Thyroid abnormalities in Egyptian children and adolescents with type 1 diabetes mellitus: A single center study from Upper Egypt

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ABSTRACT

Background: The aim of this study was to detect the prevalence of thyroid abnormalities among children and adolescents with type 1 diabetes mellitus (T1DM) in Upper Egypt and its relationship with disease-related variables. Design: Cross-sectional controlled study. Patients and Methods: The study included 94 children and adolescents with T1DM (Group 1) attending for regular follow-up in the diabetes clinic of Assiut Children University Hospital, Assiut, Egypt were enrolled in the study and 60 healthy subjects matching in age and sex were taken as a control (Group 2). History taking, clinical examination, measurement of thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine, anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies levels as well as HbA1c were measured. Results: Mean TSH levels were significantly higher in (Group 1) when compared to control (P < 0.01). Six children (6.3%) were found to have subclinical hypothyroidism in Group 1 compared with two children (2.1%) in the control group (P < 0.001) two children (2.1%) were found to have clinical hypothyroidism in Group 1 compared with non in the control group. Positive levels of anti-TPOAb and anti-TgAb were found in 9 (9.5%) and 6 (6.3%) in Group 1 compared with 2 (3.3)% and 1 (1.6)% of controls respectively (P < 0.01). Cases with hypothyroidism were significantly older, had longer duration of DM, higher body mass index and higher Hba1c compared with those without hypothyroidism. TSH had significant positive correlations to age (r = 0.71, P < 0.001), diabetes duration (r = 0.770, P < 0.001), Anti-TPO level (r = 0.678, P < 0.01), HbA1c level (r = −0.644, P < 0.01) and significant negative correlation with FT4 (r = −0.576, P = 0.01). Conclusion: The present study reported high prevalence of thyroid abnormalities in children and in children and adolescents with type 1 diabetes in Upper Egypt. The study recommended yearly evaluation thyroid function tests and thyroid antibodies in all children and adolescents with type 1 diabetes commencing from the onset of diabetes.

Key words: Anti-thyroid peroxidase antibody and anti-thyroglobulin antibody, hypothyroidism, thyroid stimulating hormone, type I diabetes mellitus

INTRODUCTION

Type 1 diabetes mellitus (T1DM) may be associated with autoimmune disorders including autoimmune thyroid disease.[1] Several studies in different countries were conducted to estimate the prevalence of thyroid dysfunction (TD) in diabetic patients, the prevalence TD in diabetic children varies from 10% to 24%.[2,3] This association has been demonstrated in some Egyptian cohorts, including those from Alexandria and Cairo.[4] Up to our best knowledge, no work has been done in Upper Egypt to assess the prevalence of TD in children and adolescents with type 1 diabetes. The aim of this study is to investigate the prevalence of TD in patients with T1DM.

PATIENTS AND METHODS

This is a cross-sectional hospital based study. It was conducted in the Pediatric Endocrinology and Diabetes Unit, Assiut University Children Hospital, Assiut, Egypt.
during the period between March 2013 and December 2013. It included 94 children and adolescents with T1DM (Group 1). In addition, 60 apparently healthy age- and sex-matched children were studied as a control (Group 2). To be included in the study, the control subjects had to be without any acute disease and without clinical conditions involving the endocrine-metabolic system. Both patients and controls were recruited from Pediatric Endocrinology Outpatients Clinic in Assiut University Children Hospital. The study protocol was approved by the Ethical Committees of Assiut University.

Children Hospital, Egypt. Written informed consents were obtained from the parents of both patients and controls.

Inclusion criteria
• Definite diagnosis of T1DM according to the criteria of American Diabetes Association (ADA)[6]
• On insulin replacement therapy
• Age range 3-18 years
• Duration of DM longer than 1 year.

Exclusion criteria
• Associated other autoimmune diseases
• Diabetic children with abnormal lipid profile
• Use of corticosteroids or amiodarone
• Secondary DM.

Methods
All children were subjected to:
• A thorough history: The demographic data were obtained from a survey. The following variables were assessed: Gender, age, duration of DM, type and dose of insulin, in addition to symptoms suggestive of hypothyroidism (pubertal delay, puffy features, swelling in neck, cold intolerance, etc.) or hyperthyroidism (emotional lability, weight loss, and restless sleep, some degree of exophthalmos, etc.)
• Calculation of body mass index (BMI) (kg/m²) and percentile according to Egyptian growth curves using the measured weight and height on the day of the research visit[7]
• Signs of TD and estimation of goiter by a qualified endocrinologist, and graded as per the WHO grading system.[8]

Laboratory investigation
• Routine general laboratory tests, if needed
• Thyroid stimulating hormone (TSH) serum level was determined by ultrasensitive immunometric assays (Immulite™ 2000 Third Generation, Diagnostic Products Corporation, Los Angeles, CA). Free thyroxine (FT4) and free triiodothyronine (FT3) were determined by radioimmunoassay using an automated system (Roche diagnostics) the reference range for TSH was 0.4-4.0 mU/L, for FT3: 3.5-5.5 pmol/L and for FT4: 10.0-26.0 pmol/L. The coefficients of variations (CV) were 5.0% and 5.1% at TSH concentrations of 4.0 mU/L and 10.0 mU/L respectively. For FT4, the CV was 6.5% at 10.0 pmol/L and FT3: 8.9% at 3.5 pmol/L.
• Serum anti-thyroid peroxidase (anti-TPO Ab) and anti-thyroglobulin (anti-Tg Ab) were measured by Rapid enzyme-linked immunosorbent assay (Genesis Diagnostics, Littleport, UK). Anti-Tg Ab and anti-TPO Ab concentrations more than 100 IU/mL and 75 IU/mL respectively were considered positive. Positivity of at least one antibody was considered as havingAIT.
• Assessment of glycemic control by calculating the mean glycosylated hemoglobin (HbA1c) over the last year was performed using high performance liquid chromatography technique.

