# Association of Cardiac Function and Endothelial Dysfunction with Osteoprotegerin in Children and Adolescents with Type 1 Diabetes Mellitus

#### **Thesis**

# Submitted for partial fulfillment for Master Degree in Pediatrics

By

#### Moaaz Gamal Ibrahim Buckour

(M.B., B. Ch.)

Faculty of Medicine, Cairo University

Supervised by

## Prof. Dr. Eman Monir Sherif

Professor of Pediatrics

Faculty of Medicine – Ain Shams University

## Dr. Nermine Hussein Amr

Assistant Professor of Pediatrics
Faculty of Medicine – Ain Shams University

## Dr. Omneya Ibrahim Youssef

Lecturer of Pediatrics

Faculty of Medicine – Ain Shams University

Pediatric Department
Faculty of Medicine
Ain Shams University

# LIST OF CONTENTS

Title	Page No.
Introduction	1
Aim of the work	4
Diabetes Mellitus	5
osteoprotegerin	38
Cardiovascular complication	63
Flow mediated dilation of brachial artery	98
Subjects and methods	114
Results	132
Discussion	167
Conclusion	299
Recommendations	303
References	190
Arabic summary	

# Acknowledgments

First and foremost, I would like to express my deepest gratitude and thankfulness to Allah for giving me the will and strength to fulfill this work.

My sincere gratitude and unlimited thanks are addressed to Prof. Dr. Eman Monir Sherif, professor of pediatrics, Ain Shams University for her constant advice, encouragement and sincere remarks. It has been a great honor and extreme pleasure for me to proceed with this work under her supervision.

Words cannot express my appreciation to Dr. Nermine
Hussein Amr, assistant professor of Pediatrics Ain Shams
University, for her utmost help, kind indispensable guidance,
cooperative attitude and encouragement in performing this
work. I would like to express my thanks to Dr. Omneya
Ibrahim Youssef, lecturer of pediatrics Ain Shams University,
for her helpful support and cooperation.

I would like to express my thanks to Prof. Dr. Huda Ezelarab, professor of clinical pathology, Ain Shams University and Dr. Karim Ahmed Abd El-Tawab, lecturer of Radiology, Ain Shams University, for their helpful guidance and cooperation to complete this work.

I also extend my sincere thanks and appreciation for the patients who helped me a lot to accomplish this work and wish them good health and wellness.

Finally, I would like to dedicate my work to my family who gave me unconditional encouragement and support, beloved father & mother & uncle Abd El-Ghany and thanks my beloved wife & malek

