in children and adolescents with type 1 diabetes mellitus. Also, to determine carotid intima media thickness (CIMT) in those patients. Finally, to assess correlation of plasma orosomucoid and CIMT together and with other clinicopathologic characteristics of those patients.

Subjects and Methods: A total of 60 type 1 diabetic patients participated in the study with mean age (12.8 ± 3.9 years) and 60 healthy age and sex matched controls mean age (12.3 ± 3.3 years). They were subjected to assessment of fasting blood glucose, HbA1c, total cholesterol ,triglycerides, plasma orosomuciod and CIMT by B-mode ultrasound.

***Results*:** There was significant elevation in plasma orosomucoid (1850±940µg/ ml; p<0.001), CIMT (0.7±0.1mm; p<0.001) in diabetic patients compared to controls. Plasma orosomucoid was correlated positively with CIMT (r=0.950; p<0.001). Patients in different albuminiric stage showed significant elevation in microalbuminiric group (2150±710µg/ml; CIMT 0.8±0.1mm; p<0.001).Also, plasma orosomucoid was correlated positively with age, disease duration, FBG, HbA1c, triglycerides, cholesterol and hs-CRP.

Conclusions: The significant elevation in plasma orosomucoid in children and adolescents with type 1 diabetes mellitus with their correlation with CIMT may reflect the role of acute phase protein in the development of atherosclerosis in young type 1 diabetic patients.

Key words: plasma orosomucoid, CIMT, type 1 diabetes mellitus.

INTRODUCTION

Type I diabetes mellitus (T1DM) is an autoimmune disease characterized by pancreatic -cell destruction and an absolute deficiency of insulin. It accounts for approximately 5% to 10% of all cases of diabetes *(Petrovsky and Schatz, 2003, ADA, 2012)*. Diabetes and impaired glucose tolerance have been associated with increased plasma concentrations of various inflammation-sensitive plasma proteins, including fibrinogen, haptoglobin, Alpha-1-antitrypsin, serum amyloid A, C-reactive protein, and orosomucoid *(McMillan, 1989)*.

Orosomucoid is one of the acute phase proteins (APPs) which include C-reactive protein (CRP), serum amyloid A, fibrinogen, mannose binding proteins, complement components. Its normal plasma level concentration between 0.6-1.2 mg/ml (1-3% of plasma protein) *(Tsiakalos et al., 2009)*. Levels of APPs can either increase like orosomucoid or decrease several folds soon after the onset of a systematic inflammatory reaction and synthesized predominantly in the liver *(Ananian et al., 2005)*.

APPs, a known marker of low-grade chronic inflammation, are increased in patients with type 1 diabetes probably independently of glycemic control and the presence of clinical microvascular or macrovascular disease. Increased orosomucoid was an independent, powerful predictor of cardiovascular mortality in normoalbuminuric diabetic patients. Also, it may

be a marker of low-grade inflammation in patients with diabetes *(Christiansen et al., 2005).*

DM is a risk factor for atherosclerosis as a macrovascular complication and the major cause of morbidity and mortality in these patients *(Brownlee, 2001).* Patients with T1DM have more severe progressive coronary artery atherosclerosis *(Cleary et al., 2006).* Carotid intima media thickness (CIMT) is a sensitive screening tool for cardiac evaluation in cardiovascular diseases in T1DM *(Aashima et al., 2013).* Advances in imaging techniques identify early vascular changes through noninvasive ultrasound as Echo & Doppler; these findings include impaired vasodilation and thickening of the artery wall *(Woodman & Watts, 2003).*

Many prospective studies have reported relationships between moderately increased plasma concentrations of inflammation-sensitive plasma proteins and cardiovascular diseases as carotid artery wall thickness which are not completely explained *(Klein et al., 2004).*

It has been suggested that inflammation contributes to the increased incidence of cardiovascular diseases among diabetic subjects *(Lind et al., 2001).*