Detection of Silent Myocardial Ischemia In Asymptomatic Diabetic Patients

Thesis
Submitted in partial fulfillment for the requirement of M.Sc degree in Cardiology

By

Walid Mohamad Sabry El –Tahlawy
M.B.B.CH.

Supervised by

Prof. Dr. Salah El-Din H. Demerdash

Professor of Cardiology
Faculty of Medicine -Ain Shams University

Dr. Mona Mostafa Ryan

Asst. Prof of Cardiology
Faculty of Medicine -Ain Shamas University

Dr. Mona Mohamad Abdel Salam

Lecture of Internal Medicine & Endocrinology
Faculty of Medicine -Ain Shams University

Faculty of Medicine
Cardiology Department
Ain Shams University
٢٠١١

Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Patients

By:

Walid Mohamad Sabry El –Tahlawy
M.B.B.Ch.

ABSTRACT

Given the elevated risk of cardiovascular events and the higher prevalence of silent ischemia of coronary artery disease in diabetic patients.

OBJECTIVE: To assess the incidence and risk factors of silent myocardial ischemia in asymptomatic patients with type ٢ diabetes.

PATEINT AND METHODS: ٣٠ patients with type ٢ diabetes, aged ٣٥-٦٨ years, with no known or suspected coronary artery disease, were assigned to stress-rest technetium-٩٩m sestamibi SPECT myocardial perfusion imaging.

RESULTS:Thirty three (٣٣,٣٪) of screened patients had perfusion defects suggestive of ischemia. These patients were older with larger duration of uncontrolled diabetes mellitus. Microalbuminuria (٨٠٪) was prevalent among patients with silent ischemia. These patients had exercise induced symptoms (٦٠٪) and ECG changes (٤٠٪) suggestive of ischemia. The risk for silent myocardial ischemia is increased with advanced age, longer duration of diabetes mellitus, as well as smoking and positive family history of IHD. Patients with uncontrolled diabetes mellitus and/or with microalbuminemia are at increased risk for myocardial ischemia. The development of symptoms or the presence of ECG changes during stress test in asymptomatic diabetic patients should warrant a deeper and specific testing for CAD.Male and female with type II diabetes mellitus are under comparable risk for CAD.

CONCLUSION: In light of the results of the present study we concluded that: Silent myocardial ischemia was found in ٣٣,٣٪ of diabetic patients. The risk for silent myocardial ischemia is increased with advanced age, longer duration of diabetes mellitus, as well as smoking and positive family history of IHD. Patients with uncontrolled diabetes mellitus and/or with microalbuminemia are at increased risk for myocardial ischemia. The development of symptoms or the presence of ECG changes during stress test in asymptomatic diabetic patients should warrant a deeper and specific testing for CAD. Male and female with type II diabetes mellitus are under comparable risk for CAD.

CONTENTS

LIST OF ABBERVIATIONS

CAD	*coronary artery disease*
SMI **MPI**	*silent myocardial ischemia* *myocardial perfusion scan*
SPECT	*Single-photon Emission Computer Tomography.*
PPAR	*peroxisome proliferator-activated receptor*
AGEP	*advanced glycation end products.*
CRP	*C-reactive protein.*
PAI-١	*plasminogen activator inhibitor-1.*
SAA	*serum amyloid A protein.*
TF	*tissue factor.*
TPA	*tissue-type plasminogen activator.*
NF-kappa-B	*nuclear factor-kappa-B*
HDL	*high-density lipoprotein*
LDL	*low-density lipoprotein*
cGMP	*cyclic guanosine monophosphate*
cAMP	*cyclic adenosine monophosphate*
TNF-alpha	*Tumor Necrosis Factor-alpha*
VCAM-١	*vascular cell adhesion molecule-1*
IL-٦	*Interleukin-6*
ACS	*Acute Coronary Syndrome*
STEMI	*ST-segment elevation myocardial infarction*
NSTEMI	*non-ST-segment elevation myocardial infarction*
٩٩mTc	*Technetium-99m*
CMR	*cardiac magnetic resonance*
MRA	*magnetic resonance angiography*
MRI	*magnetic resonance Imaging*
rtPA	*Tissue plasminogine activator*
PAD	*Peripheral arterial disease*
PVD	*peripheral vascular disease*
CHD	*coronary heart disease*
ED	*erectile dysfunction*
ETT	*exercise treadmill test*
CAC	*coronary artery calcification*
EBCT	*electron beam computed tomography*
PTCA	*Percutaneous Coronary Angiography*
PCI	*Percutaneous Coronary Intervension*
LAD	*Left Anterior Descending*
MPI	*Myocardial Perfusion Imaging*
LAO **RAO**	*left anterior oblique* *Right anterior oblique*
PET	*Positron emission tomography*
BATO	*Boronic acid adducts of technetium dioxime*
MET	*Metabolic equivalents*
SBP	*Systolic Blood Pressure*
AF	*Atial fibrillation*
SVT	*Supraventricular tachycardia*
OADs	*Oral Anti Diabetics*
IHD	*Ischemic heart disease*

