

Evaluation of the Relationship between Glycated Albumin and Peripheral Diabetic Neuropathy

Thesis

Submitted for Fulfillment of Master Degree
in Endocrinology

By

Radwa Abdelnaser Ahmed
M.B.B.CH

Under supervision by

Prof. Mohamed Hesham El Gayar

*Professor of Internal Medicine and Endocrinology
Faculty of Medicine - Ain Shams University*

Dr. Mona Mohamed Abdelsalam

*Assistant Professor of Internal Medicine and Endocrinology
Faculty of Medicine - Ain Shams University*

Dr. Hanan Mahmoud Ali

*Lecturer of Internal Medicine and Endocrinology
Faculty of Medicine - Ain Shams University*

Faculty of Medicine
Ain Shams University

2018

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لَسْبَدَانُكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgment

*First and foremost, I feel always indebted to **ALLAH**, the Most Kind and Most Merciful.*

*I'd like to express my respectful thanks and profound gratitude to **Prof. Mohamed Hesham El Gayar**, Professor of Internal Medicine and Endocrinology - Faculty of Medicine- Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

*I am also delighted to express my deepest gratitude and thanks to **Dr. Mona Mohamed Abdelsalam**, Assistant Professor of Internal Medicine and Endocrinology, Faculty of Medicine, Ain Shams University, for her kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

*I am deeply thankful to **Dr. Hanan Mahmoud Ali**, Lecturer of Internal Medicine and Endocrinology, Faculty of Medicine, Ain Shams University, for her great help, active participation and guidance.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Last but not least my sincere thanks and appreciation to all patients participated in this study.

Radiwa Abdelnaser Ahmed

List of Contents

Title	Page No.
List of Tables	5
List of Figures.....	7
List of Abbreviations	9
Introduction	1
Aim of the Work	3
Review of Literature	
▪ Diabetic Neuropathy	4
▪ Nerve Conduction Velocity Test.....	49
▪ Glycated Albumin.....	58
Subjects and Methods.....	68
Results	76
Discussion.....	112
Summary	121
Conclusion	127
Recommendations	128
References	129
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table (1):	Summary of medication used in DN	45
Table (2):	Motor nerve conduction studies.....	56
Table (3):	Sensory nerve conduction studies	56
Table (4):	Common diseases	57
Table (5):	Methods for detection of GA.....	62
Table (6):	Demographic and clinical characteristics among group-I	78
Table (7):	Laboratory and neurological findings among group-I	79
Table (8):	Demographic and clinical characteristics among group-II.....	81
Table (9):	Laboratory and neurological findings among group-II.....	82
Table (10):	Comparison between group-I and group-II regarding demographic and clinical characteristics	84
Table (11):	Comparison between group-I and group-II regarding laboratory findings using independent t-test.....	88
Table (12):	Comparison between group-I and group-II regarding neurological findings.....	92
Table (13):	Correlations between HbA1c & glycated albumin and demographic& clinical characteristics Using Pearson correlation.....	95
Table (14):	Correlations between HbA1c & glycated albumin and laboratory findings (using Pearson correlation).....	97
Table (15):	Correlations between HbA1c & glycated albumin and neural findings.....	100

List of Tables (cont..)

Table No.	Title	Page No.
Table (16):	Comparison between neuropathy types regarding glycemic findings in group-I	103
Table (17):	Comparison between cases with and without retinopathy regarding glycemic findings in group-I	105
Table (18):	Comparison between cases with positive and negative pinprick test regarding glycemic findings in group-I.....	107
Table (19):	Diagnostic performance of glycemic findings in diagnosing neuropathy.....	109
Table (20):	Diagnostic characteristics of HbA1c $\geq$ 8.8 and glycated albumin $\geq$ 12.5 in diagnosing neuropathy	111

