Assessment of level of IVS1 −397T>C Estrogen Receptor α Polymorphism and its relation to levels of FSH and LH in Egyptian girls with Type 1 Diabetes mellitus

Thesis

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BY

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Abstract

40 young regularly menstruating girls with type 1 diabetes mellitus were recruited from the Paediatric Diabetes Clinic, Children's hospital, Ain Shams University in the interval from April, 2015 to November, 2015. Their age ranged 11.54 - 17.93 years with mean age 15.44 years.

All patients were subjected to a detailed medical history, physical examination, anthropometric measurments, pubertal assessment, investigation from previous follow up records (last RBS, last FBS, mean FBS in the last 6 months, last HbA1C, mean annual HbA1C and microalbuminuria), and measurements of IVS1-397T>C estrogen receptor alpha genotypes, FSH and LH.

Key words: Insulin autoantibodies - Hypothalamic-pituitary-gonadal - Diabetic ketoacidosis

INTRODUCTION

Type1 diabetes mellitus (T1DM) is among the most common chronic illnesses in adolescents ***(Liese et al., 2006; Patterson et al., 2009).*** Effective treatments exist, but non-adherence remains a major source of preventable medical expenditure and suffering ***(Borus and Laffel, 2010)***.

The prevention of diabetes is a serious worldwide challenge, but it is clear that the successful prevention of diabetes will depend on the reduction of risk factors along with better methods of screening and early detection. Type 1 diabetes mellitus is an autoimmune disease resulting from the selective destruction of pancreatic β cells. Its incidence in different ethnic groups is extremely variable, suggesting the involvement of genetic as well as environmental elements ***(Taplin and Barker, 2008)***.

The fact that diabetic patients have late sexual maturation and higher timing of menarche, especially when the disease begins before puberty. Diabetics may have normal or low gonadotropin levels and low response to gonadotropin-releasing hormone (GnRH), indicating that they probably have a limited ability to maintain an adequate pituitary reserve. In girls that manifest the first symptoms of the disease after age 11 years (expected timing of menarche), menarche occurred much later than in nondiabetics, indicating a disorder in the hypothalamic - pituitary-gonadal (HPG) axis ***(Arrais and Dib, 2006)***.

Late pubertal development due to disease duration and degree of metabolic control has been described in diabetics. Studies done twenty years ago mention a puberty delay of roughly 12 to 16 months, but studies published in the last 5 years reduce the delay to less than 6 months most likely because of the recent treatment advances, contributing to better disease control ***(Garcia-Garcia et al., 2011)***.

One of the most analyzed genetic factors that control autoimmunity is polymorphism of certain genes, which in case of particular alleles contributes to the protection against some autoimmune diseases. Conversely, however, some genetic variants induce the development and the progression of such illnesses ***(Tang et al., 2013).***

Estrogen receptor is a ligand-activated transcription factor involved in the regulation of cellular pathways that are of potential importance in vascular physiology and disorders ***(Mendelsohn and Karas, 1999).***

The human estrogen receptor has two isoforms: estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ), which are members of the steroid/thyroid hormone superfamily of nuclear receptors and encoded by separate genes ***(Cheung et al., 2003)***. ERα is expressed in chondrocytes, stromal cells, and osteoblasts ***(Oshima et al., 2007)***.

Aim of the Work

This study is designed to assess level of IVS1 −397T>C Estrogen Receptor α polymorphism and its relation to level of FSH and LH in young girls with type 1 diabetes mellitus.

Chapter 1
TYPE 1 DIABETES MELLITUS

Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disease in which destruction or damaging of the beta-cells in the islets of Langerhans results in insulin deficiency and hyperglycemia. For sure that the autoimmunity is the predominant effector mechanism of T1DM, but may not be its primary cause ***(Van Belle et al., 2011).***

Type 1 Diabetes Mellitus is the most common metabolic disease of childhood. About 1 in every 400-600 children and adolescents has T1DM. In adults, T1DM constitutes approximately 5% of all diagnosed cases of diabetes ***(Centers for Disease Control and Prevention, 2011).***

T1DM is found worldwide and is regarded as one of the main risks to human health ***(Rewers, 2012).*** T1DM is characterized by varying levels of morbidity in different populations and its prevalence increase in the majority of developed countries during the last 30 years ***(Tuomilehto, 2013; Kolesnikova et al., 2014).***

