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

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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<0.005). 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 [7]. 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

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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.

Table 1

| Groups     | Gender | Age (years) | P       |
|------------|--------|-------------|---------|
|            | Male   | Female      | > 0.05  |
| Control    | 500    | 184 (36.8)  | 316 (63.2%) | 10.16 ± 0.07 |
| IDDM       | 500    | 184 (36.8)  | 316 (63.2%) | 9.66 ± 0.08  |

IDDM vs. Control; NS: Non Significant

Table 2

| Gender | Age (years) | Diabetes Duration (years) | Glucose (mg/dl) | Hba1c (mg/dl) |
|--------|-------------|---------------------------|----------------|---------------|
|        | Control     | IDDM                     | P              |              |
|        | Total       |                           | 4.15 ± 0.06    | 84.13 ± 0.49  |
|        | Girls       |                           | 4.18 ± 0.08    | 84.00 ± 0.62  |
|        | Boys        |                           | 4.11 ± 0.11    | 84.35 ± 0.82  |

IDDM vs. Control; NS: Non Significant (P>0.05)

Table 3

| Gender | TSH (μU/ml) | FT3 (pg/ml) | FT4 (ng/dl) | Anti TPO (IU/ml) |
|--------|-------------|-------------|-------------|----------------|
|        | Control     | IDDM        | P           | Control        | IDDM         |
|        | Total       |             | < 0.001     | 2.73 ± 0.02    | 2.44 ± 0.01  |
|        | Girls       |             | < 0.001     | 2.78 ± 0.01    | 2.45 ± 0.01  |
|        | Boys        |             | < 0.001     | 2.65 ± 0.03    | 2.43 ± 0.02  |

IDDM vs. Control; NS: Non Significant (P>0.05)

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.

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.
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 patient with positive anti-TPO. 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 1 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 hormones 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 hypothalamo-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

1. Atkinson MA, Eisenbarth GS (2001) Type 1 diabetes: new perspectives on disease pathogenesis and treatment. Lancet 358: 221-229.
2. Sathish R, MohanV (2003) Diabetes and thyroid diseases - A Review. Int J. Diab Dev Countries 23: 120-123.
3. Roos A, Bakker SJ, Links TP, Gans RO, Wollfenbuttel BH (2007) Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab 92: 491-496.
4. Kordonouri O, Deiss D, Danne T, Dorow A, Bassir C, et al. (2002) Predictivity of thyroid autoantibodies for the development of disorders in children and adolescents with type 1 diabetes. Diabet Med 19: 519-521.

5. Severinski S, Banac S, Severinski NS, Ahel V, Cvijovic K (2009) Epidemiology and clinical characteristics of thyroid dysfunction in children and adolescents with type 1 diabetes. Coll Antropol 33: 273-279.

6. American Diabetes Association (ADA) (2007) Expert committee on the diagnosis and classification of diabetes mellitus: Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes care 30: 54-541.

7. Melmed S, Geola FL, Reed AW, Pekary AE, Park J, et al. (1982) A comparison of methods for assessing thyroid function in nonthyroidal illness. J Clin Endocrinol Metab 54: 300-306.

8. Midgeley JEM (2001) Direct and indirect free thyroxine assay methods. Therory and practice. Clin Chem 42: 1353-1359.

9. Hopton MR, Harrap JJ (1986) Immunoradiometric assay of thyrotropin as a first line thyroid function test in the routine laboratory. Clin Chem 32: 691-695.

10. Horster, FA (1988) Die Bedeutung von MAK, TAK, TRAK und Thyreoglobulin bei der Diagnose von Schilddrüsenkrankheiten. Internist 29: 538-540.

11. Barham D, Trinder P (1972) An improved colour reagent for the determination of blood glucose by the oxidase system. Analyst 97: 142-145.

12. Nuttall FQ (1998) Comparison of percent total GHB with percent HbA1c in people with and without diabetes. Diabetes care 21: 1475-1480.

