Study of Presence of Pancreatic Islet Cells Antibodies in A Sample of Egyptian Women with Gestational Diabetes and its Relation to the Development of Type 1 Diabetes Mellitus

Thesis

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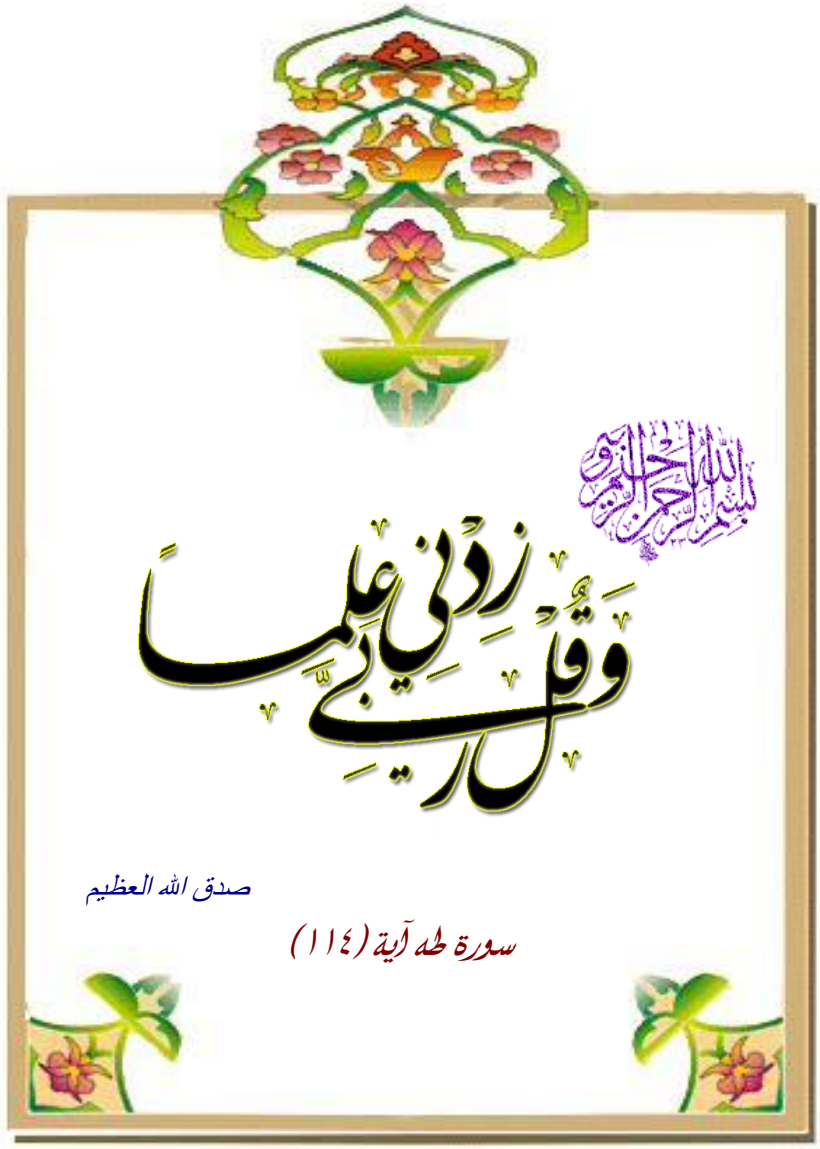

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Wesam Ahmed Mohmed

Contents

List of Abbreviations

2hPP	2- hour postprandial plasma glucose
ADA	American Diabetic Association
BG	Blood glucose
BMI	Body mass index
CAMP	Cyclic adenosine monophosphate
CD	Cluster of differantiation
DAAS	Diabetes autoantibodies
DAFNE	Dose Adusjment For Normal Eating
DAISY	The Diabetes Autoimmunity Study in The young
DBP	Diastolic blood pressure
DPT-1	The Diabetes prevention Trail
DRA	diabetes releated autoantibodies
FBG	Fasting blood glucose
GADA	Glutamic acid decarboxylase antibodies
GDGS	Guidline Development Groups
GDM	Gestational diabetes mellitus
GLP	Glucagon like peptide
GPCRS	G protein coupled receptors
ACOG	American college of obstericians and gynecologist
HCS	Human chorionic somato-mammo-tropin
hDAF	Human decay accelerating factor
HDL	High-density lipoprotein
HMD	Hyaline membrane disease
HNF	Hepatocyte nuclear factor

List of Abbreviations (Cont.)

HOMA-IR	Homeostatic model assessment of insulin resistance
IA2	Insulinoma- associated autoantibodies
IAAS	Insulin autoantibodies
ICA	Islet cell autoantibodies
IDDM	Insulin dependent diabetes mellitus
IPF	Insulinoma promotor factor
IPS CELLS	Induced pluripotent stem cells
IU	International unit
LADA	Latent autoimmune diabetes of adults
MAbs	Monoclonal antibodies
MNT	Medical nutrition therapy
MODY	Maturity onset diabetes of the young
NICE	National institute for Health and clinical Excellence
NPH	Neutral protamine Hagerdon
OGTT	Oral glucose tolerance test
PCOS	Polycystic ovary syndrome
PERV	Porcine endogenous retro-viruses
PP	Pancreatic polypeptides
SBP	Systolic blood pressure
SMBG	self-monitoring of blood glucose
TEDDY	The Enviromental Determinants in Diabetes of the young
TH-CELL	T-helper cell
VIP	Vasoactive intestinal peptide
WHO	World Health Organization
ZN T8	Zinc transporter 8

