A Study to Assess Type 1 Diabetes-Associated Disorders; Single Center Experience

Thesis

Submitted for Partial Fulfillment of M.Sc degree in

Pediatrics

BY

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Introduction

DM is a group of pandemic debilitating metabolic diseases featuring chronic hyperglycemia which results from defective insulin secretion and/or insulin actions. Such chronic hyperglycemia typically elicits dysfunction and failure of various organs, particularly the eyes (diabetic retinopathy and cataract), kidneys (diabetic nephropathy), nerves (diabetic neuropathy), heart (diabetic cardiomyopathy) and blood vessels (microangiopathy) ***(ADA, 2009).***

The current estimated prevalence of diabetes worldwide is 285 million people of which 5 – 10% are of the Type 1 variety (IDF- Diabetes Atlas). Most cases of Type 1 diabetes are thought to have an autoimmune basis, with various environmental factors interacting with an underlying genetic predisposition, leading to selective autoimmune destruction of pancreatic beta cells ***(Foulis, 1987).*** In keeping with the autoimmune etiology, other (organ-specific) autoimmune diseases occur with increased frequency in this situation. These include Addison's disease (adrenocortical failure), Grave's hyperthyroidism, hypothyroidism, hypogonadism, coeliac disease, pernicious anemia and vitiligo ***(Williams and Pickup, 1999).*** The term

autoimmune polyendocrine syndromes encompass some of these associations ***(Eisenbarth and Gottlieb, 2004)***

Autoimmune thyroid disease (AITD) is the most frequent autoimmune disease associated with type 1 diabetes mellitus. The prevalence of thyroid autoimmunity in patients with type 1 diabetes has been reported to be two to four times more frequent than in control population. In control population the prevalence of thyroid autoimmunity ranges from 2.9% to 3.2%, while in young patients with type 1 diabetes the prevalence is higher, ranging from 19% to 23.4% ***(Kakleas et al., 2009)*** Dyslipidemia and arrhythmia are the main features frequently accompanying impaired thyroid gland function in non-diabetic subjects. Moreover, thyrotoxicosis can worsen metabolic control of diabetes and increase its liability often with a need for increased insulin dosage. Hypothyroidism can lead to increased frequency of hypoglycemia in diabetic patients. The screening and diagnosis of AITD are based on the assessment of autoantibodies to thyroid peroxidase (anti-TPO) and thyroglobulin (anti-TG). The prevalence of these autoantibodies is dependent on gender, age of patient, and age at the onset of diabetes. It also varies in different geographic regions and is known to be higher in regions

with higher iodine intake ***(De Block et al., 2001, and Premawardhana et al., 2000).***

The prevalence of thyroid autoantibodies in children with type I DM varies between 3% and 50% in different countries ***(Radetti et al., 1995).*** Thyroid autoantibodies against microsomes (AMA) tend to have more correlation with thyroid dysfunction than does autoantibody against thyroglobulin (ATA) ***(Nordyke et al., 1993).*** Detection of antibodies against thyroid peroxidase (anti-TPO), a major antigen for microsomal autoantibody, appears to obviate the need for AMA and ATA measurement because of the improvement in specificity and sensitivity of the method ***(Feldt-Rasmussen, 1996).*** The prevalence of anti-TPO antibodies in type 1 diabetic patients who are clinically euthyroid have been reported to vary from 10% to 21.8%, but progression to overt thyroid disorders in individuals with significant titers of anti- TPO occurs in about 50% of them within 3-4 years ***(Kordonouri et al., 2002).*** The diagnosis of thyroid dysfunction is often made late in type 1diabetic population.

A symmetric, painless goiter is usually the first presentation of autoimmune thyroid disease, while atrophic thyroid gland is observed in 10% of patients. A subclinical hypothyroidism has been reported up to 58% of patients

with thyroid autoantibodies. Early recognition and treatment of hypothyroidism is important, since the decrease in basal metabolism may exert weight gain, dyslipidemia, atherosclerotic heart disease, sometimes goiter, and may negatively affect metabolic control. Hypothyroidism is confirmed by low free thyroxin and high TSH levels. Compensated hypothyroidism mean normal thyroxine levels with increased TSH. Substitutive L-thyroxin treatment exerts normalization of TSH levels and goiter regression when present. Treatment with L-thyroxin in patients with type 1 diabetes, thyroid autoantibodies and thyroid enlargement is safe and effective to reduce thyromegaly, with no effect on thyroid autoantibodies titer ***(Brown, 2007, Kordonouri et al, 2007, Karges et al. 2007).***

In young patients with type 1 diabetes mellitus overt hyperthyroidism is rarely encountered. It may be expression of Graves' disease or the transient hyperthyroid phase of Hashimoto's thyroiditis. Unstable metabolic control despite strict compliance, weight loss despite regular food intake, agitation, tremors, tachycardia, insomnia, heath intolerance, thyroid enlargement and characteristic eye signs are the main clinical features ***(Kordonouri et al, 2009).***

Aim of the Work

To co-relate the presence of autoimmune thyroiditis to type 1 diabetic children and adolescents regularly attending the pediatric diabetes clinic and its relation to insulin antibodies, metabolic control (hypoglycemic and hyperglycemic attacks) and long term diabetic complications

Patients and Methods

The study will evaluate 150 type 1 Diabetes mellitus Children and adolescents recruited consecutively from those patients regularly attending and under follow up at the Pediatric diabetes clinic at Ain Shams University. An informed consent will be obtained from each patient or their legal guardians before enrollment in the study.

Inclusion Criteria:

All type 1 Diabetes mellitus children and adolescents regularly attending and follow up at the pediatric diabetes clinic.

Exclusion Criteria:

All patients above age of 18^{th}.

All included patients will be subjected to the following;

1. Detailed Medical history taking with special emphasis on;

- Age of onset of the disease.
- Duration of the disease.
- Insulin dosage in units /day, mean HbA1c over the last year.

- Symptoms suggestive of diabetic complications; retinopathy, nephropathy, neuropathy, cardiovascular and cerebrovascular diseases.
- History of hypoglycemia.
- Symptoms suggestive of autoimmune thyroiditis; thyroid enlargement (goiter), menstrual disorder, short stature, nervousness in girls, constipation, exophthalmoses, hot or cold intolerance, weight loss or gain, sweating.

2. Clinical examination laying stress on the following;

- General examination; including vital data measures as pulse & blood pressure
- Local examination; chest, heart, abdomen, skin and neurological examination
- Neck examination for thyroid enlargement
- Anthropometric measures; weight, height, BMI plotted against relevant centiles.

3. Investigations;

- Random blood sugar
- Serum HbA1c in the last visit
- Mean Serum HbA1c
- Micro albumin in urine.
- Serum thyroid peroxidase antibodies (Anti-TPO) measured by ELISA and serum thyroglobulin

antibodies (ANTI-TG) autoantibodies to thyroglobulin measured by ELISA ***(Chang et al., 1998).***

- Insulin antibodies.

4. Statistical Analysis;

- Data will be analyzed Using SPSS 22.

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