Moaaz Gamal Buckour

**ACE** : angiotensin converting enzyme

**ACR** : albumin/creatinine ratio

**ADA** : American Diabetes Association

**AGEs** : advance glycation end products

**aIMT** : aortic intimal medial thickness

**A** LV : peak mitral atrial velocity during late diastole of

left ventricle

**Am**: peak late diastolic myocardial velocity of left

ventricle

**AMI** : acute myocardial infarction

**AO** : aortic diameter

A RV :peak mitral tricuspid velocity during late diastole

of right ventricle

At :peak late diastolic myocardial velocity of right

ventricle

**BA** :brachial artery

**bFGF** :basic fibroblast growth factor

**BG** :blood glucose

**BMI** :Body mass index

**BSA** :bovine serum albumin

**CAD** :coronary artery disease

cIMT :carotid intimal medial thickness

**CHD** :chronic heart disease

cm/sec :centimeter per second

**CSII** :Continuous subcutaneous insulin infusion

**CVD** :cardiovascular disease

**DBP** :diastolic blood pressure

**DCCT** : the Diabetes Control and Complications Trial

**DM** :Diabetes Mellitus

**DKA** :diabetic ketoacidosis

**DT LV** :deceleration time of left ventricle

**DT RV** :deceleration time of right ventricle

**ECD** :Endothelial cell dysfunction

**EDV** :end diastolic volume

**Ef** :ejection fraction

**ELISA** :enzyme Linked immunosorbant assay

E LV :peak early mitral filling velocity of left

ventricle

E RV : peak early tricuspid filling velocity of right

ventricle

**Em** : peak early diastolic myocardial velocity of left

ventricle

**ESV** :end systolic volume

**Et** : peak early diastolic myocardial velocity of right

ventricle

**FDCR-1** :follicular dendritic cell-associated receptor 1

**FMD** :flow-mediated dilation

**Fs** : fractional shortening

FT1DM : fulminant type 1 diabetes mellitus

**HbA1c** :Glycosylated hemoglobin

**HC** : Hip circumference

**HDL** :high-density lipoprotein cholesterol

**HF** :heart failure

HLA :human leucocyte antigen

**HNF** :Hepatocyte nuclear factor

**HS** :highly significant

ISPA :International Society for Pediatric and

Adolescent Diabetes

**IMT** :intima-media thickness

**IVRT LV**: isovolumic relaxation time of left ventricle

**IVRT RV**: isovolumic relaxation time of right ventricle

LADA :Latent Autoimmune Diabetes of the Adult

LAD :left atrial diameter

LDL :low-density lipoprotein cholesterol

LVEDD :left ventricular end diastolic dimension

LVESD :left ventricular end systolic dimension

LVMI :left ventricular mass index

**MODY** : Maturity onset diabetes of the young

ms :milliseconds

NO :nitric oxide

**NOD** :non-obese diabetic

**NPH** :Neutral Protamine Hagedom insulin

NS :non significant

**OCIF** :osteoclastogenesis inhibitory factor

**OPG** :osteoprotegerin

**PAD** :Peripheral Artery Disease

**PDGF** :platelet-derived growth factor

**PPAR**γ :peroxisome proliferator-activated receptor gamma

**PWT** :posterior wall thickness

**QUICKI** :Quantitative Insulin Sensitivity Index

**RANKL** :Receptor Activator for Nuclear Factor κ B

Ligand

**RVESP** :right ventricular end systolic pressure

**RVMI** :right ventricular mass index

S :significant

**SBP** :systolic blood pressure

**SD** :standard deviation

**SDS** :standard deviation score

siRNA :short interfering RNA

Sm :peak systolic myocardial velocity of left

ventricle

**SMBG** :self-monitoring of blood glucose

**SMR** :standardized mortality rate

**sRANKL** :soluble receptor activator of nuclear factors-κB

ligand

St :peak systolic myocardial velocity of right

ventricle

SV :Stroke volume

**SWT** :septal wall thickness

**T1D** :Type 1 diabetes mellitus

**T2D** :type 2 diabetes mellitus

TC :Total cholesterol

**TDI** :Tissue Doppler Imaging

TG :Triglycerides

**TNF** :tumor necrosis factor

**TRAIL** :TNF-related apoptosis inducing ligand

**VECs** :vascular endothelial cells

**VSMCs** :vascular smooth muscle cells

**WC** :Waist circumference

**WHO** :world health organization

**WHR** :waist to hip ratio

# **LIST OF TABLES**

Tab. No.	Title Pa	ge No.
Table (1):	Etiological classification of diabetes mellitus	6
Table (2):	The International Society for Pediatric and	
	Adolescents Diabetes's (ISPAD) diagnostic	
	criteria for diabetes	23
Table (3):	The International Society for Pediatric and	
	Adolescents Diabetes's (ISPAD) diagnostic	
	criteria for Diabetes Ketoacidosis	25
Table (4):	different groups of insulin according to their of	onset
	and duration of action	31
Table (5):	Causes of excessive and deficient angiogenes	is
	in diabetes	72
Table (6):	Screening, risk factors and interventions for	
	vascular complications among children and	
	adolescents with type 1 diabetes recommended	d
	by International Society for Pediatric and	
	Adolescents Diabetes	94
Table (7):	Clinical data of the patient group	132

# List of Tables

Tab.	No.	Title	Page No.
Table	e (8):	Clinical data of the control group	133
Table	e (9) :	Laboratory data of the patient group	134
Table	e (10) :	Laboratory data of the control group	134
Table	e (11) :	Radiological data of the patient group	135
Table	e (12) :	Radiological data of the control group	135
Table	e (13)	Echocardiographic findings by M -mode of the patient group	
Table		Echocardiographic findings by M -mode of t control group	
Table		Echocardiographic Doppler data of the patient group	137
Table		Echocardiographic Doppler data of the control group	. 138
Table	e (17) :	Tissue Doppler data (TDI) of the patient group	. 139
Table	e (18) :	Tissue Doppler data (TDI) of the control group	. 140
Table	e (19) :	Left and Right ventricles Tei index values of the patient group	141
Table	e (20) :	Left and Right ventricles Tei index values of the control group	141

Tab.	No.	Title Pag	e No.
Table	e (21) :	Sex distribution among patients and controls	142
Table	e (22) :	Comparison between patients and controls regarding anthropometric data	142
Table	e (23) :	Comparison between patients and controls rega	rding
		blood pressure measurement	143
Table	e (24) :	Comparison between patients and controls	
		regarding laboratory data	144
Table	e (25) :	Comparison between patients with and withou	t
		microalbuminuria as regards serum OPG level.	. 145
Table	e (26) :	Relation between serum osteoprotegerin level	
		and pubertal stage	145
Table	e (27) :	Comparison between patients and controls rega	rding
		FMD of brachial artery, cIMT and aIMT	146
Table	e (28) :	Comparison between patients and controls reg	arding
		Echocardiographic findings by M -mode	147
Table	e (29) :	Comparison between patients and controls reg	arding
		Echocardiographic Doppler data	148

Tab. No.	Title Page	No
Table (30):	Comparison between patients and controls rega	arding
	Tissue Doppler data	. 150
Table (31):	Comparison between patients and controls rega	arding
	Left and Right ventricles Tei index values	152
Table (32):	Correlations between serum osteoprotegerin leand lipid profile in patient group	vel 152
Table (33):	Correlations between serum osteoprotegerin leand disease duration and HbA1C % among patients	evel 154
Table (34):	Correlations between serum osteoprotegerin le and anthropometric data and blood pressure va	
	among patients	154
Table (35):	Correlations between serum osteoprotegerin le	evel
	and cIMT, aIMT and FMD among patients	155
Table (36):	Correlations between total cholesterol level ard different echocardiographic and radiological variables	nd 156
Table (37):	Correlations between Triglycerides level and different echocardiographic and radiological variables.	158
Table (38):	Correlations between serum LDL level and difference and control of the control of	

# List of Tables

Tab. No.	Title	Page No.
Table (39) :	Correlations between HDL level and difference of the concardiographic and radiological variables.	
Table (40):	Multi-Regression Analysis model 1	165
Table (41):	Multi-Regression Analysis model 2	166
Table (42):	Multi-Regression Analysis model 3	166
Table (43):	Multi-Regression Analysis model 4	166