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Polyol pathway	8
Figure (2):	Diabetic polyneuropathy.....	19
Figure (3):	128-Hz tuning fork.....	35
Figure (4):		36
Figure (5):		37
Figure (6):		40
Figure (7):		50
Figure (8):	Maillard reaction illustration	60
Figure (9):	Comparison between GA and HbA1c.....	64
Figure (10):	Comparison between study group-I and group-II regarding BMI	85
Figure (11):	Comparison between group-I and group-II regarding duration of DM.....	86
Figure (12):	Comparison between group-I and group-II regarding blood pressure	86
Figure (13):	Comparison between group-I and group-II regarding HbA1c	89
Figure (14):	Comparison between group-I and group-II regarding glycated albumin	89
Figure (15):	Comparison between group-I and group-II regarding RTML.....	93
Figure (16):	Comparison between group-I and group-II regarding RTMA	94
Figure (17):	Comparison between group-I and group-II regarding RTMCV.....	94
Figure (18):	Correlations between HbA1c and eGFR in group-I.....	98
Figure (19):	Correlations between glycated albumin and RTML in group-I	101

List of Figures (Cont...)

Fig. No.	Title	Page No.
Figure (20):	Correlations between glycated albumin and RTML in group-I	102
Figure (21):	Correlations between glycated albumin and RTML in group-I	102
Figure (22):	Comparison between neuropathy types regarding glycated albumin in group-I.....	104
Figure (23):	Comparison between cases with and without retinopathy regarding in group-I HbA1c.....	106
Figure (24):	Comparison between cases with and without retinopathy regarding in group-I glycated albumin.....	106
Figure (25):	Comparison between cases with positive and negative pinprick test regarding glycated albumin.....	108
Figure (26):	ROC curve for predicting glycemic findings in diagnosing neuropathy	110

List of Abbreviations

Abb.	Full term
<i>A1C or HbA1c.....</i>	<i>Glycated hemoglobin</i>
<i>ADA.....</i>	<i>American Diabetes Association</i>
<i>AGEs.....</i>	<i>Advanced glycation end products</i>
<i>ALA.....</i>	<i>Alpha lipoic acid</i>
<i>BCP.....</i>	<i>Bromocresolpurple</i>
<i>CAN.....</i>	<i>Cardiovascular autonomic neuropathy</i>
<i>CKD.....</i>	<i>Chronic kidney disease</i>
<i>CLD.....</i>	<i>Chronic liver disease</i>
<i>DC.....</i>	<i>Direct current</i>
<i>DM.....</i>	<i>Diabetes mellitus</i>
<i>DN.....</i>	<i>Diabetic neuropathy</i>
<i>DPN.....</i>	<i>Diabetic peripheral neuropathy</i>
<i>DPP.....</i>	<i>Diabetes Prevention Program</i>
<i>DSPN.....</i>	<i>Distal symmetric polyneuropathy</i>
<i>ED.....</i>	<i>Erectile dysfunction</i>
<i>ELBIA.....</i>	<i>Enzyme-linked boronate immunoassay</i>
<i>ELISA.....</i>	<i>Enzyme Linked Immunosorbent Assay</i>
<i>ER.....</i>	<i>Extended release</i>
<i>FDA.....</i>	<i>The Food and Drug Administration</i>
<i>GA.....</i>	<i>Glycated albumin</i>
<i>GSH.....</i>	<i>Glutathione</i>
<i>GSSG.....</i>	<i>Glutathione disulfide</i>
<i>Hb.....</i>	<i>Hemoglobin</i>
<i>HDL.....</i>	<i>High-density lipoprotein</i>
<i>HPLC.....</i>	<i>High performance liquid chromatography</i>
<i>HRV.....</i>	<i>Heart rate variability</i>
<i>IFG.....</i>	<i>Impaired fasting glucose</i>
<i>IGT.....</i>	<i>Impaired glucose tolerance</i>

List of Abbreviations (cont...)

