Prevalence of Thyroid Disorder in Egyptian Children with Type I Diabetes Mellitus and the Prevalence of Thyroid Antibodies Among them

Ghada Z A Soliman*, Nehal M Bahagt2 and Zeinb EL-mofty1

1Assistant Professor of Biochemistry, National Nutrition Institute, Cairo, Egypt
2Assistant Professor of Physiology, Faculty of Medicine, Ain Shams University, Egypt

Abstract

Type I diabetes mellitus (IDDM) may be associated with an autoimmune disorders including autoimmune thyroid disease (reaction to thyroid antigens including thyroid peroxidase (anti-TPO) so we aimed to see prevalence of thyroid disorder in a sample group of Egyptian children (8-12 years) with type I diabetes mellitus and to investigate the prevalence of thyroid auto antibodies among them. Five hundred children with prior diagnosis of type I diabetes mellitus and 500 normal euthyroid non diabetic children were included. Glucose, HbA1c, antibodies to thyroperoxidase (anti-TPO), FT3, FT4 and thyroid-stimulating hormone (TSH) levels were determined. Mean age was 10.16 ± 0.07; 9.66 ± 0.08 for control and diabetic children respectively. Mean duration of diabetes was 4.10 ± 0.06 year. The anti-TPO antibody test was positive in 56 out of the 500 children studied (11.2%), resulting in prevalence of 11.2%. Children with positive anti-TPO antibodies had abnormal TSH levels (subclinical hypothyroidism). Mean glycated hemoglobin was higher in IDDM children (8.55 ± 0.03 vs. 4.95 ± 0.03 (P<0.05)). TSH was significantly higher in children with thyroid autoimmunity ((diabetic with TSH < 5 μU/ml vs. diabetic with TSH > 5 μU/ml); and 5.88 vs. 3.0 μU/ml (diabetic vs. normal control); P<0.001). 56 children of 500 (11.2%) had TSH over 5 μU/ml (range 5.05: 6.9 μU/ml). Subclinical hypothyroidism was observed in 11.2% among children with thyroid autoimmunity.

Keywords: IDDM; Thyroid disorder; Anti-TPO

Aim

Aim of the study was to see prevalence of thyroid disorder in a group of Egyptian children (8-12 years) with type I diabetes mellitus and to investigate the prevalence of thyroid auto antibodies among them.

Introduction

Insulin Dependent Diabetes Mellitus (IDDM) is caused by autoimmune destruction of insulin producing β-cells of the pancreas in genetically susceptible individuals [1]. Diabetes Mellitus (DM) and thyroid diseases are two common endocrinopathies seen in general population [2]. Thyroid stimulating hormone (TSH) is released from the pituitary gland and stimulates the thyroid gland to release thyroid hormones T3 and T4. Measuring levels of TSH is one way to assay the function of a child's thyroid gland. Typically, levels of TSH are quite high immediately after birth, and fall to adult levels by school age. TSH levels in school-age children normally ranges from 0.6 to 5.5 μunits/ml of blood.

There are several reports indicating an association between thyroid hormone levels and insulin resistance in euthyroid subjects. An inverse correlation was found between free thyroxine (FT4) levels and insulin resistance in euthyroid subjects [3].

Thyroperoxidase is a marker of autoimmune thyroiditis, which is often clinically silent but may progress to either overt or subclinical hypothyroidism [4]. Hypothyroidism can lead to growth delay, weight gain, menstrual abnormality, hyperlipidemia, and cardiovascular complications in diabetic patients [5].

Materials and Methods

The study was approved by the ethical comity and an informed verbal consent was taken from each and every child's parent.

The children were selected from the governmental (GO) and non governmental organization (NGO's) with pre-diagnosed Type I diabetes mellitus located in Cairo. The study population consisted of 1000 children aged 8-12 years, 500 children with pre-diagnosed type I diabetic children and 500 healthy euthyroid non diabetic children. The criteria for diagnosis of type I diabetes were the American Diabetic Association criteria [6]. All children with diseases that may affect thyroid function were excluded. The children on medications that can affect thyroid function were also excluded. The non diabetes children without history of diabetes mellitus whose fasting blood glucose were less than 110 mg /dl were taken as the control samples. The controls were not taking any drugs.

Venous blood sample were withdrawn and assayed for thyroid function such as FT4, FT3, TSH, Anti TPO, fasting blood glucose and glycated haemoglobin (HbA1c). Free triiodothyronine (FT3) were assayed using Accu-bind ELISA microwells kits 1325-300, Monobind Inc., Lake forest, CA, USA according to [7]. Free thyroxine (FT4) were assayed using Accu-bind ELISA microwells kits 1225-300, Monobind Inc., Lake forest, CA, USA according to [8]. Thyrotropin or thyroid stimulating hormone (TSH) were assayed using Accu-bind ELISA microwells kits 325-300, Monobind Inc., Lake forest, CA, USA according to [9]. Anti TPO were determined using Anti-TPO, ORG 503 kits of ORGENTEC Diagnostika GmbH, Carl-Zeiss-Straße 49, 55129 Mainz according to [10]. Glycated was determined using Randox kit.
according to [11]. HbA1c was determined using Human kits (Human Gesellschaft Für Biochemica und Diagnostica, mbh, Wiesbaden, Germany) according to [12].

