

# **Relations of Epicardial Adipose Tissue Volume, Thyroid Axis Hormones and Microalbuminuria to Coronary Artery Calcium in Type 2 Diabetic Patients**

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا

إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ

الْعَلِيمُ الْكَرِيمُ﴾

(سورة البقرة: ٣٢)



*My work is dedicated to:*

*My dear Family.*



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## List of Abbreviations

2h PG	2 hours plasma glucose during OGTT
<sup>18</sup> F-FDG	<sup>18</sup> F-fluorodeoxyglucose
ABPI	The ankle brachial pressure index
ACCF/AHA	American College of Cardiology Foundation/American Heart Association
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACS	Acute coronary syndrome
ADA	American Diabetic Association
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AGES	Advanced glycation end products
AITD	Autoimmune thyroid dysfunction
Akt2	Protein kinase B
AMPK	5' adenosine monophosphate activated protein kinase
ANDROMEDA	European Trial of Dronedarone in Moderate to Severe Congestive Heart Failure
ANGPTL2	Angiopoietin-like protein 2
ANS	Autonomic Nervous System
ASA	Acetylsalicylic acid
AT	Adipose tissue
AUC	Area under the curve
BAT	Brown adipose tissue
BP	Blood pressure
CAC	Coronary artery calcium
CAD	Coronary artery disease
CAN	Cardiovascular Autonomic Neuropathy
CARDS	Collaborative Atorvastatin Diabetes Study
CCL2	CC-chemokine ligand 2
CCTA	Coronary CT Angiography
CHD	Coronary heart disease
ChREBP	Carbohydrate response element binding protein
C-IMT	Carotid intima media thickness
CRP	C-reactive protein;
CT	Computed tomography
CVD	Cardiovascular diseases
CXCL5	CXC-chemokine ligand 5
D	Deiodinase



## List of Abbreviations

DCCT/EDIC	Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications
DIAD	Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects
DIO2	Deiodinase type 2
DPP	The Diabetes Prevention Program
EAT	Epicardial adipose tissue
EBCT	Electron beam computed tomography
EISNER	Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research
FFA	Free fatty acids;
FFAs	Free fatty acids
FIELD	The Fenofibrate Intervention and Event Lowering in Diabetes study
FPG	Fasting plasma glucose
FRS	Framingham Risk Score
Gi	Inhibitory G protein
GLUT	Glucose transporter
HATS	The HDL Atherosclerosis Treatment Study
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
ICAM	Intercellular adhesion molecule
IFN	Interferon
IL	Interleukin
IL-1Ra	Interleukin-1 receptor antagonist;
iNOS	Inducible nitric oxide synthase
JNK	c-Jun N-terminal kinase;
LDL	Low density lipoprotein cholesterol
MAU	Microalbuminuria
MCP	Monocyte chemoattractant protein
MDCT	Multi-detector computed tomography
MESA	The Multi-Ethnic Study of Atherosclerosis
MI	Myocardial infarction
MMP	Matrix metalloproteinase;
MRI	Magnetic-resonance imaging
mTOR	Mammalian target of Rapamycin
MDCT	Multidetector computed tomography
NADPH	Nicotinamide adenine dinucleotide phosphate
NAMPT	Nicotinamide phosphoribosyltransferase
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III Guidelines



## List of Abbreviations

NE	Norepinephrine
NF- $\kappa$ B	Nuclear factor kappa-B
NGF	Nerve growth factor;
NHANES	National Health and Nutrition Examination Survey
n-HDL	Non- high density lipoprotein
NOS	Nitric oxide synthase
PAI	Plasminogen activator inhibitor
PC	Pyruvate carboxylase
PEPCK	Phosphoenolpyruvate kinase
PET	Positron-emission tomography
PGC-1 alpha	PPAR gamma coactivator-1 alpha
PGK	Phosphoglycerate kinase
PKC	The activation of protein kinase C
PPAR	Peroxisome proliferator-activated receptor
PRDM16	Brown adipocyte differentiation transcription factor PR-domain-missing16
PREDICT	Patients with Renal Impairment and Diabetes undergoing Computed Tomography,
PVAT	Perivascular adipose tissue
OGTT	Oral glucose tolerance test
oxLDL	oxLDL
RANTES	Regulated upon activation normal T cell and secreted
RBP4	Renitol-binding protein 4
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
rT3	Reverse T3
SBP	Systolic blood pressure
sFRP5	Frizzled-related protein 5
SMI	Silent myocardial ischemia
sPLA2-IIA	Secretory type II phospholipase A2
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
T3	Triiodothyronine
TGs	Triglycerides
T <sub>H</sub>	T helper
TH	Thyroid hormones
TLRs	Toll-like receptors
TNF	Tumor necrosis factor
TR	Thyroid receptor
TSH	Thyroid-stimulating hormone





## List of Abbreviations

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UACR	Urinary albumin/ creatinine ratio
UAE	urinary albumin excretion
UCP-1	Uncoupling protein-1
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
VCAM-1	Vascular cell adhesion molecule-1;
VEFG	Vascular endothelial growth factor;
VLDL	Very low-density lipoprotein cholesterol,
VSMC	Vascular smooth muscle cells
WAT	White adipose tissue
WHO	World Health Organization



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# Protocol



## Introduction

Visceral adipose tissue (VAT) may be important in sustaining the proinflammatory background of cardiovascular disease. Epicardial, mesenteric and omental fat are the most important VATs and share the same origin from the splanchnopleuric mesoderm (**Wang et al., 2012**).

Epicardial adipose tissue (EAT) is a special visceral fat depot which surrounds the major branches of the coronary artery and myocardium and is supplied by the coronary artery branches sharing the same myocardial circulation. This close anatomical relationship between EAT and the adjacent coronary artery and myocardium further promotes local paracrine interactions between these tissues (**Sacks and Fain, 2007**).

Also, EAT is related to impaired fasting plasma glucose levels, insulin resistance and hypertension. In addition, its volume is increased in type 2 diabetes mellitus (T2DM) patients and is associated with unfavorable components of metabolic syndrome and coronary atherosclerosis (**Wang et al., 2009**).

Cardiovascular disease is the most significant cause of mortality in T2DM and is responsible from 75% of the deaths. The risk of coronary artery disease (CAD) in patients with T2DM is 2 to 4 times higher compared with normal population. The risk of developing MI in patients with DM without history of CAD is identical with persons with CAD without DM (**Karabulut et al., 2012**).

Microalbuminuria has long been recognized as an important biomarker to predict micro- and macrovascular complications and mortality for patients with T2DM. It is also considered an independent predictor of