13. Kapelari K, Kirchlechner1 C, Högler1 W, Schweitzer1 K, Virgolini I, et al. (2008) Pediatric reference intervals for thyroid hormone levels from birth to adulthood: a retrospective study. BMC Endocrine Disorders 8: 15-25.

14. Djemli A, Van Vliet G, Belgoudi J, Lambert M, Delvin EE (2004) Reference intervals for free thyroxine, total triiodothyronine, thyrotropin and thyroglobulin for Quebec newborns, children and teenagers. Clin Biochem 37: 328-330.

15. Glastras SJ, Craig ME, Verge CF, Chan AK, Cusumano JM, et al. (2005) The role of autoimmunity at diagnosis of type 1 diabetes in the development of thyroid and celiac disease and microvascular complications. Diabetes Care 28: 2170-2175.

16. O'Grady, Cody D (2010) Review: Subclinical hypothyroidism in childhood. Arch Dis Child (doi:10.1136/adc.2009.181800).

17. Hansen D, Bennedbaek FN, Haier-Madsen M, Hegedüs L, Jacobsen BB (2003) A prospective study of thyroid function, morphology and autoimmunity in young patients with type 1 diabetes. Eur J Endocrinol 148: 245-251.

18. Araujo J, Brandão LA, Guimarães RL, Santos S, Falcão EA, et al. (2008) Prevalence of autoimmune thyroid disease and thyroid dysfunction in young Brazilian patients with type 1 diabetes. Pediatr Diabetes 9: 272-276.

19. Faranak S, Leila G, Noruudin M (2008) Thyroid Function and Anti-Thyroid Antibodies in Iranian Patients with Type 1 Diabetes Mellitus: Influences of Age and Sex. Iran J Allergy Asthma Immunol 7: 31-36.

20. Kordonouri O, Klinghammer A, Lang EB, Grüters-Kieslich A, Grabert M, et al. (2002) Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. Diabetes Care 25: 1346-1350.

21. Ramos AJ, Costa ADM, Benicio AVL (2003) Prevalence of thyroid autoimmune disease in patients with type 1 diabetes. Arq Bras Endocrinol Metabol 47: 177–182.

22. Okten A, Akcay S, Cakir M, Girisken I, Kosucu P, et al. (2006) Iodine status, thyroid function, thyroid volume and thyroid autoimmunity in patients with type 1 diabetes mellitus in an iodine-replete area. Diabetes Metab 32: 323-329.

23. Boehm BO, Kühnl P, Lötger C, Ketzler-Sasse U, Holzberger G, et al. (1993) HLA-DR3 and HLA-DR5 confer risk for autoantibody positivity against the thyroperoxidase (mic-TPO) antigen in healthy blood donors. Clin Investig 71: 221-225.

24. Vaidya B, Pearce S (2004) The emerging role of the CTLA-4 gene in autoimmune endocrinopathies. Eur J Endocrinol 150: 619-626.

25. Shah SN (1984) Thyroid disease in diabetes mellitus. J Assoc Physicians India 32: 1057-1059.

26. McIntosh RS, Aghar MS, Weetman AP (1997) The antibody response in human autoimmune thyroid disease. Clin Sci (Lond) 92: 529-541.

27. Kordonouri O, Hartmann R, Deiss D, Wilms M, Grüters-Kieslich A (2005) Natural course of autoimmune thyroiditis in type 1 diabetes: association with gender, age, diabetes duration, and puberty. Arch Dis Child 90: 411-414.

28. Dayan CM (2001) Interpretation of thyroid function tests. Lancet 357: 619-624.

29. Smith AF, Becket GJ, Walker SW, Rae PWH (1998): Abnormalities of thyroid function. Lecture Notes on Clinical Chemistry, Sixth edition. Oxford: Black-well Science Ltd. pp 91-104.

30. Suzuki J, Nanno M, Gemma R, Tanaka I, Taminato T, et al. (1994) The mechanism of thyroid hormone abnormalities in patients with diabetes mellitus. Nippon Niabunpi Gakki Zasshi 7: 465-470.