The ADA published the target age-specific Hg A1c as follow: <6 years, 7.5-8.5%; from 6 to 12 years, ≤8%; from 13 to 18 years, ≤7.5%.[9] According to the target level of HgA1c for age, recommended by the ADA,[9] patients were classified as either having good glycemic control or poor glycemic control.

Subclinical hypothyroidism was defined as an elevated TSH level >4.0 mU/L, together with normal serum thyroid hormone levels. Clinical hypothyroidism was defined as an elevated TSH together with a decreased serum thyroid hormone level. Subclinical hyperthyroidism was defined as a decreased TSH <0.3 mU/L together with normal thyroid hormone levels and clinical hyperthyroidism was defined as a decreased TSH together with elevated thyroid hormone levels.[10]

Statistical analysis
Analysis was carried out using SPSS (Statistical Program for Social Science) statistical package (SPSS Inc) version 16 (SPSS Inc, Chicago, IL, USA). Simple statistics such as frequency, arithmetic mean and standard deviation were used. For comparison of the two groups, Student’s t-test was used for parametric data and the Mann-Whitney U-test was used for nonparametric data. Linear correlations were performed by Spearman’s or Pearson’s test. For all analyses, P < 0.05 provides statistical significance.

Results
Table 1 shows demographic and metabolic characteristics of the studied groups. TSH level was significantly higher in (Group 1) in controls (Group 2) (P < 0.001). No,


statistically significant difference between the Groups 1 and 2 regarding age, sex, FT3 and FT4.

Table 2 shows thyroid function and antibodies in children and adolescents with T1DM compared to the controls. Six children (6.3%) were found to have subclinical hypothyroidism in Group 1 compared to two children (2.1%) in the control group \((P < 0.001)\) two children (2.1%) were found to have clinical hypothyroidism in Group 1 compared with non in the control group. The mean anti-TPO Ab and anti-Tg Ab in Group 1 children were significantly higher than those in the control. Both anti-TPO and anti-Tg Ab positivity was reported in 2.1% in children and adolescents with T1DM.

None of the studied children (Groups 1 and 2) had either clinical or sub clinical hyperthyroidism.

Table 3 shows the comparison between children with hypothyroidism and those without hypothyroidism among cases with T1DM. Cases with hypothyroidism were significantly older, had longer duration of DM, higher BMI percentile and higher HbA1c compared with those without hypothyroidism.

Table 4 shows correlation coefficient between TSH and clinical and laboratory data of studied cases, TSH had significant positive correlations to age \((r = 0.71, P < 0.001)\), diabetes duration \((r = 0.770, P < 0.001)\), anti-TPO level \((r = 0.678, P < 0.01)\), HbA1c level \((r = 0.644, P < 0.01)\) and significant negative correlation with FT4 \((r = -0.576, P = 0.01)\).

**Discussion**

Our result revealed that six children (6.3%) were found to have subclinical hypothyroidism in (Group 1) compared to one child (1.6%) in the control group \((P < 0.001)\). Moreover, two children (2.1%) were found to have clinical hypothyroidism in (Group 1) compared with non in the control group. This in agreement with Mohamed et al.[11] who reported a similar result. Subclinical hypothyroidism may be associated with increased risk of symptomatic hypoglycemia and with reduced linear growth. Furthermore, thyroxine replacement therapy started early in patients with subclinical hypothyroidism reduces the risk of hyperlipidemia and atherosclerotic heart disease.[12]
In this study, the rate of anti-TPO and anti-Tg Ab in studied diabetic cases (Group 1) was reported to be 9.5% and 6.3%, respectively. Moreover, the mean anti-TPO Ab and anti-Tg Ab in Group 1 were significantly higher than those in the control. Studies done on Brazilian children with T1DM for detection of anti-TPO Ab reported average prevalence of 16.7% as reported by Mantovani et al.[13] Meanwhile, European whites had prevalence of 11.1%.[14] On the other hand, a figure as high as 35% was quoted among American Hispanic patients[15] and 39.6% among Iranian children as reported by Sharifi et al.[16] The difference in the prevalence of thyroid autoimmunity between various studies may be attributed the difference in number and age of the studied cases, duration of diabetes, genetic variability and difference in cut-off points of laboratory tests.[17]

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. 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 risk alleles or CTLA4 gene and PTPN22 gene could play a role.[18]

In this study, cases with hypothyroidism were older, had more duration of diabetes and higher HbA1c than those without hypothyroidism [Table 3]. Moreover, TSH correlated positivity with age, duration of diabetes, Anti-TPO Ab and HbA1c [Table 4]. DM 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. Poor glycomic control cause 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.[19] The positive correlation of TSH with Anti-TPO Ab may be due to the direct involvement of autoantibodies in the pathophysiologic mechanism of thyroid gland destruction or may be due to the association of these autoantibodies with tissue destruction by thyroid-infiltrating T-cells.[20]

Conclusions and Recommendations

This study reported high prevalence of thyroid abnormalities in children and in children and adolescents with type 1 diabetes in upper Egypt. The study recommended yearly evaluation thyroid function tests and thyroid antibodies in all children and adolescents with type 1 diabetes commencing from the onset of diabetes.

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