HbA١c as a Predictor of the Severity of Systolic Heart Failure in non-Diabetic Patients

Thesis

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Presented by

Mohamed Anwar Tawfic
M.B.B.Ch.

Under Supervision of

Prof. Dr/ Ihab Mohamed Attia
Professor of Cardiology
Faculty of Medicine - Ain Shams University

Dr / Mohamed Abd-Elkader Saleh
Lecturer of Cardiology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
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List of Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin Converting Enzyme
AF	Atrial Fibrillation
AGE	Advanced Glycosylation End product
AHA	American Heart Association
ARBs	Angiotensin II Receptor Blockers
BBB	Bundle Branch Block
BIPS	Bezafibrate Infarction Prevention Study
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
bpm	Beat Per Minute
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CV	Cardiovascular
DM	Diabetes Mellitus
DYS	Dyslipidemia
ECG	Electrocardiogram
EF	Ejection Fraction
EMME	Eastern Mediterranean and Middle East
FDA	Food and Drug Administration
FFA	Free Fatty Acid
FH	Family History
FPG	Fasting Plasma Glucose
FS	Fractional Shortening
Hb	Hemoglobin
HbA\c	Glycated Hemoglobin
HF	Heart Failure
HR	Heart Rate
Hrs	Hours
HTN	Hypertension
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance

IHD	Ischemic Heart Disease
LBBB	Left Bundle Branch Block
LV	Left Ventricle
LVEDD	Left Ventricular End Diastolic Dimension
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End Systolic Dimension
LVSD	Left Ventricular Systolic Dysfunction
LVWMI	Left Ventricular Wall Motion Index
MR	Mitral Regurgitation
NHLBI	The National Heart, Lung, and Blood Institute
NO	Nitric Oxide
NPP	Negative Predictive Value
NYHA	New York Heart Association
OGTT	Oral Glucose Tolerance Test
PAS	Periodic Acid-Schiff
PPAR-gamma	Peroxisome Proliferator-Activated Receptor-gamma
PPV	Positive predictive value
RAAS	Renin-Angiotensin-Aldosterone System
RBBB	Right Bundle Branch Block
SD	Standard Deviation
SNS	Sympathetic Nervous System
SOLVD	Studies of Left Ventricular Dysfunction
SPSS	Statistical Package for Social Science
TNF-alpha	Tumor Necrosis Factor alpha
TZDs	Thiazolidinediones
VEGF	Vascular Endothelial Growth Factor
VO^{2}	Oxygen consumption
WHO	World Health Organization

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Introduction

Hyperinsulinemia, impaired glucose tolerance (IGT), and insulin resistance are risk factors for developing heart failure (HF), independent of diabetes mellitus (DM) and other established risk factors ***(Ingelsson et al., ٢٠٠٥).***

Dysglycemia, in the absence of DM, is common in HF. In a substudy involving ٦٦٣ patients with New York Heart Association (NYHA) class II–IV HF, ٢٧٪ had documented DM. Of the 'non-diabetics', ١١٪ met diagnostic criteria for DM (newly diagnosed during the study), ١٢٪ had impaired fasting glucose (IFG) and ٣٤٪ had elevated plasma insulin concentrations and insulin resistance ***(Suskin et al., ٢٠٠٠).***

The presence of insulin resistance, hyperinsulinemia, or IFG is associated with lower functional capacity and more severe symptoms. Reduced peak oxygen consumption (VO_2) is an independent predictor of insulin resistance in non-diabetic patients with HF ***(Swan et al., ١٩٩٧).***

Insulin resistance, in the absence of DM, is an independent prognostic indicator in HF ***(Doehner et al., ٢٠٠٥)***. Similarly, an admission blood glucose of >١٨٠ mg/dl is a predictor of mortality, independent of DM, in patients with a first hospitalization for HF ***(Newton and* Squire, ٢٠٠٦)**.

Insulin resistance occurs in HF of both ischemic and non-ischemic etiology, but why it is so prevalent is not fully

understood. Many mechanisms have been suggested, including sympathetic nervous system (SNS) overactivity, sedentary lifestyle, endothelial dysfunction, loss of skeletal muscle mass, and influence of cytokines such as tumor necrosis factor alpha (TNF-alpha) and leptin on peripheral insulin sensitivity ***(Witteles and Fowler, ٢٠٠٨).***

Patients with HF have persistent activation of their SNS. Excessive activation of the SNS may lead to insulin resistance. In healthy subjects, acute SNS activation reduces insulin-induced stimulation of muscle glucose uptake by ٢٥٪ ***(Scherrer and* Sartori, *١٩٩٧)***. Furthermore, stimulation of β-receptors increases lipolysis resulting in raised plasma free fatty acid (FFA) levels ***(Schiffelers et al., ٢٠٠١)***. FFAs impair insulin-mediated glucose disposal in human skeletal muscle and can stimulate hepatic gluconeogenesis, further potentiating hyperglycemia. Catecholamines have also been shown to inhibit pancreatic insulin secretion in humans and stimulate hepatic gluconeogenesis and glycogenolysis, further worsening hyperglycemia ***(Nonogaki*, *٢٠٠٠*; *Boudina and Abel, ٢٠٠١)***.

Aim of the Work

To study the association between HbA١c levels and the severity of systolic heart failure among non-diabetic patients during a follow-up period of ٦ months.

Epidemiology of Heart Failure

Congestive heart failure (CHF) is an increasing, global epidemic, particularly in the elderly, that results in significant health care expenditure, disability, and mortality. Coronary artery disease (CAD), hypertension, and diabetes mellitus are the major etiologic risk factors. Ironically, advances in the treatment of coronary artery disease and acute ischemic syndromes, which have saved lives, have resulted in a growing population of survivors with left ventricular dysfunction who are destined to develop the heart failure syndrome. Preventive measures that have evolved over the last ٢٥ years, including hypertension management, have not reduced the incidence of heart failure. Congestive heart failure is the leading indication for hospitalization in the United States for patients older than ٦٥ years. Heart failure is a chronic disease amenable to an intensive multidisciplinary care model (disease management program) designed to prevent hospital admissions through patient education, focused outpatient initiatives, and adherence to management guidelines that should enhance cost effectiveness and improve quality of life ***(Garg et al., ١٩٩٣).***

The National Heart, Lung, and Blood Institute (NHLBI) estimates that ٧٥٪ of patients with heart failure have antecedent hypertension. Major advances in the treatment of coronary artery disease and acute ischemic syndromes that have saved countless lives have resulted in a growing population of patients