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Abdulmoein Al-Agha, Ali Ocheltree, Amr Hakeem

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Thyroid Dysfunction in Children and Adolescents with Type 1 Diabetes Mellitus

Abdulmoein Al-Agha, Ali Ocheltree, Amr Hakeem

Abstract:

Background and Objectives: Patients with type 1 diabetes mellitus (T1DM) are at risk of thyroid disease (TD). The incidence of TD among diabetic patients is higher than that of the general population. Our objective was to review the prevalence of TD among children and adolescents with T1DM and determine the factors affecting its prevalence in our population. **Methodology:** A retrospective review was conducted on children and adolescents with T1DM, ages between 1–18 years (n=398, 226 females, 172 males, 190 pre-pubertal and 208 post-pubertal) attending the pediatric endocrine clinic at King Abdul Aziz University Hospital from 2006-2010. A review of patient serum analysis was done. Mean and standard deviation (SD) for patient age were 12.05 ± 4.03 years. **Results:** In our cohort, 63 patients (15.83%) had hypothyroidism [female; 40 (63.49%), male; 23 (36.51%), pre-pubertal; 26 (41.3%), post-pubertal; 37 (58.7%)]; 5 had primary hypothyroidism and 58 had subclinical hypothyroidism. Mean and SD for age were 11.6 ± 4.01 years in patients with hypothyroidism and 12.14 ± 4.02 years for euthyroid children, P-value 0.325. Mean and SD for HbA1c were $9.4 \pm 2.4\%$ in hypothyroid subjects and $8.1 \pm 1.3\%$ in euthyroid subjects, P-value < 0.01. **Conclusions:** Hypothyroidism was prevalent in our cohort. It had a higher prevalence among females. Subclinical hypothyroidism was the commonest TD encountered. Gender, pubertal status, and glycemic control affected the prevalence of TD in our cohort. We recommend the promotion of annual routine screening programs for hypothyroidism among children and adolescents with T1DM.

Keywords: Hypothyroidism, type 1 diabetes mellitus, children, thyroid stimulating hormone.

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Introduction

Thyroid disease (TD) and type 1 diabetes mellitus (T1DM) are both prevalent endocrinopathies. Asymptomatic TD is prevalent among diabetic patients, particularly T1DM patients. Thyroid function is generally affected in diabetes mellitus, as Miguel Fernandez-Castaner et al [1] reported, that nearly one-third of newly diagnosed T1DM patients have coexistent TD [2]. Females with T1DM are more prone to hypothyroidism than males [3]. Post-pubertal T1DM patients also have a higher incidence of TD when compared to pre-pubertal T1DM children [4,5]. Moreover, 13 to 20% of T1DM patients have elevated serum thyroid stimulating hormone (TSH) levels; a significant number of these patients are prone to TD [6]. Indeed, TD may appear at any age among T1DM pediatric patients, the onset may be insidious or even asymptomatic for a long time [4]. Although, many children with Hashimoto's thyroiditis are hypothyroid, there is a sub-group who have subclinical hypothyroidism. Individuals in this sub-

Abdulmoein Al-Agha, Ali Ocheltree,
Amr Hakeem

The Pediatric Department, Faculty of Medicine, King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia

Correspondence author:
Abdulmoein Al-Agha, MD

Consultant Pediatric Endocrinologist, Department of Pediatrics, King Abdulaziz University Hospital
P.O. Box 80215, Jeddah 21589,
Kingdom of Saudi Arabia
Telephone: 00966 -2 -6408327
Fax: 00966 -2 -6408353
E-mail: aagha@kau.edu.sa

group might deteriorate as they age, experiencing a decrease in their basal metabolic rate and poor glycemic control [7,8]. The aim of the present study

was to review the prevalence of TD among children and adolescents with T1DM, attending the pediatric endocrine clinic at King Abdul Aziz University Hospital, between years 2006-2010 and determine what factors affecting the prevalence of TD in our pediatric population.

Material and methods

Study design and site:

This is a retrospective cross-sectional study conducted on children and adolescents attending the pediatric endocrine clinic at King Abdul-Aziz University Hospital, from year 2006 to 2010. The study population was divided into two age groups; pre-pubertal and post-pubertal, according to the Tanner staging system. All laboratory information was taken from King Abdul Aziz University Hospital laboratory phoenix database system. At King Abdul-Aziz University Hospital, serum glucose and HbA1c are measured via the SEIMENS dimension clinical chemistry system. GLU flex reagent cartridge is used. The laboratory test is conducted via the hexokinase method.

Study Subjects:

The study population was 398 children and adolescents with T1DM aged from 1 to 18 years. Mean and standard deviation (SD) for age were 12.05 ± 4.03 years, respectively, [172 patients were males (43.21%), 226 were females (56.78%), 190 were pre-pubertal (47.74%) and 208 were post-pubertal (52.26%)]. Local patients of multiple nationalities were enrolled in this study.

The inclusion criteria were: patients who attended the pediatric endocrine clinic for more than 3 month and less than 4 years, ages between 1 to 18 years, HbA1c $\geq 6.5\%$ and normal serum iodine levels.

