Glycated Albumin as a predictor of early diabetic Nephropathy in patients with Type 2 Diabetes Mellitus

Thesis

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By

Engy Eshak Gedy Wisa
(M.B.,B.Ch.)

Supervised by

Prof. Dr. Mohamed Saad Hamed

Professor of Internal Medicine, Diabetes and Endocrinology
Faculty of Medicine - Ain Shams University

Dr. Ahmed Mohamed Bahaa Eldin

Assistant Professor of Internal Medicine, Diabetes and Endocrinology
Faculty of Medicine - Ain shams University

Dr. Bassem Murad Mostafa

Lecturer of Internal Medicine, Diabetes and Endocrinology
Faculty of Medicine - Ain shams University

Faculty of Medicine
Ain Shams University
2019

List of Contents

List of Abbreviations

ABI	Arterial Blood Index
ACE	Angiotensin-Converting Enzyme
ACR	Albumin-to-Creatinine Ratio
AGEs	Advanced Glycation End Products
AKI	Acute Kidney Injury
AP-1	Activator Protein-1
APD	Action Potential Duration
ARBs	Angiotensin II Receptor Blockers
ARBs	Angiotensin Receptor Blockers
AT-II	Angiotensin II
BUN	Blood Urea Nitrogen
CAD	Coronary Artery Disease
CD36	Cluster of Differentiation 36
CFR	Coronary Flow Reserve
CKD	Chronic Kidney Disease
CTGF	Connective Tissue Growth Factor
CVD	Cardiovascular Disease
DKA	Diabetic Ketoacidosis
DKD	Diabetic Kidney Disease
DN	Diabetes Mellitus
EC	Excitation-Contraction Coupling
ECM	Extracellular Matrix
ESA	Erythropoiesis-Stimulating Agents
ESRD	End-Stage Renal Disease
FA	Fructosamine
FFA	Free Fatty Acid
GA	Glycated Albumin

List of Abbreviations

GDM	Gestational Diabetes Mellitus
GFR	Glomerular Filtration Rate
HAS	Human Serum Albumin
Hb	Haemoglobien
HbA1C	Glycated Hemoglobin
HDL	High Density Lipoprotein
HHS	Hyperosmolar Hyperglycemic State
IL	Interleukin
JAK	Janus kinases
LADA	Late Autoimmune Diabetes of Adults
MCP-1	Monocyte Chemoattractant Protein-1
MDCT	Multidetector Computed Tomography
MMP-2	Matrix Metalloproteinase-2
MODY	Maturity-Onset Diabetes of the Young
mPTP	Mitochondrial Permeability Transition Pore
MR	Magnetic Resonance
NADPH	Nicotinamide Adenine Dinucleotide Phosphateoxidase
NADPH	Nicotinamide Adenine Dinucleotide Phosphate-Oxidase
NAP	Non-Albumin Proteinuria
NF-kB	Nuclear Factor-kB
OGTT	Oral Glucose Tolerance Test
PA	Plasminogen Activator
PAI-1	Plasminogen Activator Inhibitor-1
PKC	Protein Kinase C

List of Abbreviations

PVD	Peripheral Vascular Disease
RAAS	Renin-Angiotensin-Aldosterone System
RAGEs	Receptors for Advanced Glycation Products
RHoA-GTPase	RHoA Regulator of Cytokinesis
ROS	Reactive Oxygen Species
RPN	Renal Papillary Necrosis
SCr-II	Scavenger Receptor II
SGLT2	Sodium–Glucose Cotransporter 2
SMC	Smooth Muscle Cell
SR	Sarcoplasmic Reticulum
STAT	Signal Transducer and Activator of Transcription
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TGF-β	Transforming Growth Factor-β
TNF-α	Tumor Necrosis Factor-α
UTIs	Urinary Tract Infections
VEGF	Vascular Endothelial Growth Factor

List of Tables

List of Tables (Continued)

List of Tables (Continued)

List of Figures

List of Figures (Continued)

List of Figures (Continued)

