

**Circulating Osteopontin Levels in
Patients with Type 1 Diabetes Mellitus
and Its Association with Vascular
Complications**

Thesis

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Pediatrics*

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ABSTRACT

Objective: Osteopontin (OPN) is a sialoprotein implicated in different immunity and metabolic pathways. OPN plays a significant role in the development/progression of several autoimmune diseases; interestingly, it was also shown to participate in the acute pancreatic islets response to experimentally-induced diabetes in NOD mice. Furthermore, OPN promotes adipose tissue dysfunction, systemic inflammation and insulin resistance.

Aims of this study: To evaluate circulating Osteopontin (OPN) levels in patients with Type 1 DM in comparison to healthy controls and to explore clinical and biochemical correlates of OPN concentrations in those patients and its association with carotid intima media thickness (CIMT) as a marker of subclinical carotid atherosclerosis.

Design: Cross sectional study.

Methods: We enrolled 60 children and adolescents with type 1 diabetes mellitus and 30 healthy sex and age-comparable controls.

Study population: Underwent medical history taking, clinical evaluation, blood sampling for biochemistry and screening for diabetes complications. Serum OPN levels were measured by enzyme linked immunosorbent assay (ELISA).

Carotid intima media thickness (CIMT) as a marker of subclinical carotid atherosclerosis.

Results:

T1DM patients had significantly higher serum OPN levels than controls (5 (4.75 – 10) v.s 1.3 (1 – 1.5) $\mu\text{g/l}$, $p=0.000$). OPN levels in T1DM were positively correlated with disease duration ($p<0.01$), diastolic blood pressure, albumin excretion rate and Carotid intima media thickness (CIMT) ($p<0.05$).

OPN levels were significantly increased in patients with micro-vascular complications ($p=0.000$).

T1DM patients had significantly increased carotid intima media thickness (CIMT) compared to control group ($p=0.000$) with 21.7% had increased CIMT ($p=0.006$).

CIMT was significantly increased in patients with micro-vascular complications ($p=0.009$). 67.6% of patients with micro-vascular complications had increased CIMT ($P=0.022$).

Analysis of OPN levels in relation to CIMT revealed significant higher levels among patients with increased CIMT than those with normal CIMT ($p=0.014$).

Conclusions: This Cross sectional study demonstrated that patients with T1DM had increased serum OPN levels and CIMT than controls and higher OPN concentrations are associated with an unfavorable metabolic profile and positive micro-vascular complications in these patients.

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List of Abbreviations

Abb.	Full term
ACE	Angiotensin converting enzyme
ADA	American Diabetes Association
AER	Albumin excretion rate
Ang I\II	Angiotensin I\II
ATR	Angiotensin receptor
AUC	Area under the curve
BMI	Body mass index
BMPs	Bone morphogenetic proteins
CIMT	Carotid intima media thickness
CNS	Central nervous system
CSII	Continuous subcutaneous insulin infusion
CT	Computed tomography
CVD	Cardio vascular disease
CVD	Coronary heart disease
DBP	Diastolic blood pressure
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DR	Diabetic retinopathy
ECM	Extra cellular membrane
ECM	Extracellular matrix
ED	Emergency department
EDTA	Ethylene diamine tetra-acetic acid
EEG	Electroencephalography
EGF	Epidermal growth factor
ELISA	Enzyme Linked Immunosorbent Assay
ERK	Extracellular signal regulated kinase
FOXO3	Forkhead box O3
FPG	Fasting plasma glucose
GAD	Glutamic acid decarboxylase

List of Abbreviations (Cont...)

Abb.	Full term
GADA	Glutamic Acid Decarboxylase Antibody
GDM	Gestational Diabetes Mellitus
GFR	Glomerular filtration rate
GIP	Gastric inhibitory polypeptide
GRGDS\ RGD ..	Glycine-Arginine-Glycine-Aspartate-Serine
HBA1c	Glycosylated hemoglobin
HCC	Hepato cellular carcinoma
HDL	High density lipoprotein
HGF	Hepatocyte growth factor
HHS	Hyperglycemic hyperosmolar state
HLA	Human leukocyte antigen
HNF	Hepatocyte nuclear factor
IAA	Insulin autoantibodies
ICA	Islet cell antibodies
IDDM	Insulin-Dependent Diabetes Mellitus
IFG	Impaired Fasting Glucose
IFN	Interferon
IGT	Impaired Glucose Tolerance
IHC	Immunohistochemistry
IL-1\2	Interlukine-1/2
INGAP	Islet neogenesis associated protein
IPF	Insulin promoter factor
IVGTT	Intravenous Glucose Tolerane Test
LADA	Latent autoimmune diabetes of the adult
LDL	Low density lipoprotein
LXRs	Liver X receptors
MALT	Mucosa associated lymphoid tissue
MCP-1	Monocyte chemoattractant protein-1
MMPs	Matrix metalloproteinases

List of Abbreviations (Cont...)

Abb.	Full term
MODY	Maturity onset diabetes of the young
NAFLD	Non-alcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NIDDM	Non Insulin-Dependent Diabetes Mellitus
NO	Nitric oxide
OD	Optical density
OGTT	Oral glucose tolerance test
OPN	Osteopontin
PAD	Peripheral artery disease
PTEN	Phosphatase and tensin homolog
RA	Rheumatoid arthritis
RAS	Renine-angiotensin system
ROC	Receiver Operating Characteristic
RT-PCR	Real-Time Polymerase Chain Reaction
SBP	Systolic blood pressure
SDS	Standard deviation score
SIBLING	Small integrin-binding ligand N-linked glycoprotein
SMAD7	Mothers against decapentaplegic homolog 7
SMC	Smooth muscle cells
STZ	Streptozotocin
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TG	Triglycerides
TGF	Transforming growth factor
TGF-β	Transforming growth factor- β
Th1	T helper1
TLRs	Toll-like receptors
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor