Impact of Antidiabetic Therapy on Infarction Size and Viability in Diabetic Patients with ST Segment Elevation Myocardial Infarction

Thesis
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بسم الله الرحمن الرحيم

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List of Abbreviations

^{201}Tl	Thallium-۲۰۱
^{99m}Tc	technetium-۹۹m
A_1	Subtype ۱ of adenosine receptor
A۱c	Glycosylated hemoglobin
A_3	Subtype ۳ of adenosine receptor
AGIs	α -Glucosidase inhibitors
AHA	American Heart Association
AMI	Anterior Myocardial Infarction
ATP III	Adult Treatment Panel III
CMR	Cardiac Magnetic Resonance
Cx	Circumflex Artery
DCCT	Diabetes Control and Complications Trial
DM	Diabetes Mellitus
EF	Ejection Fraction
Fig	Figure
FPG	Fasting plasma glucose
GAD	Glutamic acid decarboxylase antibodies
GDM	Gestational diabetes mellitus
HNF	Hepatocyte nuclear factor
IFG	Impaired fasting glucose
ICA	Islet cell antibodies
IGT	Impaired glucose tolerance
K_{ATP}	ATP dependent potassium channel
LAD	Left anterior descending
LVEF	Left Ventricle Ejection Fraction
MBG	Myocardial Blush Grade
MFT	Myocardial filling time
MI	Myocardial Infarction
MODY	Maturity onset diabetes
MRI	Magnetic Resonance Imaging
NCEP	National Cholesterol Education Program
NO	Nitric oxide
OGTT	Oral glucose tolerance test
PCI	Percutaneous Intervention
PKC	Protein Kinase C
PKC-ε	Epsilon isoform of PKC
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTP	Permeability transition pore
SPECT	Single Photon Emission Computed Tomography
SRS	Summed rest score
SSS	Summed stress score
STEMI	ST segment elevation myocardial infarction
SUR	Sulfonylurea receptor
TIMI	Thrombolysis In Myocardial Infarction
TZDs	Thiazolidinediones
UGDP	University Group Diabetes Program

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INTRODUCTION

Diabetes mellitus is a chronic progressive disease characterized by deteriorating glucose control and increased risk of micro and macrovascular complications. About ٨% of population have diabetes and among them the great majority have type II diabetes **(Wild et al., ٢٠٠٤)**. The two most common oral pharmacologic strategies to manage type II diabetes include the use of agents that promote insulin release (e.g., sulfonylureas) or improve insulin sensitivity (e.g., metformin and thiazolidinediones). These strategies reduce hyperglycemia to a similar degree, but how they affect mortality and morbidity remains under investigation **(Inzucchi, ٢٠٠٢)**.

Any discussion of potentially detrimental effects of the sulfonylureas is based on the increased cardiovascular mortality observed in the UGDP study that was published in ١٩٧٠s. Patients treated with tolbutamide in the UGDP had a significantly higher cardiovascular rate of death than those given placebo **(Meinert et al., ١٩٧٠)**. Despite the UGDP observations sulfonylureas have been the mainstay of therapy. This treatment choice persisted probably because the UGDP study design had a lot of controversy **(Schwartz et al., ٢٠٠٤)**.

In ١٩٨٦, Murry and colleges discovered ischemic preconditioning. It is the phenomenon by which myocardium develops a tolerance to brief periods of ischemia after which an episode of prolonged ischemia will cause less damage than might otherwise be expected. This makes a likely explanation for the results found in UGDP **(Tomai et al., ١٩٩٤)**.

In ٢٠٠٦, Simpson and colleagues proved that higher exposure to sulfonylureas was associated with increased mortality among patients newly treated for type II diabetes. This implies that ***the manner in which blood***

glucose concentration is lowered may be as important as achieving the recommended glucose targets.

AIM OF THE WORK

The aim of this study is to investigate the effect of antidiabetic therapy on infarction size and viability in diabetic patients with ST segment elevation myocardial infarction.

REVIEW OF LITERATURE

DIABETES MELLITUS

Diabetes mellitus is a group of metabolic disorders 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 various organs, especially the eyes, kidneys, nerves, heart, and blood vessels **(American Diabetes Association, ٢٠٠٧)**.