The manifestation and development of T1DM in girls often occur during formation of reproductive system (in Russia from 20% to 50% of patients under 15 years of age) ***(Dedov, 2012).*** This pathology may affect the course of pubertal growth and development, onset of menarche and the violation of

menstrual function in girls ***(Kolesnikova et al., 2015).*** Pubertal changes induce glucose metabolism or specific insulin resistance. Recent data have shown that puberty greatly increases the risk of diabetes complications and the management of this transitional age is critically important ***(Codner, 2013).***

Classification of diabetes mellitus:

Table (1): Etiological Classification of Disorders of Glycemia*:*

<table>
<tr><td colspan="2">I. Type 1
β -cell destruction, usually leading to absolute insulin deficiency
a. Autoimmune
b. Idiopathic</td></tr>
<tr><td colspan="2">II. Type 2
May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance</td></tr>
<tr><td colspan="2">III. Other specific types</td></tr>
<tr><td>A. Mongenic defects of β -cell function
1. HNF-1α MODY (MODY 3),
2. Glucokinase MODY (MODY 2)
3. HNF-4 α MODY (MODY 1)
4. Insulin promoter factor1(MODY 4)
5. HNF-1β MODY (MODY 5)
6. WFS1 Wolfram syndrome
7. Neonatal diabetes
8. Other MODY</td><td rowspan="2">F. Drug- or chemical-induced
1. Glucocorticoids
2. Vacor
3. Pentamidine
4. Nicotinic acid
5. Thyroid hormone
6. Diazoxide
7. β-adrenergic agonists
8. Thiazides
9. Dilantin
10. α -Interferon
11. Others</td></tr>
<tr><td>B. Mitochondrial diabetes</td></tr>
<tr><td>C. Genetic defects in insulin action
1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others</td><td>G. Infections
1. Congenital rubella
2. Cytomegalovirus
3. Others</td></tr>
<tr><td>D. Diseases of the exocrine pancreas
1. Fibrocalculous pancreatopathy
2. Pancreatitis
3. Trauma / pancreatectomy
4. Neoplasia
5. Cystic fibrosis
6. Haemochromatosis
7. Others</td><td>H. Uncommon forms of immune-mediated diabetes
1. Insulin autoimmune syndrome (antibodies not insulin)
2. Anti-insulin receptor antibodies
3. “Stiff-man” syndrome
4. Others</td></tr>
<tr><td>E. Endocrinopathies
1. Acromegaly
2. Cushing syndrome
3. Glucagonoma
4. Phaeochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Others</td><td>I. O ther genetic syndromes sometimes associated with diabetes
1. Down syndrome
2. Klinefelter’s syndrome
3. Turner syndrome
4. Friedreich’s ataxia
5. Huntington’s chorea
6. Laurence-Moon-Biedl syndrome
7. Myotonic dystrophy
8. Porphyria
9. Prader-Willi syndrome
10. Others</td></tr>
<tr><td colspan="2">IV. Gestational diabetes</td></tr>
</table>

(American Diabetes Association, 2013)

Epidemiology of type 1 Diabetes Mellitus:

In most western countries, T1DM accounts for over 90% of childhood and adolescent diabetes, although less than half of individuals with T1DM are diagnosed before the age of 15 years ***(Thunander et al., 2008).***

There is a clear seasonal variation in diagnosis of diabetes, and among children who had a preceding, perhaps precipitating, infection. However, seasonal factors could influence not only precipitating mechanisms just before diagnosis, but also initiating or promoting mechanisms very early in the disease process. Seasonal pattern was evident at diagnosis and at birth, which is more common during summer ***(Ismail et al, 2008).***

Pathogenesis of type 1 Diabetes Mellitus:

Genetic susceptibility:

T1DM is a disease that involves many genes. Depending on locus or combination of loci, they can be dominant, recessive, or somewhere in between. The strongest gene, IDDM1, is located in the MHC Class II region on chromosome 6, at staining region 6p21. Certain variants of this gene increase the risk for decreased histocompatibility characteristic of T1DM. Such variants include DRB1 0401, DRB1 0402, DRB1 0405, DQA 0301, DQB1 0302 and DQB1 0201, which are common in North Americans of European ancestry and in Europeans. Some variants also appear to be protective ***(Bluestone et al., 2010).***

For the child of a parent with T1DM, the risk varies according to whether the mother or the father has diabetes. Children whose mother has T1DM have a 2-3% risk of developing the disease, whereas those whose father has the disease have a 5-6% risk. When both parents are diabetic, the risk rises to almost 30%. In addition, the risk for children of parents with T1DM is slightly higher if onset of the disease occurred before age 11 years and slightly lower if the onset occurred after the parent's 11th birthday ***(Khardori and Griffing, 2013)***.

