Difficult Glycemic Control in Relation to the Presence of Diabetes-Autoantibodies among Type 1 Diabetic Patients

Thesis

Submitted for Partial Fulfillment of Master Degree in Endocrinology & Metabolism

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2018

سورة البقرة الآية: ٣٢

Acknowledgment

At first and foremost all praises and thanks to "ALLAH" who gave me the power to finish this work.

No words can ever express my deepest appreciation and gratitude to ***Professor Dr. Mohammed Saad Hamed,*** ***Professor of Internal Medicine & Endocrinology,*** *Ain Shams University, for his outstanding kind support, precious suggestions and continuous guidance throughout all stages of this work.*

I would like to thank ***Dr. Merhan Samy Nasr,*** ***Assistant Professor of Internal Medicine & Endocrinology,*** *Ain Shams University, who was very kind, supportive and helpful throughout this project.*

My great respect and thanks to ***Dr. Hanan Mahmoud Ali,*** ***Lecturer of Internal Medicine & Endocrinology,*** *Ain Shams University, for her morals, scientific support and continuous encouragement that helped me to finish my job smoothly.*

My deepest thanks are also to ***Dr. Nesma Ali Ibrahim,*** ***Lecturer of Internal Medicine & Endocrinology,*** *Ain Shams University, for her close clinical supervision and kind help.*

I am also deeply grateful to ***my dear family,*** *for their great support and help offered throughout this study.*

Noha Yehia

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List of Abbreviations

Abb.	Full term
ACEIs	*Angiotensin-converting enzyme inhibitors*
ADA	*American Diabetes Association*
AGE	*Advanced glycosylation end products*
ARBs	*Angiotensin receptor blockers*
BMI	*Body mass index*
CDE	*Certified diabetes educator*
CSII	*Continuous subcutaneous insulin infusion*
DAA	*Diabetes autoantibodies*
DCCT	*Diabetes Control and Complications Trial*
DKA	*Diabetic ketoacidosis*
DM	*Diabetes mellitus*
DPP-4	*Dipeptidyl peptidase-4*
DSME	*Diabetes self–management education*
EASD	*European Association for the Study of Diabetes*
ELISA	*Enzyme Linked ImmunoSorbent Assay*
FPG	*Fasting Plasma Glucose*
GABA	*Gamma-AminoButyric Acid*
GADA	*Glutamic Acid Decarboxylase Autoantibodies*
GDM	*Gestational Diabetes mellitus*
GLP1	*Glucagon like peptide 1*
HbA1c	*Glycosylated hemoglobin*
HHS	*Hyperglycemic hyperosmolar state*
HLA	*Human leukocyte antigen*
HMG-CoA	*3-hydroxy-3-methyl-glutaryl-coenzyme A*
HNF-1α	*Hepatocyte nuclear factor 1alpha*
HNF-1β	*Hepatocyte nuclear factor 1beta*
HNF-4α	*Hepatocyte nuclear factor 4 alpha*
HOMA IR	*Homeostatic model assessment of insulin resistance*

List of Abbreviations (Cont...)

Abb.	Full term

IAA .....*Insulin Autoantibodies*
ICA .....*Islet Cell Cytoplasmic Autoantibodies*
IDDM .....*Insulin Dependent Diabetes Mellitus*
IPF1.....*Insulin promotor factor 1*
LADA.....*Latent Autoimmune Diabetes of Adults*
MDI .....*Multiple daily injections*
MHC .....*Major Histocompatibility Complex*
MODY.....*Maturity Onset Diabetes of Young*
NOD mice.....*Non obese diabetic mice*
NGSP .....*National Glycohemoglobin Standardization Program*
OGTT .....*Oral Glucose Tolerance Test*
RBS .....*Random Blood Sugar*
SGLT-2.....*Selective sodium glucose transporter-2*
SHBG.....*Sex hormone binding globulin*
TDD.....*Total daily dose*
TIA.....*Transient ischemic attack*
WHO.....*World Health Organization*
2HrPP.....*2 hours postprandial blood glucose*

ABSTRACT

The present study revealed that the most common auto-antibody found in those patients was the GADA, it was found in 94.4% of patients, while ICA and IAA were found in 83.3% and 66.7 % respectively.

The present study also showed a high statistically significant positive correlation between GADA level and HbA1c levels (r = 0.361**,P=0.005) on the other hand there was a highly statistically significant negative correlation between GADA level and the duration of diabetes mellitus (r =-0.437**,P=0.000) also it revealed a statistically significant positive correlation between IAA level and HbA1c level (r =0.305*, P=0.018).

By doing the multivariate regression analyses we found that HbA1c level, total number of insulin units per day and the duration of developing diabetes mellitus were significant predictive factors for the presence of diabetes autoantibodies; (P=0.007), (P=0.033) and (P=0.043) respectively.

Keywords: Insulin Autoantibodies - Hepatocyte nuclear factor 4 alpha

INTRODUCTION

Diabetes mellitus is a clinic-laboratory syndrome characterized by chronic hyperglycemia due to defect in insulin secretion or action or both leading to disturbance of metabolism of carbohydrate, protein, fat, water and electrolytes.

Diabetes mellitus is the leading cause of chronic renal failure, lower limb amputations and adult blindness ***(Gupta and Mukherjee, 2014).***

There are three main types of Diabetes mellitus: type 1 DM, type 2 DM and Gestational diabetes mellitus ***(American Diabetes Association, 2017).***

An expert committee of the American Diabetes Association has recommended dividing type 1 DM into type 1A (immune-mediated*)* and type 1B (other forms of type 1 DM that include virus-triggered autoimmune response in which the immune system attacks virus-infected cells along with the beta cells in the pancreas (Coxsackie virus family or Rubella), genetic factors and idiopathic ***(Imagawa et al., 2000).***

Autoantibodies are strongly associated with the development of type 1 diabetes mellitus. The appearance of autoantibodies to one or more of the auto-antigens (Glutamic acid decarboxylase 65, Islet cell cytoplasm, or Insulin) signals an autoimmune pathogenesis of β-cell killing ***(Ziegler et al., 2013).***

Although their appearance does not follow a distinct pattern, the presence of multiple autoantibodies has the highest positive predictive value for type 1 diabetes mellitus ***(Pihoker et al., 2005).***

It is widely recognized that the presence of two or more auto-antibodies has a high sensitivity and specificity for rapid progression to insulin dependency within 5 years and may help clarify the diagnosis in some patients ***(Ziegler et al., 2013),*** In cases in which no evidence of autoimmunity can be detected, the classification used is idiopathic type 1 DM ***(American Diabetes Association, 2014).***

The autoantibodies that are associated with type 1 diabetes include (GAD65, ICA and IAA) ***(Bingley, 2010).***

GADA65 is the most commonly detected autoantibodies in newly diagnosed type 1 diabetics, it is positive in 75% of patients at time of diagnosis ***(Anna and Waytt, 2017).***

GADA is an autoantibody directed towards Glutamic acid decarboxylase GAD the enzyme that synthesizes gamma-amino-butyric acid GABA from glutamic acid, GAD is present in 'GABA-ergic' nerve cells and non-neural cells and organs such as the pancreas, where GABA is stored in synaptic-like vesicles in islet beta cells, GABA plays a role in the release of insulin, therefore the presence of GAD autoantibodies cause depleted insulin secretion ***(Fiorina, 2013).***