Statistical Analysis

All the data are represented as mean ± SEM. using SPSS (Statistical Program for Social Science) statistical package (SPSS Inc) version 11 (SPSS Inc, Chicago, IL, USA). The correlation coefficients were determined by Pearson’s simple linear regression analysis (SPSS, v 11). A value of P < 0.05 was considered statistically significant.

Determination of Normal Range or Cut-off Limits (Point) of Thyroid Function Hormone(s) and Anti-TPO

For full term newborns, the range of normal TSH levels is quite large. TSH can vary between 1.3 and 16 micro units per milliliter of blood. After about a month, this range narrows to 0.9 to 7.7 μU/ml, and by school age it decreases to 0.6 to 5.5 μU/ml. This gradual decrease in TSH levels is normal, though levels of free thyroid hormone (FT4) in the blood will remain relatively stable over the same time period.

During our research in the internet, little articles were present to determine normal range or cut off limits (point) of thyroid function hormone(s) and Anti-TPO for children especially here in Egypt (Cairo). Determining reference range is critical since it determine whether or not thyroid disease is even diagnosed at all. A reference range is obtained by taking a large group of people in the population, here it will be euthyroid children aging 8-12 years, measuring their TSH, FT3, FT4 and Anti TPO levels and then calculating a mean value. In our survey we found that serum TSH reference range was 0.42-6.8-4.32 μU/ml, and for plasma free T3 (FT3) and free T4 (FT4) concentrations were 2.53-3.01 pg/ml, 1.25-1.74 ng/dl respectively and 18.57-23.17 IU/μIU/ml, and for plasma free T3 (FT3) and free T4 (FT4) concentrations were 0.9-4.4 mU/l; FT3: 4.6-7.3 F, 4.8-7.2 M also agrees to somewhat with [13] where they reported ranges of TSH, FT3, FT4 as follow: TSH: 0.9-4.0, M: 1.0-3.7 mU/l; and FT4: F: 9.6-14.5, M: 9.7-14.2 pmol/l.

In USA, the official "normal" reference range for the Thyroid Stimulating Hormone (TSH) blood test runs from approximately 0.5 to 4.5/5.0.

The following guidelines for detection of thyroid dysfunction were considered: Normal when FT3, FT4, and TSH were within the normal range; Subclinical hypothyroidism when TSH is more than 5.0 μU/ml and FT3, FT4 is within the normal range and absence of symptoms; Subclinical hyperthyroidism when TSH is less than 0.42 μU/ml and FT3, FT4 are within the normal range. Also diagnosis of thyroid dysfunction was based on elevated TSH levels (> 5 μU/ml) according to [15,16], and/or documentation of thyroid dysfunction (hypo- or hyperthyroidism) made by a paediatric endocrinologists in children files.

Results

Five hundred children with pre-diagnosed IDDM and 500 controls were enrolled into the study. Age and sex distribution were comparable between diabetic children and those with normal thyroid function (Table 1).

Table 2 revealed that diabetic children (both sex, girls and boys) had significantly (P<0.01) higher levels of fasting blood sugar and HbA1c than corresponding control.

In general serum TSH level of diabetic children was significantly lower than normal control despite that the mean of both (normal and diabetic) laid in the normal range. Serum TSH concentration was abnormal in 56/500 (11.2%) diabetic children (5.88 vs. 2.01 (diabetic with TSH < 5 μU/ml vs. diabetic with TSH > 5 μU/ml); and 5.88 vs. 3.0 μU/ml (diabetic vs. normal control); P<0.001). Prevalence of subclinical hypothyroidism among subjects with elevated serum thyroid antibodies was 100% with significant female preponderance (7.2% vs. 4% (vs. total 500), table 4 which disagree with [5] where he found that prevalence of hypothyroidism was 8.1% with no significant differences in sex distribution and prevalence of hypothyroidism among subjects with elevated serum thyroid antibodies was 52.2% with significant male preponderance. Table 3 reveal level of FT3 and FT4 with no significant difference between diabetic and control children.

Antibodies to thyroperoxidase (anti-TPO) were determined in all children. In general Anti-TPO level of diabetic children was significantly elevated serum thyroid antibodies was 52.2% with significant male preponderance (7.2% vs. 4% (vs. total 500), table 4 which disagree with [5] where he found that prevalence of hypothyroidism was 8.1% with no significant differences in sex distribution and prevalence of hypothyroidism among subjects with elevated serum thyroid antibodies was 52.2% with significant male preponderance. Table 3 reveal level of FT3 and FT4 with no significant difference between diabetic and control children.

