

Anti Glutamic Acid Decarboxylase 65 in Type 2 Diabetes Mellitus

Thesis

**Submitted for Partial Fulfillment of Master Degree
in Internal Medicine**

By

Ibrahim Salama Ibrahim Ali

M.B.B.Ch, Faculty of Medicine, AL-Azhar University

Supervised by

Prof. Dr. Mohammed Saad Hamed

Professor and Head of Department of Internal Medicine

Faculty of Medicine, Ain-Shams University

Dr. Ahmed Mohamed Bahaa El-Din

Assistant Professor of Internal Medicine

Faculty of Medicine, Ain-shams University

Dr. Bassem Murad Mostafa

Lecturer of Internal Medicine

Faculty of Medicine, Ain-Shams University

Faculty of Medicine
Ain-Shams University

2019

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لسبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢



Acknowledgments

*First and forever, thanks to **Allah**, Almighty for giving me the strength and faith to complete my thesis and for everything else.*

*I had great honor that my work under the supervision of **Prof/ Mohammed SaadHamed**. I would like to express my profound gratitude and sincere appreciation for his kind supervision, continuous encouragement and unlimited support in every step throughout this work,*

*I would like also to thank **Dr/Ahmed Mohamed Bahaa El-Din**, for his valuable advice and encouragement throughout this work,*

*I would like to express my deepest thanks and sincere appreciation to **Dr/Bassem Murad Mostafa**, for his continuous support, great encouragement, great help, his patience and valuable advisement in every step throughout this work,*

Last but not the least, I would like to express all my feelings of love and appreciation to all my senior staff and my colleagues in internal medicine department for their lovely help throughout this work,

 **Ibrahim Salama Ibrahim Ali**

List of Contents

<i>Subject</i>	<i>Page No.</i>
List of Abbreviations.....	i
List of Tables.....	iv
List of Figures	vi
Introduction	1
Aim of the Work.....	3
Chapter I: Type 2 Diabetes Mellitus (T2DM).....	4
Chapter II: Glutamic Acid Decarboxylase (GAD)	22
Chapter III: Autoimmune Aspects of Type 2 Diabetes Mellitus and Role of GAD65 Antibodies.....	40
Patients and Methods.....	57
Results.....	62
Discussion	81
Conclusion.....	88
Recommendations and Limitations.....	89
Summary	90
References	93
Arabic Summary	—

List of Abbreviations

Abbr.	Full-term
Ab+	Antibody positive
ACE	Angiotensin converting enzyme
ACR	Albumin:creatinine ratio
ADA	American Diabetes Association
AER	Albumin excretion rate
AGREE	Appraisal of Guidelines for Research and Evaluation
BDR	Background diabetic retinopathy
BFST	Behavioural family systems therapy
BMI	Body mass index
BMI-SDS	Body mass index – standard deviation score
BSPED	British Society for Paediatric Endocrinology and Diabetes
CASCADE	Child and Adult Structured Competencies Approach to Diabetes Education
CBT	Cognitive behavioural therapy
CGMS	Continuous glucose monitoring system
CHF	Chronic heart failure
CI	Confidence interval
CO₂	Carbon dioxide
CSII	Continuous subcutaneous insulin infusion
CST	Coping Skills Training
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DQOLY-SF	Diabetes Quality of Life for Youth – Short Form
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EDIC	Epidemiology of Diabetes Interventions and Complications
EED	Economic Evaluation Database

eGFR	Epidermal growth factor receptor
ESRD	End-stage renal disease
FPG	Fasting plasma glucose
GABA	gamma-Aminobutyric acid
GAD	Anti-glutamic acid decarboxylase
GAD65, GAD65+	Glutamic acid decarboxylase autoantibody 65 (positive)
GADA	Anti-glutamic acid decarboxylase antibody
GP	General practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRP	Guideline review panel
HAEM	Haemoglobin
HbA1c	Glycatedhaemoglobin
HDL	High-density lipoprotein
HR	Hazard ratio
HTA	Health Technology Assessment
IAA	Insulin autoantibody
IA-2	Insulinoma-associated autoantibody
IA-2A+	Insulinoma-associated autoantibody-positive
IA-2β-A	Insulinoma-associated beta autoantibody
ICA	Islet-cell antibodies
ICA512	Anti-islet cell antibody 512
ICER	Incremental cost effectiveness ratio
ICU	Intensive care unit
IFCC	International Federation of Clinical Chemistry
IGRP	Islet-specific glucose-6-phosphatase catalytic subunit
IQR	Interquartile range
ISPAD	International Society for Pediatric and Adolescent Diabetes
ITU	Intensive care unit
KICK-OFF	Kids In Control OF Food
LADA	Latent autoimmune diabetes of adulthood
LDL	Low-density lipoprotein
LVH	Left ventricular hypertrophy