Diagnosis of Hypothyroidism:

A review of serum levels of TSH, free T4 and HbA1c was conducted for all patients enrolled in this study. The existence of hypothyroidism was established via certain evidence, such as greater than normal levels of TSH and low or normal free thyroxin levels. Primary hypothyroidism was defined as greater than normal levels of TSH and below normal levels of free T4; subclinical hypothyroidism was defined as greater than normal levels of TSH and normal levels of free T4. Hyperthyroidism was defined as lower

than normal levels of TSH and greater than normal levels of free T4. The onset of normal puberty was defined as the development of thelarche by the age of 8 years or older in girls and testicular enlargement (> 4 ml in volume), measured by Prader's orchidometer, by the age of 9 years or older in boys. The normal serum ranges for TSH, free T4 and HbA1c used in this study were (0.27 – 5 μ IU/L), (12-22 pmol/l) and ($< 6.5\%$), respectively. At King Abdul-Aziz University Hospital, serum TSH and FT4 are measured via the cobas clinical chemistry system trademark of Roche diagnostics. The method is an immunoassay for the in vitro quantitative determination of TSH and FT4 in the serum. It is done via 2 incubation assays of the sample using the sandwich principle for TSH and the competition principle for FT4. The first incubation is to form an immunocomplex and the second is to bind the complex to a solid phase. After unbound substances are removed the reaction mixture is aspirated magnetically onto an electrode, a photomultiplier is used to measure a voltage induced emission. Results are determined via a calibration curve.

Statistical analysis:

The data was gathered digitally on an excel spreadsheet from the university hospital centralized phoenix database. Tables were exported to the SPSS (version 16) software, where the data was analyzed. Descriptive characteristics were calculated from the data collected; age, gender, HbA1c, TSH and free T4. Characters such as mean and SD of HbA1c, TSH, and age were calculated. All data was plotted to determine individual variable distribution and the Shapiro-Wilk test was performed to assess for normality. Student t-test, Mann-Whitney U or the Kruskal-Wallis tests were used, as appropriate. The level of significance was expressed as P-value; $P > 0.05$ = non-significant (NS), $P < 0.05$ = significant (S), and $P < 0.001$ = highly significant (HS).

Results

In our cohort, 63 patients (15.83%) had hypothyroidism, [female; 40 (63.49%), male; 23 (36.51%), pre-pubertal; 26 (41.3%), post-pubertal; 37 (58.7%)]. Mean and SD for age were 11.6 ± 4.01 years in patients with hypothyroidism and 12.14 ± 4.02 years in children with normal thyroid function, P-value 0.325 (NS). Mean and SD for TSH levels among subjects with TD were 13.6 ± 18 μ IU/L in

females and 7.54 ± 3.47 μ IU/L in males, P-value 0.048 (S). Only 2 patients within our population (0.5%) had hyperthyroidism. Of the hypothyroid patients in our cohort, (7.94%) had clinical hypothyroidism and (92%) had subclinical hypothyroidism. Mean and SD for HbA1c were $9.2 \pm 2.2\%$, respectively. Mean and SD for HbA1c were $9.4 \pm 2.4\%$ in hypothyroid subjects and $8.4 \pm 1.3\%$ in euthyroid subjects, P-value < 0.01 (S). Among hypothyroid patients, mean and SD for HbA1c were $9.7 \pm 2.8\%$ in females and $9.1 \pm 2.1\%$ in males, P-value 0.5 (N.S).

Discussion

Both genetic and immunological factors contribute to the co-occurrence of TD and T1DM [9]. In the present study 15.83% of children and adolescents with T1DM had hypothyroidism, some studies had similar findings [10], and others reported a lower prevalence [11]. In our cohort the prevalence of TD was higher among females than males, as was reported by other studies [10,11]. On the other hand, we did not find a significant difference in age between euthyroid subjects and those with thyroid dysfunction in our cohort, unlike what other studies have reported [4]. The majority of patients with TD developed subclinical hypothyroidism (92%), few developed clinical hypothyroidism (7.94%) and only (0.5%) developed hyperthyroidism, other studies reported that subclinical hypothyroidism had a higher prevalence than clinical hypothyroidism [11]. Also, the prevalence of TD was higher among post-pubertal adolescents than pre-pubertal children in our cohort. Incidentally, we found that children and adolescents with T1DM in our cohort had an overall high HbA1c.

Prevalence studies showed that TD is common among children and adolescents with T1DM. Perros et al [4], reported that thyroid dysfunction was seen in up to (31.4%) of females with T1DM. In our cohort, thyroid dysfunction was seen in 10.1% of females with T1DM. Furthermore, metabolic control of T1DM in our cohort was worse among those with TD when compared to subjects with euthyroid. A case-control study conducted on 36 children and adolescents with T1DM and 30 healthy individuals, reported that TSH levels were significantly elevated among T1DM patients when compared to healthy individuals, which was indicative of hypothyroidism. T1DM patients had a high prevalence of TD in their

study. Furthermore, they reported that insulin and thyroid hormones are both involved in cellular metabolism, thus an excess or deficiency of either of these hormones would affect the function of the other [12].

In our study, gender, pubertal status, and glycemic control were the factors affecting the prevalence of TD among T1DM pediatric patients. With respect to the high prevalence of both T1DM and TD, it is important to screen all children and adolescents with T1DM for TD [13,14]. TSH in particular, should be tested several weeks after the diagnosis of T1DM, after metabolic control has been established. Even if TSH levels were normal, annual routine follow up of thyroid function should be conducted on children and adolescents with T1DM. Furthermore, we would like to point out that iodine deficiency is not endemic in Saudi Arabia [15].

Conclusion

TD was prevalent among children and adolescents with T1DM. In our cohort, sub-clinical hypothyroidism had a higher prevalence than clinical hypothyroidism. Gender, pubertal status, and glycemic control, represented in HbA1c, were the factors affecting the prevalence of TD in our cohort. The occurrence of hypothyroidism was higher among T1DM females than males. HbA1c readings were higher among subjects with TD when compared to those without. We emphasize on the importance of annual routine screening for TD among children and adolescents with T1DM, especially among females, in hope of early intervention and a decrease in the overall long term preventable complications of TD among children and adolescents with T1DM.

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