Abstract

Background: One of the most common complications of T2DM is diabetic nephropathy (DN), which is a major cause of end stage renal disease (ESRD) and death among T2DM patients. The increase in Glycated albumin concentrations plays role in diabetic nephropathy through stimulation of collagen and fibronectin expressionin mesangial cells, or through stimulation of reactive oxygen species (ROS). **Aim of the work:** to assess the role of GA as a predictor of early diabetic nephropathy in T2DM.**Subjects and methods:** Case control study including 60 patients with T2DM divided into 2 groups; group 1 (30 patients) with HbA1c >7 and further subdivided into 2 groups (15 diabetics with microalbuminuria (A/C ratio 30-300 mg/g) and 15 diabetics with normoalbuminuria (A/C ratio <30)), group 2 (30 patients) with HbA1c <7 and further subdivided into 2 groups (15 diabetics with microalbuminuria (A/C ratio 30-300 mg/g) and 15 diabetics with normoalbuminuria (A/C ratio <30)), and 30 age and sex matched control group. The patients were recruited from Internal Medicine Department of Ain Shams University Hospital over period of sex months for measurement of GA. **Results:** Significant difference in glycated albumin between diabetic nephropathy and diabetic without nephropathy (P value<.001), highly statistically significant difference was detected between uncontrolled, controlled and control as regards GA (P value< .05), GA was correlated with both HbA1c and fasting blood glucose (P value .001), also significant correlation between GA and A/C ratio (with P value <.001). GA has 93.33% sensitivity and 93.33 specificity for renal tubular injury. Significant negative correlation between GA and serum albumin and no statistically significant difference between the studied groups as regards serum creatinine.**Conclusion:** GA plays a double role in diabetes complications. In addition to being a marker for glycation, GA has been directly implicated to have a role in diabetic nephropathy.

Key words: Type2 diabetes mellitus, diabetic nephropathy, Glycated albumin.

INTRODUCTION

Diabetes is an important metabolic disorder which is characterized by hyperglycemia with variable degree of insulin resistance, impaired insulin secretion and increased glucose level for type-1(insulin-dependent) and type-2 (non-insulin dependent) diabetes mellitus ***(Yadav et al., 2016).*** Presently, DM is worldwide epidemic and great challenge to health care systems everywhere. The International Diabetes Federation (IDF) estimates that one in eleven adults have DM, totalizing approximately 415 million people, and 193 million of them have not yet been diagnosed ***(International Diabetes Federation, 2015).***

Chronic hyperglycemia is frequently associated with permanent and irreversible functional and structural changes in the cell of the body particularly in vascular system which affect kidney ***(Yadav and Prakash, 2016).***

Diabetic nephropathy is a common complication of diabetes mellitus type 2. It not only occurs in 20-40% of all diabetic patient, but it is one of the major end-organ complication of diabetes and continue to be the most common cause of end stage renal disease ***(American Diabetes Association, 2015)***.

Diabetic nephropathy is characterized by an increase excretion of protein, particularly albumin, decline of the

glomerular filtration rate (GFR) and elevated blood pressure that leading to end stage renal failure ***(Mise et al., 2014).***

Glycation is non-enzymatic spontaneous reaction in which reducing sugar is added to free amino group, typically lysine or arginine present within proteins, also called as Maillard reaction ***(Ueda and Mastumotm, 2015).*** Similar to the other protiens, albumin also goes through the physiological process of glycation ***(Arasteh et al., 2014).***

GA is ketoamine produced by non-enzymatic oxidation reaction ***(Koga and Kasayama, 2010).*** Glycated albumin has been proposed to be better predictor of glucose variability and excursions than HbA1c ***(Lee et al., 2011).*** GA has been considered a useful glycemic index in patient with diabetes, especially those with chronic kidney disease, because it is not influenced by erythrocyte life span, uremia or blood transfusion, all of which can invalidate Hba1c measurement ***(Furusyo and Hayashi, 2013).***

The increase in concentration of glycated albumin plays role in the pathogenesis of diabetic nephropathy through stimulation of collagen and fibronectin expression in mesangial cell, also glycated albumin stimulates reactive oxygen species (ROS) form in mesangial cell**s** ***(Li and Wang, 2010).***

Glycated albumin may also be directly toxic to glomerular mesangial and epithelial cells by promoting monocyte secretion of inflammatory cytokines and enhancing oxidative stress ***(Arasteh et al., 2014).***