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

Thesis
Submitted for Partial Fulfillment of M.D. Degree in Endocrinology and Metabolism

BY

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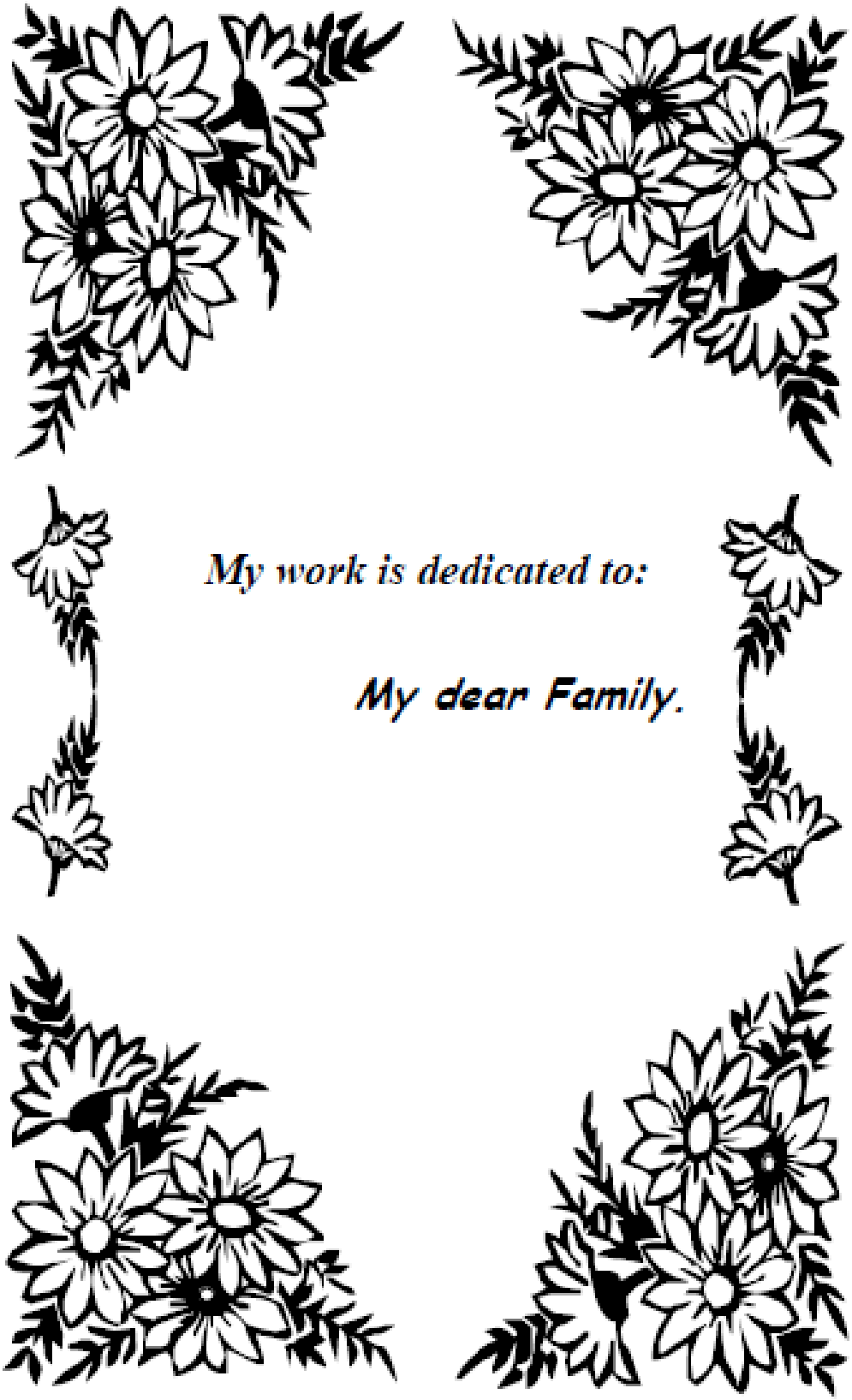
بسم الله الرحمن الرحيم

﴿قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْحَكِيمُ﴾

(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 |
| $^{18}$F-FDG | $^{18}$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 |

| | |
|---|---|
| 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 metalloproitenase; |
| 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 |

| | |
|---|---|
| NE | Norepinephrine |
| NF-κβ | Nuclear factor kappa-β |
| 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 |
| $T_H$ | T helper |
| TH | Thyroid hormones |
| TLRs | Toll-like receptors |
| TNF | Tumor necrosis factor |
| TR | Thyroid receptor |
| TSH | Thyroid-stimulating hormone |

| | |
|---|---|
| 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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# 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