Abb.	Full term
KORA.....	<i>(Cooperative Research in the Region of Augsburg) study</i>
LDDP.....	<i>Length-dependent diabetic polyneuropathy</i>
NAD+.....	<i>Nicotinamide adenine dinucleotide</i>
NADPH.....	<i>Nicotinamide adenine dinucleotide phosphate</i>
Nav.....	<i>Voltage-gated sodium channels</i>
NBT	<i>Nitroblue tetrazolium</i>
NCS	<i>Nerve conduction studies</i>
NCV	<i>Nerve conduction velocity</i>
NGT	<i>Normal glucose tolerance</i>
NP.....	<i>Neuropathic pain</i>
OGTT.....	<i>Oral glucose tolerance test</i>
OS	<i>Oxidative stress</i>
PAGE electrophoresis:	<i>Polyacrylamide gel electrophoresis</i>
PDN	<i>Proximal diabetic neuropathy</i>
PKC.....	<i>Protein kinase C</i>
RAGE.....	<i>Receptor for advanced glycation endproducts</i>
ROS.....	<i>Reactive oxygen species</i>
RPMA	<i>Right peroneal motor amplitude</i>
RPMCV.....	<i>Right peroneal motor velocity</i>
RPML.....	<i>Right peroneal motor latency</i>
RSSA	<i>Right sural sensory amplitude</i>
RSSCV.....	<i>Right sural sensory velocity</i>
RSSL.....	<i>Right sural sensory latency</i>
RTMA	<i>Right tibial motor amplitude</i>
RTMCV.....	<i>Right tibial motor velocity</i>
RTML	<i>Right tibial motor latency</i>
SNAP.....	<i>Sensory nerve action potential</i>

List of Abbreviations (cont...)

Abb.	Full term
<i>SNRI</i>	<i>Serotonin norepinphrine reuptake</i>
<i>SSRI</i>	<i>Selective serotonin reuptake inhibitor</i>
<i>SWME</i>	<i>Semmes-Weinstein Monofilament Examination</i>
<i>TCA</i>	<i>Tricyclic antidepressant</i>
<i>TTX-R</i>	<i>Tetrodotoxin-Resistant</i>

INTRODUCTION

Diabetes: 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 (*American Diabetes Association, 2012*).

Diabetes has become one of the largest global health-care problems of the 21st century. The number of people with diabetes worldwide is predicted to double between 2000 and 2030, reaching a pandemic level of 366 million people (*Hossain et al., 2007*).

Diabetes causes a wide variety of acute, chronic, focal, and diffuse neuropathy syndromes. By far the most common is DPN, which accounts for 75% of diabetic neuropathy, Diabetic polyneuropathy (DPN), which has a lifetime prevalence of approximately 50%, is the most common diabetic complication; DPN is a leading cause for disability due to foot ulceration and amputation, gait disturbance, and fall-related injury. Approximately 20 to 30% of patients with DPN suffer from neuropathic pain, DPN significantly lowers quality of life and substantially increases health costs associated with diabetes (*Tesfaye and Selvarajah, 2012*).

Glycated albumin (GA): a ketoamine formed by non-enzymatic glycation of serum albumin, reflects short-term (2–3 weeks) mean glycemic levels (*Furusyo and Hayashi, 2013*).

HbA1c, the result of the non enzymatic glycation of hemoglobin, reflects average glycemia over the preceding 8–12 weeks (*Nathan et al., 2008*).

The concentration of GA in serum, with a half-life of 12–19 days, would be an excellent index of recent glycemia. In addition to directly measuring the effects of hyperglycemia on the most prevalent plasma protein, GA has been directly implicated as a causal factor in several major complications of diabetes (*Cohen and Clements, 1999*).

GA values are not affected by changes in erythrocyte lifespan (*Koseck et al., 2005*), and measurement of GA is not influenced by anemia or other conditions which invalidate HbA1c measurements in the diagnosis of diabetes (*Furusyo et al., 2013*).

AIM OF THE WORK

To evaluate the relationship between Glycated albumin and peripheral diabetic neuropathy.

Chapter 1

DIABETIC NEUROPATHY

Diabetic peripheral neuropathy (DPN) is a common complication estimated to affect 30-50% of individuals with diabetes (*Deshpande et al., 2008*).

It is the most frequent and annoying complication of diabetes mellitus (DM), leading to the greatest morbidity and mortality and giving rise to a huge economic trouble for diabetes care, 2-3% develop a foot ulcer annually (*Stockl et al., 2004*).

The neuropathies developing in patients with diabetes are known to be heterogenous by their symptoms, pattern of neurologic involvement, course, pathologic alterations, and underlying mechanisms (*Dyck et al., 2005*).

A definition of peripheral neuropathic pain (NP) in diabetes is “pain arising as a direct consequence of abnormalities in the peripheral somatosensory system in people with diabetes” (*Treede et al., 2008*).

This chapter will discuss:

- Pathophysiology of diabetic neuropathy.
- Risk factors of DN.
- Classification of DN.