THE IMPLICATION OF THE PRESENCE OF OTHER DIABETES-ASSOCIATED AUTOIMMUNE DISORDERS ON THE DISEASE OUTCOME

THESIS

Submitted for partial fulfillment of Master Degree
in Pediatrics by

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رؤية الكلية

تصبو كلية الطب جامعة عين شمس أن تكون الأولى بمنطقة الشرق الأوسط لتخريج أطباء ذوى قدرات تنافسية وأن تقود الإصلاح فى التعليم الطبى.

رسالة الكلية

تقوم كلية الطب جامعة عين شمس بإعداد خريج مدرب ذى مهارة تنافسية على المستوى المحلى والإقليمى، وقادر على التعليم والتعلم والتدرب مدى الحياة وملتزم بمعايير الخدمة الطبية والأخلاق المهني. وتسعى الكلية إلى التطوير المستمر للبرامج والمقررات ودعم وتطوير البحث العلمى مع التوسع فى الأبحاث العلمية التطبيقية وبرامج الرعاية الصحية لخدمة احتياجات المجتمع وتنمية البيئة.

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Protocol

Introduction:

The incidence of diabetes in children has increased steadily over the last 20 years and now affects around 2 per 1000 children by 16 years of age. It has been estimated that the incidence of childhood diabetes will double by 2020 in developed countries ***(Dimitri and Wales, 2012)***.

Type 1 diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas. Markers of the immune destruction of the β-cell include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to GAD (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β. One and usually more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycemia is initially detected. Also, the disease has strong HLA associations, with linkage to the DQA and DQB genes, and it is influenced by the DRB genes. These HLA-DR/DQ alleles can be either predisposing or protective. ***(American Diabetes Association, 2011)***.

This genetic predisposition may increase the liability to other autoimmune diseases such as celiac disease, thyroid disease, Addison's disease (adrenal insufficiency), vitiligo, alopecia and gastric autoimmunity***. (Dretzke et al., 2004).***

There is strong evidence for an increased occurrence of celiac disease in children with type 1 diabetes ***(Dretzke et al, 2004)*** and ***(Hill et al, 2005)***. It has been estimated that 6 to 8 % of children with type 1 diabetes have concomitant celiac disease ***(American Gastroenterological Association, 2001).***

Celiac sprue is a chronic intestinal disorder caused by hypersensitivity to prolamins, the glutamine- and proline-rich gluten proteins contained in wheat, rye, and barley. Genetically predisposed subjects who ingest cereal proteins develop an inflammatory enteropathy characterized by proliferation of intraepithelial lymphocytes, crypt hyperplasia, and partial or complete atrophy of small intestinal villi. The inflammatory response is induced by cross-linking and transamidation of gluten peptides by tissue transglutaminase, an enzyme localized to the connective tissue (lamina propria or endomysium) underlying the epithelial cells of the small intestine. Posttranslational modification of gluten enhances its uptake by dendritic cells and its binding to HLA-DQ2 and DQ-8, which induce T-cell activation and cytokine release. The resulting inflammation is accompanied by development of circulating antibodies to transglutaminase and to the endomysium ***(Schuppan and Hahn, 2002).*** That's why Anti-tissue transglutaminase and endomysial autoantibodies are the most sensitive and specific markers for screening of celiac disease***. (Setty et al., 2008)***

Inflammation of the villous surface gives rise to malabsorption of foodstuffs, folate, fat-soluble vitamins, and iron. Young children with classical symptomatic celiac disease may present with diarrhea and growth failure, muscle wasting, hypotonia, pallor, edema, anemia, and in some cases, rickets. Older children and adults with classical celiac disease may have episodic diarrhea, steatorrhea, weight loss, and osteoporosis, and the risk of gastrointestinal malignancy is increased ***(Farrell and Kelly, 2001) (Collin et al., 2002).***

Early identification of celiac disease and subsequent treatment improves growth and diabetic control in children with Type 1Diabetes ***(Saadah et al., 2004) and (Peretti et al., 2004).*** Most diabetic children with celiac disease have silent or subclinical forms of the illness ***(Farrell and Kelly, 2001)*** and only a small minority (48 of 400 in a recent meta-review) is identified by clinical symptomatology ***(Collin et al., 2002***). Most patients have no gastrointestinal complaints or history of food intolerance or food avoidance; some have mild abdominal discomfort, but this is often ascribed to glycemic instability, diabetic gastropathy, or gastroesophageal reflux.

Erratic absorption of nutrients in symptomatic celiac disease may increase the risk of severe hypoglycemia in diabetic patients; the effects on glycemic control and HbA1c are more variable. Recurrent or severe hypoglycemia may compromise neurologic

function in diabetic children. ***(Holmes, 2001), (Collin et al., 2002) and (Amin et al., 2002).***

Untreated subclinical celiac disease in diabetic children may increase the risk of hypoglycemia, while early identification and treatment may reduce hypoglycemic risk ***(Mohn et al., 2001).***

Guidelines from the American Diabetes Association ***(Silverstein et al, 2005)*** recommend that children and adolescents with type 1 diabetes should be screened for celiac disease. The ADA recommends celiac disease testing soon after the diagnosis of diabetes and subsequently if growth failure, failure to gain weight, weight loss, or gastroenterologic symptoms occur. The ADA also states that consideration should be given to periodic re-screening of children and adolescents with negative antibody levels. Guidelines from the National Collaborating Centre for Women's and Children's Health recommend screening children and adolescents with type 1 diabetes for celiac disease at diagnosis and at least every 3 years thereafter. ***National Collaborating Centre for Women's and Children's Health (2004)***

Aim of the Work:

To co-relate the presence of Anti-insulin Antibody and / or Anti-tissue Transglutaminase Antibody in type 1 diabetic patients regularly attending the pediatric diabetes clinic at Ain Shams University with the short and long term complications.

Patients and Methods:

Inclusion criteria:

This cohort study will include 150 Type 1 diabetes mellitus children and adolescents regularly attending the Pediatric diabetes clinic at Ain Shams University. The patients will be taken consecutively from those patients following up at the Diabetes clinic. An informed consent will be obtained from each patient or their legal guardians before enrollment in the study.

Exclusion criteria:

All patients aged more than 18 years old.

All included patients will be subjected to the following:

- Detailed medical history taking with special emphasis on:
  - Age of onset and duration of the diabetes mellitus.
  - Insulin dosage in units per day.

- Symptoms suggestive of hypoglycemia or diabetic complications such as renal, ophthalmological, neurological or bones affection.
- Symptoms suggestive of celiac disease such as failure to thrive, chronic diarrhea or abdominal distention.
- Patients' files will be reviewed for frequency of decrease or increase in glycemic control during the last 2 years.

- Clinical examination including:
  - General examination:

  Vital data as pulse, blood pressure…

  Anthropometric measures as weight, height, BMI and plot them against relevant centiles.
  - Local examination: system review
- Investigations: Blood and urine samples will be collected from all patients to detect:
  - RBS and serum HbA1c of the last visit.
  - Serum Mean HbA1c and Mean RBS over the last year.
  - Serum Anti insulin Ab. by ELISA.***(WilleinT et al., 1985)***
  - Serum Anti Tissue Transglutaminase Ab. by ELISA.***(Giersiepen K et al., 2012)***

Statistical Analysis:

All data collected will be analyzed using SPSS software.

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