Triggering of autoimmunity:

Individuals with type 1 Diabetes Mellitus have an absolute deficiency of insulin secretion. Most cases are primarily due to T-cell mediated pancreatic islet β-cell destruction, which occurs at a variable rate. There are usually serological markers of an autoimmune pathologic process, including islet cell antibodies (ICA), insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD), the insulinoma-associated 2 molecule (IA-2) and zinc transporter 8 (ZnT-8) ***(Craig, 2009).***

The prevalence of T1DM is increased in patients with other autoimmune diseases, such as Graves disease, Hashimoto thyroiditis, and Addison disease. ***Pilia et al.*** found a higher prevalence of islet cell antibodies (ICA) and anti-GAD antibodies in patients with autoimmune thyroiditis ***(Pilia et al., 2011).***

Diet:

Cow's milk, and in particular its albumin component, has been proposed to promote islet autoimmunity, because cross-reactivity was found between serum antibodies to albumin and ICA-1 (p69), a beta-cell surface protein ***(Karjalainen et al., 1992).*** Some studies suggested early introduction of cow's milk as a predisposing factor as opposed to prolonged duration of breast feeding during infancy ***(Van Belle et al., 2011).***

Infection:

Several viruses have been identified to be associated with the development of T1DM with the strongest evidence linking the rubella virus. Individuals with congenital rubella have 20 percent likelier to develop T1DM in later life ***(Niina et al., 2005).*** Infection with enterovirus, cytomegalovirus, coxackie virus, parovirus B19, and rotavirus in susceptible individuals have been also implicated to play a role in the causation of T1DM ***(Roivainen, 2006).***

Early upper respiratory infection may also be a risk factor for T1DM. In an analysis of data on 148 children considered genetically at risk for diabetes, upper respiratory infections in the first year of life were associated with an increased risk for T1DM ***(Beyerlein et al., 2013; Melville, 2013).***

Vaccination:

Another risk factor which became very important of developing T1DM is childhood vaccination, there is a temporal association between the widespread introduction of general childhood immunizations and the increase in the incidence of T1DM in developed countries and it has been observed that specific vaccines prevent T1DM in murine models and others induce it ***(Hviid et al., 2004).***

Vitamin D deficiency:

Since vitamin D has a role in regulating the immune system and a strong anti-inflammatory effect, it has been theorized that vitamin D deficiency could contribute to autoimmune diseases such as multiple sclerosis (MS), T1DM, rheumatoid arthritis, and autoimmune thyroid disease. Scientists have suggested that vitamin D deficiency in the winter months may be the seasonal stimulus that triggers influenza outbreaks in the winter ***(Cannell et al., 2006).***

