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Immunological Relation Of Atopy With Type1 Diabetes in Children

Thesis
Submitted for Partial Fulfillment
Of Master Degree in Childhood Studies

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Introduction

There has been considerable interest in defining the relationship between the expression of allergic and autoimmune diseases in populations of patients. Many questions that appeared as if patients that have autoimmune diseases is‘protected’ from developing allergic diseases? Does an atopic phenotype reduce the risk of the subsequent development of autoimmune diseases? **(Martinez, 2007)**

Type 1 diabetes mellitus is a multisystem disease with both structural and biochemical consequences. It is a chronic disease of carbohydrate, fat and protein metabolism due to defect in insulin which results from marked inability of the pancreas to secrete insulin because of autoimmune destruction of the beta cells **(Joergensen et al., 2011)**.

Insulin is produced by the beta cells of the islets of Langerhans located in the pancreas, and the absence, destruction, or other loss of these cells results in type 1 diabetes (insulin-dependent diabetes mellitus [IDDM]). Most children with diabetes have type 1 diabetes mellitus (T1DM) and a lifetime dependence on exogenous insulin**(Rosenbloom et al., 2009).**

Type 1 diabetes occurs at any age. It occurs commonly at childhood but it also occurs in adults, especially in last 30s and early 40s **(Philippe et al., 2011)**.

Atopy is the propensity of an individual to produce IgE antibodies in response to various environmental antigens and to develop strong immediate hypersensitivity (allergic) responses. People who have allergies to environmental antigens, such as pollen or house dust are said to be atopic **(Abbas and Lichtman,2008)**.

Atopic disease occurs when the immune system is dysregulated, resulting in allergic inflammation. Genetic and environmental factors determine the dysregulation and the development of an atopic disease.

T-helper 1 (Th1) and T-helper 2 (Th2) cells play a key role in type 1 diabetes and atopic diseases, respectively. Because theTh1 and Th2 cells mutually inhibit each other (McGeady, 2004), it has been speculated that patients with type 1 diabetes have a lower predisposition to atopy. However, the findings have been conflicting **(Cardwell et al., 2003)**.

An excessive proinflammatory response by Th1 lymphocytes is believed to be a common basis for autoimmune disorders, whereas excessive Th2-type cytokine production (interleukins 4, 5, and 13) is associated with of

IgE and eosinophilic responses and is believed to be the cause of allergic disorders. Data on the relationship between Th2-related atopic disorders and Th1-related autoimmune diseases are conflicting. Some epidemiologic studies have suggested that Th2-weighted imbalance, which favors allergic response, may be protective against Th1-related autoimmune disorders. For example, atopic eczema is associated with a lower risk for type 1 diabetes mellitus in children **(Stene and Joner,2004)** and another study reported a reduction in the frequency of allergic symptoms in children with type 1 diabetes **(Caffarelli et al.,2004)**.

A defining characteristic of the atopic immune system is the capacity to generate elevated IGE antibodies and disturbance to immune regulation in the differentiation pathway of T-helper 0 (Th0) cells. These precursor cells are induced to differentiate into T-helper 2 (Th2) cells that typically produce IL−4, IL−5, and IL−13. Th2 cells control the synthesis of IgE. Th1 and Th2 cells have been found to be mutually antagonistic, leading to either Th1- or Th2-dominated responses upon immunization. Because in chronic inflammatory autoimmune diseases such as insulin dependent diabetes mellitus (IDDM), Th1 cells are pathogenic and Th2 cells are protective, one might expect a negative association between atopy with Th2 phenotype and diseases with Th1 phenotype **(Friedman and Holden 2004).**

This has raised questions as to whether a decreased risk of atopy among children with type 1 diabetes is due to reciprocal effect of T helper 1 and T helper 2 immune response. **(Dahlq et al., 2000)**.

A study in adults found no relationship between atopy and a history of autoimmune disorders **(Sheikh et al.,2003)**.

Aim of the study

his study was conducted to assess immunological relation between atopic disease and type 1 diabetes mellitus .

Diabetes Mellitus

Definition:

iabetes 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, 2015).**

The major forms of diabetes due to deficiency of insulin secretion due to pancreatic B-cell damage (type 1 DM) ,or due to insulin resistance at the level of skeletal muscle ,liver ,and adipose tissue , with various degrees of B-cell impairment**(Alemzadeh and Ali, 2011)**.