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Introduction

Gestational diabetes mellitus (GDM), defined as any degree of glucose intolerance with onset or first recognition during pregnancy, affects 3-10% of pregnancies **(National Diabetes Information Clearinghouse, 2011).** All pregnant women need to be screened for gestational diabetes. The timing of the screening depends on risk factor assessment. Pregnant women with not known history of diabetes are screened at 24-28 weeks gestation. Women at high risk for GDM are screened at the first prenatal visit. A 75-g 2-hour OGTT is the test of choice in both groups **(American Diabetes Association, 2011).**

Established risk factors for GDM are advanced maternal age, obesity, prior history of GDM or delivery of a large-for-gestation-age infant (above 4000 grams or 4500 grams) ,presence of glucosuria, diagnosis of PCOS (polycystic ovary syndrome) and strong family history of diabetes in a first degree relative **(Perkins et al., 2007*)***.

Women with unmanaged gestational diabetes are at increased risk of latent autoimmune diabetes after pregnancy. Worldwide-reported incidence rates vary from 6 to 62% **(*O'Sullivan* and Hiscock, 2010)**. The risk is highest in women who needed insulin treatment, had antibodies associated with diabetes (such as antibodies against glutamate decarboxylase, islet cell antibodies),women with more than two previous pregnancies and women who were obese **(Löbner et al., 2007)**. Women requiring insulin to manage gestational diabetes have a 50% risk of developing diabetes within the next five years **(Järvelä et al., 2010).**

The appearance of diabetes-related autoantibodies has been shown to be able to predict the development of type 1

diabetes before even hyperglycemia arises, the main ones being islet cell autoantibodies (ICAs), insulin autoantibodies (IAA), glutamic acid decarboxylase autoantibodies (GAD) . By definition, the diagnosis of type 1 diabetes can be made first at the appearance of clinical symptoms and or signs, but the emergence of autoantibodies may itself be termed "latent autoimmune diabetes". The time interval from emergence of autoantibodies to frank type 1 diabetes can be a few months up to years **(Knip et al., 2009).**

Previous studies have shown that pancreatic autoantibodies during GDM are predictive for the development of type 1 diabetes **(*Füchtenbusch et al., 2009)*.** And especially when present together with ICAs, confer a higher predictive value for the development of disease. The prevalence of ICAs in GDM varied in previous studies up to 38% **(Rubenstein et al.,2011).**

Aim of the Work:

To study the presence of anti -Islet cells antibodies in a sample of Egyptian females with Gestational diabetes mellitus and to follow these females to estimate the risk of later development of type 1 diabetes within 6 month & one year after delivery.

(1)Diabetes Mellitus

Diabetes mellitus 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 **(World Health Organization Retrieved ,2014)**

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia **(Shoback et al.,2011).**

Epidemiology of diabetes mellitus:

Globally, as of 2010, an estimated 227 to 285 million people had diabetes, with type 2 making up about 90% of the cases **(Vos et al.,2012)**.This is equal to 3.3% of the population with equal rates in both women and men. In 2011 it resulted in 1.4 million deaths worldwide making it the 8th leading cause of death. This is an increase from 1 million deaths in 2000 (**Diabetes Fact sheet ,2013).**

Its rate has increased, and by 2030, this number is estimated to almost double. Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in more developed countries. The greatest increase in rates is, however, expected to occur in Asia and Africa, where most people with diabetes will probably be found by 2030.The increase in rates in developing countries follows the trend of urbanization and lifestyle changes, perhaps most importantly a "Western-style" diet. This has suggested an environmental (i.e., dietary) effect, but there is little understanding of the mechanism at present, though there is much speculation, some of it most compellingly presented **(Wild et al.,2004).**

Classification of Diabetes Mellitus:

Diabetes can be classified into the following general categories:

Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes, and "other specific types". The "other specific types" are a collection of a few dozen individual causes **(Shoback et al.,2011).**

- ***Type 1diabetes mellitus :***

This form, previously called “insulin- dependent diabetes” or “juvenile-onset diabetes,” accounts for 5-10% of diabetes and is due to cellular mediated autoimmune destruction of the pancreatic b-cells. **(Dabelea et al.,2014)** .

Autoimmune markers include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to GAD (GAD65), autoantibodies to the tyrosine phosphatases IA-2 and IA-2b, and autoantibodies to zinc transporter 8 (ZnT8**).** Type 1

diabetes is defined by the presence of one or more of these autoimmune markers. **(Ziegler el al.,2013).**

The disease has strong HLA associations, with linkage to the DQA and DQB genes. These HLA-DR/DQ alleles can be either predisposing or protective. The rate of beta-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). **(Sorensen et al.,2013)**

Children and adolescents may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis with infection or other stress. Adults may retain sufficient beta-cell function to prevent ketoacidosis for many years; such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis. At this latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes. **(Sosenko et al.,2013).**

- ***Diabetes mellitus type 2:***

Type 2 diabetes mellitus is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion .The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 diabetes is the most common type **(Shoback et al.,2011).**

In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity. At this stage, hyperglycemia can be reversed by a variety of measures