An Outline of Glucose Metabolism

Blood glucose levels are closely regulated in health and rarely stay outside the range of (٦٣-١٤٤ mg $dl^{-١}$), despite the varying demands of food, fasting and exercise. The principle organ of glucose homeostasis is liver, which absorbs and stores glucose as glycogen in post absorptive state and releases it into the circulation between meals to match the rate of glucose utilization by peripheral tissues. In addition, glucose is formed in the liver by the process of gluconeogenesis. About ٢٠٠ g of glucose is produced and utilized everyday where ٩٠% is derived from the liver glycogen and hepatic gluconeogenesis and the reminder is derived from renal gluconeogenesis **(Kumar et al., ٢٠٠٥)**.

Etiologic Classification of Diabetes Mellitus

I. Type ١ diabetes: where ß-cell destruction usually lead to absolute insulin deficiency, either immune mediated or idiopathic

II. Type II diabetes: it may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance.

III. Other Specific Types

A. Genetic defects of ß-cell function

B. Genetic defects in insulin action e.g. type A insulin resistance

C. Diseases of the exocrine pancreas e.g. pancreatitis, hemochromatosis, trauma, pancreatectomy, neoplasia and cystic fibrosis.

D. Endocrinopathies e.g. acromegaly, Cushing's syndrome, hyperthyroidism and pheochromocytoma

E. Drug- or chemical-induced e.g. Nicotinic acid, ß-adrenergic agonists, glucocorticoids, Thyroid hormone, Thiazides and α-Interferon.

F. Infections e.g. congenital rubella and cytomegalovirus.

G. Uncommon forms of immune-mediated diabetes e.g. anti–insulin receptor antibodies

H. Other genetic syndromes sometimes associated with diabetes e.g. Down's , Klinefelter's and Turner's syndromes

IV. Gestational Diabetes Mellitus (GDM): The term gestational diabetes describes women with impaired glucose tolerance that appears or is first detected during pregnancy. Women with known diabetes before conception are not considered to have gestational diabetes. Gestational diabetes usually appears in the ٢nd or ٣rd trimester, a time when pregnancy-associated insulin antagonistic hormones peak. After delivery, glucose tolerance generally (but not always) reverts to normal. However, within ٥ to ١٠ years, type II diabetes develops in ٣٠ to ٤٠%. Occasionally, pregnancy may precipitate type ١ diabetes. Gestational diabetes occurs in about ٢% of pregnant women. Although patients generally have only mild, asymptomatic hyperglycemia, meticulous treatment, often with insulin, is required to protect against hyperglycemia-associated fetal morbidity and mortality. Patients with any form of diabetes may

require insulin treatment at some stage of their disease. Such use of insulin does not classify the patient **(American Diabetes Association, ٢٠٠٧)**.

Type II Diabetes Mellitus

Type II diabetes is ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance. This form of diabetes that accounts for about ٩٠–٩٥% of those with diabetes, it includes individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency at least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive. There are probably many different causes of this form of diabetes. Although the specific etiologies are not known, autoimmune destruction of ß-cells does not occur, and patients do not have any of the other causes of diabetes **(American Diabetes Association, ٢٠٠٧)**.

Epidemiology

The number of people with diabetes mellitus, and in particular those with type II is increasing dramatically. The reasons for this epidemic increase include ageing of the population and an increase in obesity, together with less physical activity. Changing food habits also contribute, particularly in the developing world. The worldwide prevalence of diabetes mellitus in the adult population was estimated to be approximately ٤% at the end of the past millennium, but this is increased to ٥.٥ % the end of ٢٠٠٥. This will double of the number of people with diabetes from ١٥٠ to ٣٠٠ million during the first quarter of the ٢١st century **(King et al., ١٩٩٨)**.

Etiology

Environmental Factors (early and late):

A strong association was noted between low weight at birth and at ١٢ months of age and glucose intolerance later in life, particularly in those who gain excess weight as adults. The concept is that poor nutrition early in life