MA	Microalbuminuria
MCMC	Markov chain Monte Carlo
MD	Mean difference
MDI	Multiple daily injection
ME	Macular oedema (edema)
MI	Myocardial infarction; Multiple injections (see context)
MID	Minimally important difference
MIMS	Monthly Index of Medical Specialities
MMTT	Mixed meal tolerance test
MODY	Maturity onset diabetes of the young
MRI	Magnetic resonance imaging
MST	Multisystemic therapy
NA	Not applicable
NC	Not calculable
NCC	National Collaborating Centre
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NCGC	National Clinical Guideline Centre
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPH	neutral protamine Hagedorn
NPSA	National Patient Safety Agency
OR	Odds ratio
PDR	Proliferative diabetic retinopathy
PDSN	Paediatric diabetes specialist nurse
PedsQL	Paediatric quality of life
PSA	Probabilistic sensitivity analysis
PVD	Peripheral vascular disease
QALY	Quality adjusted life years
QUADAS	Quality Assessment of Studies of Diagnostic Accuracy
RCT	Randomised controlled trials
RR	Relative risk
SBP	Systolic blood pressure
SD	Standard deviation

SDS	Standard deviation score
SMBG	Self-monitoring of blood glucose
SMD	Standardised mean difference
SVL	Severe visual loss
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TRIG	Triglycerides
UCPCR	Urine C-peptide:creatinine ratio
UKPDS	UK Prospective Diabetes Study
VTE	Venous thromboembolism
WBC	White blood cells

List of Tables

Table No.	Title	Page No.
Table 1:	Diagnostic reference values	5
Table 2:	Risk factors for T2DM.....	9
Table 3:	The baseline demographic characteristics of the OAD group.....	62
Table 4:	The DM characteristics of the OAD group.....	64
Table 5:	Vital sings of the OAD group	65
Table 6:	Blood glucose test of the OAD group.....	65
Table 7:	Laboratory findings of the OAD group	66
Table 8:	The baseline demographic characteristics of the Insulin group	67
Table 9:	The DM characteristics of the Insulin group	68
Table 10:	Vital sings of the Insulin group.....	69
Table 11:	Blood glucose test of the Insulin group	69
Table 12:	Laboratory findings of the OAD group	70
Table 13:	Comparison between both groups in average Anti-GAD 65.....	71
Table 14:	Correlations between the ANTI GAD 65 of all patients included in the study to other parameters (n=100).	72
Table 15:	Correlations between the ANTI GAD 65 of OAD group to other parameters (n=50).....	73
Table 16:	Correlations between the ANTI GAD 65 of insulin group to other parameters (n=50).	74

Table 17: Comparison of Studied groups in terms of baseline characteristics.....	75
Table 18: Comparison of Studied groups in terms of DM characteristics	76

List of Figures

Figure No.	Title	Page No.
Figure 1:	The ‘ominous octet’ of hyperglycaemia in T2DM.....	12
Figure 2:	Mechanisms of insulin resistance.	19
Figure 3:	Schematic representation of the GABA shunt.	22
Figure 4:	Cycle of inactivation and reactivation of glutamate decarboxylase.....	23
Figure 5:	Immunocytochemical visualization of GABA in cortical neurons in cell culture. ...	27
Figure 6:	Islet cell autoimmunity in T2DM.	48
Figure 7:	Association between ANTI GAD 65 and Type of treatment.....	71

Introduction

Diabetes mellitus is a complex, chronic illness requiring continuous medical care with Multi factorial risk-reduction strategies beyond glycemic control. Ongoing patient self-management education and support are critical to prevent acute complications and reduce the risk of long-term complications. Significant evidence exists that supports a range of interventions to improve diabetes outcomes **(William, 2017)**.

For type 2 diabetes, there are few usual highly specific indicators, though the presence of risk factors such as obesity indicates the likelihood of developing type 2 diabetes. Hopefully, future research will reveal some specific markers of the type 2 diabetic disease process **(Kadiyala et al., 2010)**.

For the most part, in type 2 diabetic patients, positivity for Glutamic acid decarboxylase autoantibodies, as well as autoantibodies to other islet cell antigens, correlates with some of the phenotypic features consistent with those of type 1 diabetes, such as younger age at diagnosis, lower body mass index (BMI), and a loss of B-cell function. This form of disease with initial type 2-like diabetes presentation and with serological evidence of islet cell autoimmunity has been termed latent autoimmune diabetes, or type 1.5 diabetes, and has been associated with progressive decline in B-cell

function and future insulin requirement in some population **(Barinas-Mitchell et al., 2004).**

However, no study to date has assessed the progression to insulin deficiency in Glutamic acid decarboxylase antibody-positive Egyptian patients with Type 2 diabetes. This study will assess the rate of progression to insulin deficiency in Glutamic acid decarboxylase antibody positive patients with Type 2 diabetes.

Aim of the Work

This study aim to assess anti glutamic acid decarboxylase 65 levels in type 2 Egyptian diabetic patients. And if it could be used as a marker for progression to insulin deficiency and treatment with insulin.