In one category, type 1 diabetes, due to an absolute deficiency of insulin secretionm and this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers. In the other category, type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response causing hyperglycemia sufficient to cause pathologic and functional changes in various tissues, but without clinical symptoms, may for a long period before diagnosis,and an abnormality in carbohydrate metabolism can be demonstrated by measurement of fasting plasma glucose or after a challenge with an oral glucose load **(American Diabetes Association, 2015).**

Classification: **American Diabetes Association** proposed a classification distinguished the types of diabetes according to aetiology.

Table (1): Etiological Classification of diabetes mellitus

<table>
<tr><td>I. type 1Diabetes mellitus
A.Autoimmune B. Idiopathic</td><td>II. type 2 Diabetes mellitus: Ranges from relative insulin deficiency to disorders of insulin secretion and insulin resistance</td></tr>
<tr><td colspan="2">III. Other specific types of diabetes mellitus</td></tr>
<tr><td>A. Genetic defects in β-cell function

1. Chromosome 12, HNF−1α (MODY 3)

2. Chromosome 7, glycosidase (MODY 2) 3. Chromosome 20, HNF−4α (MODY 1)

4. Mitochondrial DNA 5. Monogenic diabetes</td><td>B. Genetic defects in insulin action

1. Type A insulin resistance 2. Leprechaunism

3. Rabson-Mendenhall syndrome

4. Lipotrophic diabetes</td></tr>
</table>

C. Disease of the exocrine pancreas 1. Pancreatitis 2. Pancreatectomy/trauma 3. Neoplasia 4. Cystic fibrosis 5.Hemochromatosis 6.Fibrocalcific pancreatopathy	**D. Endocrinopathies** 1. Acromegaly 2. Cushing syndrome 3. Glucagonoma 4. Pheochromocytoma 5. Hyperthyroidism 6. Somatostatinoma 7. Aldosteronom
E. **Pharmacologically or chemically induced** 1. Vacor 2. Pentamidine 3. Nicotinic acid 4. Glucocorticoids 5. Thyroid hormones 6. Diazoxide 7. β-adrenergic agonists 8. Tiazides 9. Dilantin 10. α interferon	**F. Infections** 1. Congenital rubeola 2. Cytomegalovirus
G. Infrequent forms of autoimmune diabetes 1. Stiff-man syndrome) 2. Antibodies against insulin receptors	H.Other syndromes occasionally associated with diabetes 1. Down syndrome 2. Klinefelter syndrome 3. Turner syndrome 4. Wolfram syndrome 5. Friedreich ataxia 6. Huntington's chorea 7. Lawrence-Moon-Biedel syndrome 8. Myotonic dystrophy 9. Porphyria 10. Prader-Willi syndrome
IV. Gestational diabetes mellitus Occurs in mostly in women during gestation	

(ADA,2015)

Type 1Diabetes Mellitus

Type 1 diabetes is chronic immune mediated destruction of pancreatic β-cells, causing partial, or in most cases, absolute insulin deficiency. The majority of cases (type 1A) result from

autoimmune destruction, at a variable rate, and becomes clinically symptomatic when approximately 90% of pancreatic β-cells are destroyed. (ISPAD, 2014).

Epidemiology of type 1 diabetes

An increas in type 1 diabetes incidence has been observed in recent decades **(Harjutsalo et al., 2013**). In some reports there has been a disproportionately greater increase in children under the age of 5 yr and in developing countries or those undergoing economic transition in recent decades **(Sipetic et al., 2013)**. In some reports there is evidence for a plateau in incidence in some countries in recent years **(Skrivarhaug et al., 2014)**. The rising incidence of type 1 diabetes is associated with an increased proportion of individuals with low-risk HLA genotypes in some populations, suggesting an increasing role for environmental factors in the disease etiology. **(Fourlanos et al., 2008),** gender differences in the incidence of type 1 diabetes are observed in some, but not all, populations. However, a male gender bias is generally observed in older adolescents and young adults **(Skordis et al., 2012)**

Familial aggregation is about 10% of type 1 diabetes , and more than 20% for the extended family history, with no recognizable pattern of inheritance. (**Parkkola et al., 2012)**

In the offspring of diabetic men type 1 diabetes is two to three times (3.6–8.5%) compared with diabetic women (1.3–

3.6%). The risk of type 1 diabetes is approximately 4% for offspring of adult onset (15–39 yr) type 1 diabetes, the offspring of mothers and fathers with a similar recurrence risk **(Harjutsaloet al., 2010)**

Pathogenesis of type 1 diabetes.