LIST OF TABLES

LIST OF FIGURES

Acknowledgement

First and forever I feel always indebted to ***ALLAH****, the most Gracious, and the most Merciful.*

I am greatly thankfull to my ***parents*** *for their support and encouragement.*

I would like express my gratitude ***Prof. Dr. Salah El-Din H. Demerdash*** *(Professor of Cardiology, Faculty of Medicine -Ain Shams University) who initiate and assign this work and for his faithful supervision.*

Also many many thanks goes to my kind supervisor ***Dr.Mona Mostafa Ryan.*** *(Asst.Prof of Cardiology, Faculty of Medicine -Ain Shams University) for her keen advice and sincere guidance.*

Thanks is not enough to ***Dr.Mona Mohamad Abdel Salam****. (Lecturer of internal medicine & endocrinology, Faculty of Medicine-Ain Shams University) .who really gave her effort to support this thesis.*

I would like to thank ***Dr.Abdel Maksoud Ahmad*** *(Asst.Prof of Cardiology, Faculty of Medicine, Al-Azhar University) and* ***Dr.Khaled El Sayed El Hadidi*** *(Asst.Prof of Internal Medicine, Faculty of Medicine, Beni Suief University) for their support and helping to finish this thesis.*

Walid El-Tahlawy

Introduction

Cardiovascular disease (CVD) is the leading cause of death and disability in developed nations and is increasing rapidly in the developing world. By the year ٢٠٢٠, it is estimated that CVD will surpass infectious diseases as the world's leading cause of death and disability. Diabetes is one of the main risk factors for coronary atherosclerosis since it accelerates its progression, causes endothelial dysfunction and increases platelets activity. Diabetes eliminates the protection associated with female sex against CAD [١].The pathological relationship between the disease of large and medium blood vessels and diabetes has been well established. It is known that insulin resistance and hyperinsulinism are the primary factors involved in the pathogenesis of macroangiopathy. Other risk factors include hyperglycemia, dyslipidemia, hypertension and obesity [٢].Type ٢ occurs in individuals who have some sort of insulin resistance but still maintain their ability to secrete insulin so do not develop ketosis and no obligatory need for exogenous insulin therapy like insulin dependent diabetes mellitus type ١ to keep life [٣].

Patients é diabetes can also have complications affecting various organs due to microvascular disorders (retinopathy, cataract, nephropathy, neuropathy, and atherosclerosis) however; they evolve more slowly and depend on the metabolic control of the disease [٤]. The diabetic patients who present to ED with symptoms suggestive of cute coronary syndrome (ACS) are at higher risk group than non diabetic and more often have abnormal myocardial perfusion image [٥].Silent myocardial ischemia occurs in greater than one in five asymptomatic patients with type ٢ diabetes [٦].

Nuclear cardiology has an integral role in non invasive detection of coronary artery disease, assessment of

myocardial viability and risk stratification. It imparts improved sensitivity and specificity over standard exercise stress testing. Myocardial perfusion imaging is used widely in the evaluation of patients with known or suspected CAD. The extensive clinical use of MPI for detection of CAD has resulted largely from studies demonstrating improved diagnostic sensitivity and specificity of exercise MPI compared to exercise ECG [٧]. Radionucleotide techniques that assess regional myocardial perfusion provide useful information in the detection and evaluation of CAD and in the assessment of therapies aimed at limiting the degree of ischemia. It is critical to measure perfusion both at rest and with exercise since perfusion may be normal at rest even in patients with severs CAD [٨].

Aim of the work

The aim of this study is to detect silent myocardial ischemia using SPECT in asymptomatic patients with type٢ Diabetes Mellitus.

Chapter 1

MACROVASCULAR COMPLICATIONS OF DIABETES MELLITUS

Diabetes mellitus (DM), mainly type ٢ diabetes (٩٠–٩٥٪ of diabetic patients), affects approximately ١٠٠ million people worldwide, including ١٧ million in the USA and ١,١٥ million in the UK. A ٣٠٪ increase in incidence is predicted by ٢٠٢٥, due to both the increased rate of obesity and the aging populations living in industrial countries [٩]. The incidence in Egypt is; ١١٪ (٤,٤ million) in ٢٠٠٧ and it will be ١٣,٤٪ (٧,٦ million) in ٢٠٢٥ [١٠].

Diabetes mellitus is known to be associated with a high risk of developing vascular complications which can lead to premature death and/or disability mainly by increasing the risk of myocardial infarction, stroke and peripheral vascular disease [١١]. Patients with DM are two to four times more likely to develop cardiovascular disease than those in the general population and have a ٢ to ٥ time's greater risk of dying from these diseases [١٢].

