# Value of CD36 in Type 2 Diabetes with Cardiovascular Disease

Thesis

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بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

﴿وَقَالُوا الْحَمْدُ لِلَّهِ الَّذِي هَدَانَا لِهَٰذَا وَمَا كُنَّا

لِنَهْتَدِيَ لَوْلَا أَنْ هَدَانَا اللَّهُ﴾

صدق الله العظيم

سورة الأعراف الآية ٤٣

# *Dedication*

*I would like to express my thankfulness first to* ***Allah for giving me the will and strength to fulfill this work.***

*I dedicate this work to my mother and father for their continuous help, encouragement, prayers and endless giving.*

*I also dedicate this work to my loving wife for her great understanding, support and patience, and to my son who lightened my life and gave me happiness.*

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# Abstract

Diabetes Mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

Type 2 diabetes makes up about 85 to 95% of all diabetes in high-income countries and may account for an even higher percentage in low- and middle-income countries. Type 2 Diabetes is now a common and serious global health problem. Individuals with diabetes mellitus manifest CVD rates up to 4 to 10 times higher than those observed in non-diabetic subjects. Subjects with diabetes also have been shown to have more advanced atherosclerosis.

Accelerated atherosclerosis and CVD risk in diabetes is complex. Patients with type 2 diabetes mellitus commonly have hypertension and manifest a number of abnormalities in systemic lipoprotein metabolism and in inflammatory and coagulation pathways that are predicted to be proatherogenic and to increase CVD risk.

CD36 is a multi-ligand belongs to the class B scavenger receptor family present on the surface of a number of cells such as monocytes/macrophages, platelets, endothelial and smooth muscle cells. Monocyte/macrophage CD36 has been shown to play a critical role in the development of atherosclerotic lesions by its capacity to bind and endocytose oxidized low-density lipoproteins (oxLDL), and it is implicated in the formation of foam cells.

The fatty acid transporter and scavenger receptor CD36 is increasingly being implicated in the pathogenesis of insulin resistance and its progression towards type 2 diabetes and associated cardiovascular complications.

The present study explored the value of CD36 monocytes level in Type 2 diabetes with cardiovascular diseases.

Our study showed increased CD36 expression in Type 2 DM with protective effects of insulin therapy in cholesterol accumulation and may be a useful tool of cardiovascular affection in diabetes.

## Keywords

**CD36=**Cluster of Differentiation36 **CVD=**cardiovascular disease **T2DM=**type 2 diabetes mellitus **oxLDL=**oxidized low-density lipoprotein

# *Abbreviations and acronyms*

| | |
|---|---|
| ABCD2 score | Age, BP, Clinical Features, Duration And Diabetes |
| ABI | Ankle Brachial Index |
| ACC | Acetyl Coenzyme A Carboxylase |
| ACE | Angiotensin Converting Enzyme |
| acLDL | Acetylated low density lipoprotein |
| ACoA | Acetyl-Coenzyme A |
| ACS | Acute Coronary Syndrome |
| ADA | American Diabetes Association |
| ADP | Adenosine Diphosphate |
| ADP | Adenosine Diphosphate |
| AF | Atrial Fibrillation |
| AGEs | Advanced Glycation End-Products |
| AIDS | Acquired Immunodeficiency Syndrome |
| ApoB | Apolipoprotein B |
| AT | Angiotensinogen |
| ATP | Adenosine Triphosphate |
| BBB | Blood Brain Barrier |
| BEST | Beta Blocker Stroke Trial |
| BMI | Body Mass Index |
| BMS | Bare Metal Stent |
| CABG | Coronary Artery Bypass Graft Surgery |
| CAC | Coronary Artery Calcium |
| CAD | Coronary Artery Disease |
| CARDia | Coronary Artery Revascularization In Diabetes |
| CD36 | Cluster Of Differentiation 36 |
| CE | Cardiac Efficiency |
| CHA2DS2-VASc | Cardiac Failure, Hypertension, Age, DM, Stroke And Vascular Disease |

| | |
|---|---|
| CHARM | Candesartan In Heart Failure Assessment Of Reduction In Mortality And Morbidity |
| CHD | Coronary Heart Disease |
| CIMT | Carotid Intima-Media Thickness |
| cIMT | Carotid Intima-Media Thickness |
| CLESH | CD36 LIMP-II Endothelial Microparticle Sequence Homology |
| COX-2 | Cyclooxygenase 2 |
| CPT1 | Carnitine Palmitoyl-Transferase 1 |
| CTGF | Connective Tissue Growth Factor |
| CVD | Cardiovascular Disease |
| DCCT | Diabetes Control And Complications Trial |
| DES | Drug-Eluting STENT |
| DIABHYCAR | Diabetes, Hypertension, Microalbuminuria, Cardiovascular Events And Ramipril |
| DIAMOND | Danish Investigations And Arrhythmia ON Dofetilide |
| DIG | Digitalis Investigation Group |
| DM | Diabetes Mellitus |
| EDIC | Epidemiology Of Diabetes Interventions And Complications |
| EDTA | Ethelene Diamine Tetra Acetic Acid |
| EF | Ejection Fraction |
| eNOS | endothelial nitric-oxide synthase |
| EPCs | Endothelial Progenitor Cells |
| ER | Endoplasmic Reticulum |
| ERKs | Extracellular Signal–Regulated Kinases |
| ET | Endothelin |
| FATP | The Fatty Acid Transport Protein |
| FFA | Free Fatty Acid |
| FITC | Fluorescein Isothiocyanate |
| FPG | Fasting Plasma Glucose |
| Fyn | Proto-Oncogene Tyrosine-Protein Kinase Fyn |