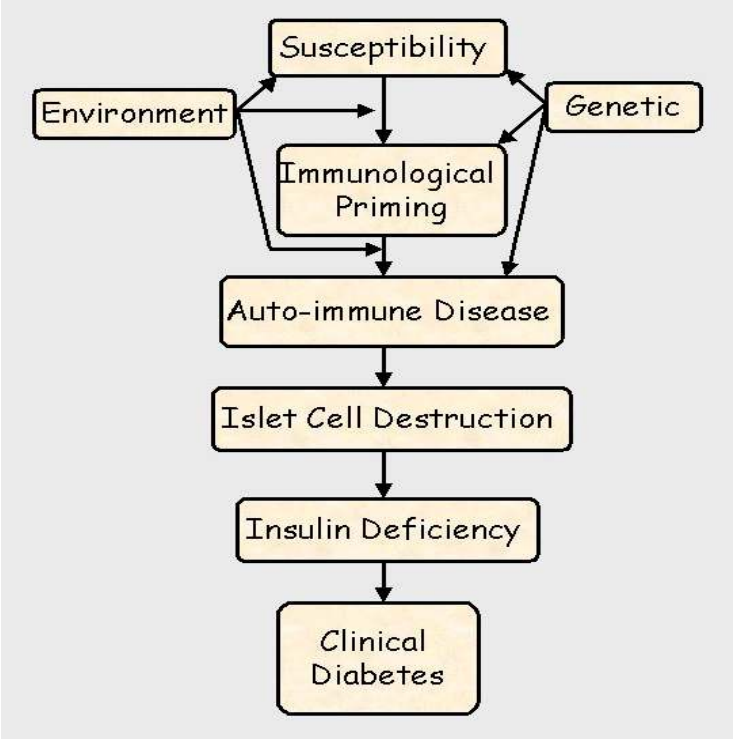

Figure (1): Possible mechanism for development of type 1 diabetes ***(Hattersley et al., 2009).***

Pathophysiology of type 1 Diabetes Mellitus:

The symptoms of hyperglycemia are similar regardless of the underlying cause and include polyuria, polydipsia, polyphagia, and (in cases of severe insulin deficiency) weight loss, blurry vision, and fatigue. Patients may be asymptomatic if mild hyperglycemia is present. Once the blood glucose concentration exceeds the capacity of the kidneys to reabsorb glucose, which is at approximately 180 mg/dL, some of this glucose is lost in the urine. This glucosuria serves as an osmotic force that increases water excretion. As urinary fluid losses

increase, the thirst center is activated to work to maintain normal hydration. The glucosuria also leads to a loss of calories, this combined with the loss of the anabolic actions of insulin results in weight loss. Insulin resistant adolescents may exhibit other signs of insulin resistance such as obesity, acanthosis nigricans of the neck, axillary area, knees, or inguinal creases, hypertension, and, in females, a history of oligomenorrhea or even amenorrhea ***(Dombrowski and Karounos, 2013).***

Insulin is essential to process carbohydrates, fat, and protein. Insulin reduces blood glucose levels by allowing glucose to enter muscle cells and by stimulating the conversion of glucose to glycogen (glycogenesis) as a carbohydrate store. Insulin also inhibits the release of stored glucose from liver glycogen (glycogenolysis) and slows the breakdown of fat to triglycerides, free fatty acids, and ketones. It also stimulates fat storage. Additionally, insulin inhibits the breakdown of protein and fat for glucose production (gluconeogenesis) in both liver and kidneys ***(Dombrowski and Karounos, 2013).***

Diagnosis of type 1 Diabetes Mellitus:

Clinical pictures type 1 Diabetes Mellitus:

Main symptoms of T1DM are polyuria, polydipsia, polyphagia, and unexplained weight loss. Other symptoms may include fatigue, nausea, and blurred vision.

The onset of symptomatic disease may be sudden. It is not unusual for patients with T1DM to present with diabetic ketoacidosis (DKA) ***(Clarke et al., 2009).***

Laboratory investigations of type 1 Diabetes Mellitus:

For decades, the diagnosis of diabetes was based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h value in the 75-g oral glucose tolerance test (OGTT) ***(ADA, 2013).***

Table (2): Criteria for Diabetes Mellitus Diagnosis: 4 options:

HbA1C ≥6.5%*   Perform in lab using NGSP-certified method and standardized to DCCT assay.
FPG ≥126 mg/dL (7.0 mmol/L)*   Fasting defined as no caloric intake for ≥8 hrs.
2-hr PG ≥200 mg/dL (11.1 mmol/L) during OGTT (75-g)*   Performed as described by the WHO, using glucose load containing the equlivalent of 75g anhydrous glucose dissolved in water.
Random PG ≥200 mg/dL (11.1 mmol/L)   In persons with symptoms of hyperglycemia or hyperglycemic crisis.
* In the absence of unequivocal hyperglycemia results should be confirmed using repeat testing.
Unless clinical diagnosis is clear, same test to be repeated using a new blood sample for confirmation, 2 discordant results? Result above cutpoint should be repeated.

Diabetes Control and Complications Trial (DCCT), fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), National Glycohemoglobin Standardization Program (NGSP), oral glucose tolerance test (OGTT), plasma glucose (PG) ***(ADA, 2015).***