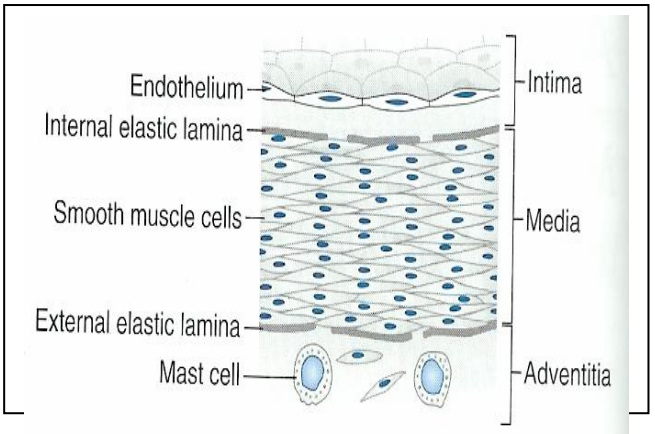
In addition to being a risk factor for cardiovascular disease in its own right, DM is associated with a higher prevalence of other risk factors such as hypertension and dyslipidaemia, which, in turn, have a more harmful effect in the presence of diabetes. Not only these complications debilitating to the patient, but they are accompanied by a significant economic burden to the patient, family members, and the nation's health care budget [١٣].

Macrovascular complications in diabetic patients were more common among males, increased with age, were more common among hypertensive patients and its prevalence increased steadily with duration of DM. Clearly, such data are important, given that macrovascular complications account for approximately ٥٠٪ of all deaths among DM patients in the industrialized countries [١٣].

Indeed, at present it is generally upheld that patients with DM should be treated as though they already have heart disease. [١٣].

The central pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system.

In response to endothelial injury and inflammation, oxidized lipids from LDL particles accumulate in the endothelial wall of arteries [١٤]. *(Fig; 1)*



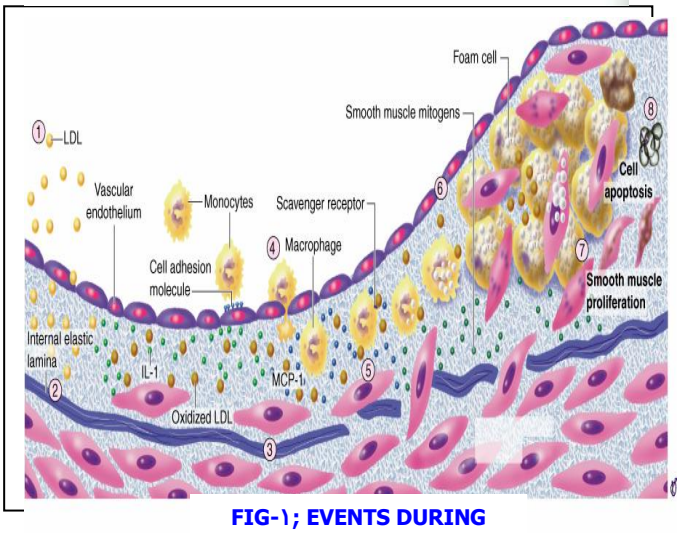


FIG-١; EVENTS DURING ATHEROGENESIS

Angiotensin II may promote the oxidation of such particles. Monocytes then infiltrate the arterial wall and differentiate into macrophages, which accumulate oxidized lipids to form foam cells. Once formed, foam cells stimulate macrophage proliferation and attraction of T-lymphocytes.T-lymphocytes, in turn, induce smooth muscle proliferation in the arterial walls and collagen accumulation [١٤].

In addition to atheroma formation, there is strong evidence of increased platelet adhesion and hypercoagulability in type ٢ diabetes. Impaired nitric oxide generation and increased free radical formation in platelets, as well as altered calcium regulation, may promote platelet aggregation [١٤].

Pathogenesis of Atherothrombosis in DM *(Fig; 2)*:

The pathophysiologic process of atherosclerosis has been schematically summarized in several steps, each of them characterized by significant involvement of humoral and cellular inflammatory elements [١٥].