| | |
|---|---|
| GCK | Glucokinase |
| GDM | Gestational Diabetes Mellitus |
| GHRP | Growth Hormone-Releasing Peptide Heraxelin |
| GIP | Gastric Inhibitory Polypeptide |
| GLP-1 | Glucagon-Like Peptide-1 |
| GLUT-4 | Glucose Transporter Type 4 |
| H3K4 | Histone H3 Methylated Lys4 |
| $HbA_{1c}$ | Hemoglobin $A_{1C}$ |
| HDL | High Density Lipoprotein |
| HIV | Human Immunodeficiency Virus |
| HMGCoA | 3-Hydroxy-3-methylGlutaryl-CoA |
| HNF | Hepatocyte Nuclear Factor |
| hsCRP | high sensitive C-reactive protein |
| hsIL6 | high sensitive Interleukin 6 |
| HSP | Hexosamine Pathway |
| IAPP | Islet Amyloid Polypeptide |
| IDF | International Diabetes Federation |
| IFG | Impaired Fasting Glucose |
| IGT | Impaired Glucose Tolerance |
| IL | Interleukin |
| iNO | Inducible Nitric Oxide |
| IPF | Insulin Promoter Factor |
| IR | Insulin Resistance |
| IRS | Insulin Receptor Substrate |
| IRS-1 | Insulin Receptor Substrate 1 |
| JNK | Jun N-Terminal Kinase |
| KDa | Dalton |
| LAD | Left Anterior Descending Artery |

| | |
|---|---|
| LCFAs | Long-Chain Fatty Acids |
| LDL | Low Density Lipoprotein |
| LEAD | Lower Extremity Artery Disease |
| LIMP-II | Lysosomal Integral Membrane Protein II |
| LV | Left Ventricular |
| LVEF | Left Ventricular Ejection Fraction |
| Lyn | Lck/Yes Novel Tyrosine Kinase |
| MAP | Mitogen Activated Protein |
| MAPKs | Mitogen-Activated Protein Kinase |
| MBL | Mannose Binding Lectin |
| MCD | Malonyl-Coenzyme A Decarboxylase |
| MCoA | Malonyl-Coenzyme A |
| MCP | Monocyte Chemotactic Protein |
| MI | Myocardial Infarction |
| MIP | Macrophage Inflammatory Proteins |
| MoAbs | Monoclonal Antibodies |
| MODY | Maturity-Onset Diabetes Of The Young |
| MPs | Microparticles |
| mRNA | Messenger Ribonucleic Acid |
| NADPH | Nicotinamide Adenine Dinucleotide Phosphate |
| NCDs | Non-Communicable Diseases |
| NDM | Neonatal Diabetes Mellitus |
| NFκB | Nuclear Factor Kb |
| NGSP | National Glycohemoglobin Standardization Program |
| NIDD KD | National Institute Of Diabetes And Digestive And Kidney Diseases |
| NLRP3 | NOD-Like Receptor Family, Pyrin Domain Containing 3 |
| NO | Nitric Oxide |
| NPV | Negative Predictive Value |

| | |
|---|---|
| OGTT | Oral Glucose Tolerance Test |
| ox-LDL | Oxidative Modified Low Density Lipoproteins |
| PAD | Peripheral Arterial Disease |
| PAI | Plasminogen Activator Inhibitor |
| PCI | Percutaneous Coronary Intervention |
| PCR | Polymerase chain reaction |
| PDH | Pyruvate Dehydrogenase |
| PDK4 | Pyruvate Dehydrogenase Lipoamide Kinase Isozyme 4 |
| PDX | Pancreatic And Duodenal Homeobox |
| PFA | Platelet Function Analyzer |
| PfEMP-1 | Plasmodium Falciparum Erythrocyte Membrane Protein 1 |
| PG | Plasma Glucose |
| PGF2α | Prostaglandin F2alpha |
| PI3K | Phosphoinositide 3-Kinase |
| PKC | Protein Kinase C |
| PPARγ | Peroxisome Proliferator Activated Receptor Gamma |
| PPV | Positive Predictive Value |
| RAGEs | Receptors Advanced Glycation End-Products |
| RAS | Renin Angiotensin System |
| RCTs | Randomized Controlled-Trials |
| ROS | Reactive Oxygen Species |
| RR | Relative Risk |
| sCD36 | Soluble Form Cluster Of Differentiation 36 |
| SOLVD | Studies Of Left Ventricular Dysfunction |
| SPSS | Statistical Program For Social Science |
| SR-B | Scavenger Receptor B |
| Src | Proto-Oncogene Tyrosine-Protein Kinase Src |
| SREBP | Sterol regulatory element binding proteins |

| | |
|---|---|
| STEMI | ST Elevation Myocardial Infarction |
| T1DM | Type 1 Diabetes Mellitus |
| T2DM | Type 2 Diabetes Mellitus |
| TGs | Triglycerides |
| TIA | Transient Ischemic Attack |
| TLR | Toll-Like Receptors |
| TNF-α | Tumor Necrosis Factor alpha |
| tPA | Tissue Plasminogen Activator |
| TSR | Thrombospondin |
| UCP | Uncoupling Protein |
| UKPDS | Uk Prospective Diabetes Study |
| UT | Urotensin |
| VADT | Veterans Affairs Diabetes Trial |
| VCAM | Vascular Cell Adhesion Molecule |
| VLDL | Very Low-Density Lipoprotein |
| VSMC | Vascular Smooth Muscle Cell |

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