Type 1 diabetes is chronic immunemediated of pancreatic β-cells destruction, leading to partial or mostly, absolute insulin deficiency. Autoimmune mediated pancreatic β-cell destruction, occurs at a variable rate, and becomes clinically symptomatic when approximately 90% of pancreatic β-cells are destroyed. The etiology is multifactorial; however, the specific roles for genetic and environmental factors, the immune system, and β cells in the pathogenesis remain unclear **(ISPAD, 2014)**

Diabetes-associated autoantibodies, which are serological markers of β-cell autoimmunity, include GAD, IA2, IAA, and ZnT8. The expression of these antibodies is age-dependent, with IAA and ZnT8 more commonly expressed in children aged <10 yr, while GAD and IA−2 are associated with older age and GAD with female gender.Susceptibility to autoimmune type 1 diabetes is detected by multiple genes; and more than 60 risk loci identified by genome-wide association studies. **(ISPAD, 2014)**

Human leukocyte antigen (HLA) genotype is approximately 50% of risk; specific combinations of HLA DR and DQ alleles detect susceptibility in the Caucasian population. Individuals who are heterozygotes for the two HLA haplotypes (DR3/4), the odds ratio is 30 for development of autoimmunity to islet, however, <10% of those with HLA conferred diabetes susceptibility genes progress to clinical disease . Combination of diabetes-associated autoantibodies, genetic markers, intravenous glucose tolerance test (IVGTT) and/or OGTT, increase risk of developing type 1 diabetes **(ISPAD, 2014)**

The environmental factors initiating destruction of pancreatic β-cell largely unknown, but usually this process begins months to years before the clinical symptoms appeare. Enterovirus have been detected in the islets of individuals with diabetes and has been associated with development of autoimmunity to islet and type 1 diabetes in many populations. Type 1B (idiopathic) is the clinical presentation of type 1 diabetes but no antibodies. Most cases are of African or Asian ancestry, however, other forms, including type 2 and monogenic diabetes, should also be considered (as shown in Table 2). Increase rate of DKA at presentation occur in areas with lower incidenceof diabetes. **(ISPAD, 2014)**

Table (2): Clinical characteristics of type 1 diabetes, type 2 diabetes and monogenic diabetes in children and adolescents**.**

Characteristic	**Type 1**	**Type 2**	**Monogenic**
Genetics	Polygenic	Polygenic	Monogenic
Age of onset	6 months to young adulthood	Usually pubertal (or later)	Often post pubertal except Glucokinase and neonatal diabetes Variable (may be incidental in glucokinase)
Clinical presentation	Most often acute, rapid	Variable; from slow, mild (often insidious) to severe	Variable (may be incidental in GCK)
Associations Autoimmunity Ketosis	Yes Common	No Uncommon	No Common in neonatal diabetes, rare in other forms
Obesity	Population	Increased frequency	Population frequency
Acanthosis nigricans	No	Yes	No

Frequency (% of all diabetes in young people) Parent with diabetes	Usually 90%+ 2–4%	Most countries 80	1–3% 90%

(ISPAD, 2014)

Phases of type 1 diabetes in children and adolescents **(ISPAD, 2014)**

1-Pre-clinical diabetes

Preclinical diabetes (stages 1–3) refers to the months or years preceding the clinical presentation of type 1 diabetes and during this period antibodies to islet as markers of autoimmunity can be detected:

- Glutamic acid decarboxylase 65 autoantibodies (GAD)
- Tyrosine phosphatase-like insulinoma antigen 2 (IA2) and islet cell antibody 512 (ICA512)
- Insulin autoantibodies (IAA)
- B-cell-specific zinc transporter 8 autoantibodies (ZnT8)

(ISPAD, 2014)

2-Presentation of type 1 diabetes