Genetic abnormality:

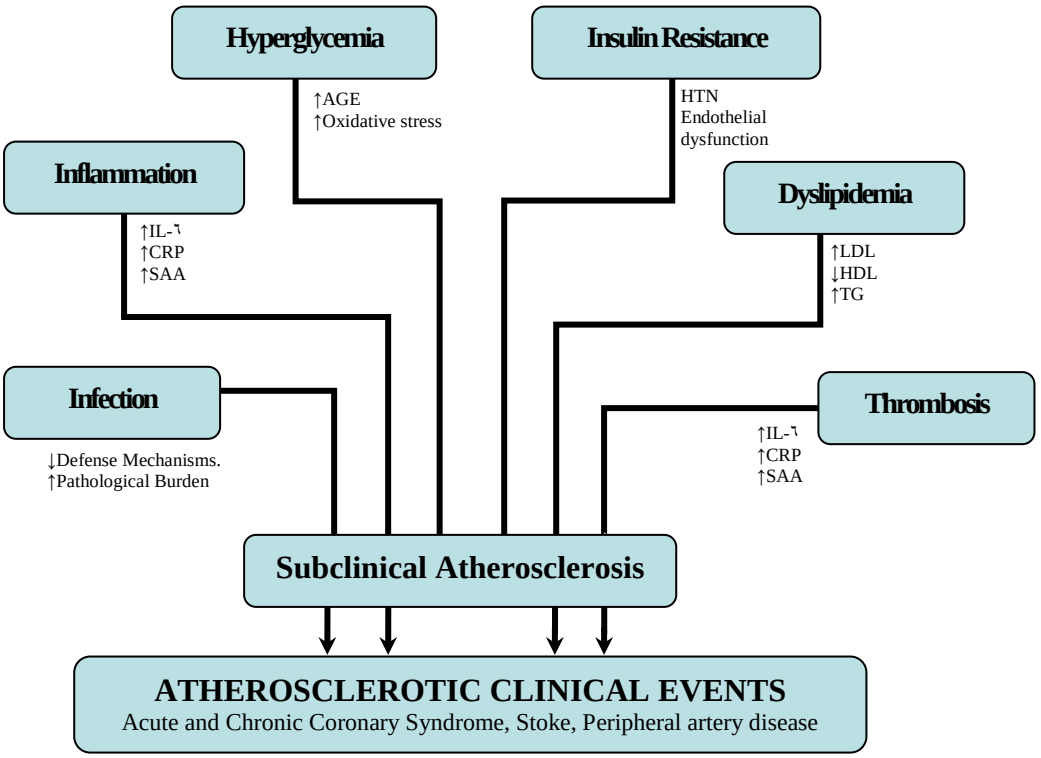
Several genetic abnormalities in glycemic metabolism have been associated with the development of diabetes, diabetic complications, or aspects of the dysmetabolic syndrome. All of these derangements could be also involved in atherogenesis. Transcription factors, such as peroxisome proliferator-activated receptor (PPAR)-alpha and -gamma, are now being intensively studied. Whereas PPAR-alpha primarily stimulates the beta-oxidative degradation of fatty acids, PPAR-gamma promotes lipid storage by regulating adipocyte differentiation. (PPAR)-alpha is the molecular target of lipid-lowering drugs such as fibrates, and PPAR-gamma interacts with insulin-sensitizer drugs such as thiazolidinediones, and they may significantly modulate atherogenicity and inflammation. In particular, mutations in the PPAR-gamma gene have recently been shown to be associated with diabetes, glucose intolerance, **and** hypertension [١٦].

Dyslipidemic abnormalities:

Diabetics usually show decreased high-density lipoprotein (HDL) cholesterol levels and increased low-density lipoprotein (LDL) cholesterol and triglyceride levels. Diabetes is most often associated with smaller, denser LDL that is more susceptible to oxidation and thus has greater atherogenicity [١٥]. Even if diabetic patients with good glycemic control may have LDL levels similar to or slightly lower than those of nondiabetic individuals, fasting and postprandial levels of triglyceride-rich lipoproteins, especially very-low-density lipoprotein, are higher and those of HDL are lower than those of nondiabetics [١٦].

Finally,Several clinical studies have shown the benefit of lipid-lowering strategies in diabetics, even in cases of modestly

increased or normal cholesterol levels, and these benefits are often greater than those found in nondiabetic patients [١٧].



Fig(٢) : The pathogenetic mechanisms involved in the initiation of subclinical atherosclerosis and progression to atherosclerotic clinical events in diabetic patients include infection, inflammation, hyperglycemia, insulin resistance, dyslipidemia, and thrombosis. AGE = advanced glycation end products; CRP = C-reactive protein; HDL = high-density lipoprotein; HTN = hypertension; IL-٦ = interleukin-٦; LDL = low-density lipoprotein; PAI-١ = plasminogen activator inhibitor-١; SAA = serum amyloid A protein; TF = tissue factor; TG = triglycerides; tPA = tissue-type plasminogen activator

Oxidative stress

Diabetics have decreased antioxidant enzyme activity and increased oxidative burden [١٨], and hyperglycemia increases the production of reactive oxygen species. These may shift the oxidant-antioxidant balance toward nonenzymatic oxidation of lipoproteins, thus contributing to atherogenic processes. It has also been hypothesized that reactive carbonyl groups may overwhelm the antioxidant mechanism of diabetic patients, leaving them unprotected to common oxidative stressors such as smoking [١٦].