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higher than normal control despite that the mean of both (normal and diabetic) laid in the normal range. The anti-TPO antibody test was not detected in 32/500 (6.4%), 62/500 (12.4%) of healthy control and IDDM children respectively table 4. The anti-TPO antibody was higher (> 50 IU/ml) in 56/500 (11.2%) diabetic children. Among the anti-TPO-positive (> 50 IU/ml) subjects, females were predominant over males (7.2% vs. 4% (vs. total 500), table 4. A total of 100% children with positive anti-TPO antibodies had abnormal TSH levels. Subclinical hypothyroidism was found in all 100% of patients with positive anti-TPO antibodies. Our results demonstrate the high prevalence of autoimmune disease in children with type I diabetes which agree somewhat with Hansen et al. [17] who found a prevalence of 5–10%. It may take years for patients with positive autoimmune serology to develop thyroid disease [4] and the need for these patients especially children for regular screening to make a precocious diagnosis of thyroid dysfunction [18].

A positive correlation was found between age or diabetes duration and serum anti-TPO in the diabetic children (r=0.64, p=0.006 for both) which agree to somewhat with [19] where they found these correlations but with older patients (age: 20.4 ± 0.9).

Discussion

Type I diabetes mellitus has been recognized as an autoimmune disease and is strongly associated with other diseases as autoimmune thyroid disease. The prevalence of autoimmune disease has been reported to be increased in subjects with type I diabetes mellitus compared with the general population, and more prevalent in female subjects with type I diabetes than in males [20-22]. However till date not much data is available about thyroid diseases in diabetes in the Egyptian children.

The pathogenetic mechanism underlying occurrence of autoimmune diseases has not been clearly understood, but some evidence exists that common genetic determinants mainly human leukocyte antigen (HLA) risk alleles [23] or CTLA4 gene and PTPN22 gene could play a role [24]. Moreover, environmental factors seem to be involved in the pathogenesis of these complex diseases.

Thyroid disease is a pathological state that adversely affects diabetic control and is commonly found in most forms of diabetes mellitus which is associated with advanced age in type II diabetes and autoimmune disease in type I diabetes. Diabetes mellitus appears to influence thyroid functions at two sites; firstly at the level of hypothalamic control of TSH release and secondly at the conversion of T4 to T3 in the peripheral tissue. Marked hyperglycemia causes reversible reduction of the activity and hepatic concentration of T4 -5 deiodinase, low serum concentration of T3, elevated levels of reverse T3 and low, normal or high levels of T4 [25].

The reason for the prevalence of some autoimmune disorders in diabetic patients may be due to a generally increased tendency to react against certain antigens, or a genetically impaired ability to acquire tolerance to some auto antigens, or certain common antigens present in the tissues of individuals prone to autoimmune diseases.

It is unknown whether these organ-specific antibodies (Anti TPO) are directly involved in the pathogenesis of the disease or whether they are just secondary to tissue destruction by thyroid-infiltrating T-cells [26]. Furthermore, it is unclear whether anti-TPO antibodies are able to induce hypothyroidism by blocking the enzyme TPO [26].

Different results were published with respect to the prevalence of hypothyroidism or subclinical hypothyroidism in children and adolescents with type I diabetes and positive anti-TPO antibodies [27]. We have found a very high prevalence (56/500, 11.2%) of thyroid dysfunction in the group of children with type I diabetes and thyroid autoimmunity. Subclinical hypothyroidism was predominant, and significantly high levels of TSH were found in 11.2% of children. High titres of anti-TPO were highly suggestive of autoimmune thyroid disease, and correlated well with thyroid dysfunction [27].

Measurement of free T4 (FT4) is indispensable to confirm diagnoses, since it directly reflects hormone production by the thyroid gland. Measurement of free T3 (FT3) only indirectly reflects thyroid hormone production but may provide additional information, since most of FT3 is produced by intracellular conversion by the deiodinases [28]. It is known that insulin, an anabolic hormone enhances the level of FT4 while it suppresses the level of T3 by inhibiting hepatic conversion of T4 to T3 [29].

Glycaemic status is influenced by insulin, which is known to modulate thyroid releasing hormone (TRH) and TSH levels. Suzuki et al. [30] attributed the abnormal thyroid hormone levels found in diabetes to the presence of thyroid hormone binding inhibitor (THBI), an inhibitor of the extra thyroidal conversion enzyme (5'-deiodinase) of T4 to T3, and dysfunction of the hypothalamic-pituitary-thyroid axis [29].

Conclusion

The results demonstrate the presence of subclinical hypothyroidism in children with type I diabetes and the need for these children for regular screening. Annual screening of thyroid antibodies in all patients especially children with IDDM is recommended, while serum TSH level should be measured in patients especially children with detected thyroid antibodies.

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References


