



Original Research Article

Thyroid Disorders Associated with Type 1 Diabetes Mellitus in Children and Adolescents from Central Province Saudi Arabia

Nasir A. M. Al-Jurayyan^{1*}, Sharifah D. A. Al Issa¹, Abdullah N. A. Al Jurayyan², Hessah M. N. Al Otaibi¹ and Amir M. I. Babiker¹

¹Department of Pediatrics (39), College of Medicine and King Khalid University Hospital, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia

²King Fahad Medical City, Riyadh, Saudi Arabia

**Corresponding author.*

| Abstract | Keywords |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| <p>A retrospective study hospital based study conducted at King Khalid University Hospital, Riyadh on 305 diabetic patients to determine the prevalence of thyroid disorders in children and adolescent with Type 1 Diabetes (T1D). All children and adolescents with T1D were screened with Thyroid-Stimulating-Hormone (TSH) and free thyroxinFT₄, and thyroid microsomal and thyroglobulin antibodies, to detect thyroid disorders at the time of diagnosis and annually thereafter. The study group included three-hundred and five Saudi children and adolescents with T1D, 163 (53.4%) patients were females and 142 (46.6%) patients were males. Thyroid dysfunction was evident in 65 (21.3%) patients, 26 (8.5%) had evidence of overt hypothyroidism, 39 (12.8%) patients had subclinical hypothyroidism, and none of our patients had either overt or subclinical hyperthyroidism. Thyroid microsomal peroxidase (TPO) and thyroglobulin (TG) antibodies were done in the sera of 114 (37.4%) patients, 76(66.7%) patients were euthyroid, 20 (17.5%) patient with overt-hypothyroidism, while in 18 (15.8%) patients were diagnosed with sub-clinical hypothyroidism. Interestingly, in 16 (80%) patients, with overt hypothyroidism were positive for both TPO and TG antibodies, while in the majority of the euthyroid patients (93.2%) both TPO and TG antibodies were negative. Children and adolescents with T1D have a significant increase risk of developing thyroid dysfunction with a high prevalence of 21.3%. A routine screening should be implemented annually with determination of anti-thyroid microsomal and anti-thyroglobulin antibodies and TSH. Patients who have positive thyroid antibodies may need the assessment of thyroid function, even, at a shorter intervals, to allow early detection and treatment, hence, avoid the associated complication.</p> | <p>Adolescents Antibodies Autoimmunity Children Thyroid disorders Type 1 diabetes</p> |

Introduction

Children and adolescents with Type 1 Diabetes Mellitus (T1DM) are prone to develop other organ-specific auto-immune diseases. AutoImmune Thyroiditis (AIT) is the most commonly encountered. It is reported to be two to four times more frequent than in general population concerning children and adolescents, the relative prevalence in the general population was found to range from 2.9% to 3.4%, while for those with type 1 DM it range from 10% to 23.4% (Akbar et al., 2006; Ghawil et al., 2011).

AutoImmune Thyroid Disease (AITD) is the most frequent autoimmune disease associated with type 1 DM. Prevalence of AITD determined by high anti-TPO and/or anti-TG titers in diabetic population and varied depending on the age, sex, ethnic origin of the individuals and increases with the duration of the disease. Studies have shown a great variation in the prevalence of anti-thyroid antibodies in children with Type 1 DM. The prevalence of positive thyroid antibodies in children with type 1 DM varies between 3% and 54.3% in different countries.

Studies that have investigated AITD in newly diagnosed type 1 DM children are few and reported prevalence rate range between 4.5-29.4%, considering the effect of age, ethnic origin, and disease duration (Lindberg et al., 1997; Feely and Isles, 1979; Barova et al., 2004; Araujo et al., 2008). Patients with type 1 DM should be screened for autoimmune thyroid disease. Measuring thyroid autoantibodies is used to identify thyroid autoimmunity, measurement of TSH may be the most sensitive way to identify patients with thyroid dysfunction. Patients with thyroid autoantibodies may be euthyroid, hypothyroidism or hyperthyroidism (Gray et al., 1979; Haket al., 2000; Cooper, 2001; Mohn et al., 2002; Bilimoria et al., 2003; Mohn et al., 2005).

The aim of this study was to investigate the prevalence of thyroid dysfunction in a cohort of 305 children and adolescents with Type 1 Diabetes Mellitus from central province of Saudi Arabia, attending the Pediatric Diabetic Clinic at King Khalid University Hospital of the King Saud University, Riyadh, Saudi Arabia between January 1995 and December 2012.

Materials and methods

This is a retrospective, hospital-based study which included children and adolescents who were diagnosed with Type 1 Diabetes Mellitus between the period January 1995 and December 2012, and followed at the Pediatric Diabetic Clinic, King Khalid University Hospital of the King Saud University, Riyadh, Saudi Arabia. Patients were screened for thyroid dysfunctions by Thyroid Stimulation Hormone (TSH), and Free Thyroxine (FT₄), at the time of diagnosis and annually thereafter.

Antithyroid microsomal and thyroglobulin antibodies were also estimated using haemagglutination method, and a titer of 1/100 or more was considered positive. Thyroid function tests (TSH and FT₄) were made by method using commercially available kits. The quality control of the assay was monitored by the Middle East Extended Quality Assessment Scheme (MEEQAS) in Riyadh. Diagnosis of subclinical autoimmune thyroiditis (Hashimoto's) was based on high levels of TSH, more than 5 mU/L, associated with the presence of at least one thyroid autoantibody on two or more consecutive occasion's, while clinical hypothyroidism (overt hypothyroidism) was associated, in addition to the above, with low FT₄ levels, and/or the presence of goiter. The study was approved by the Institutional Review Board (Ethical and Research Committees) of the College of Medicine of King Saud University, and the study was conducted according to the principles of Helsinki Declaration.

Results

The study group included three-hundred and five Saudi children and adolescents with Type 1 diabetes mellitus, 163 (53.4%) patients were females and 142 (46.6%) patients were males. The age ranged between 0.6 to 16 years, with a mean age of 9.5 years. The duration of diabetes was ranging between one and 13 years, with a mean of 7.5 years. Thyroid dysfunction was evident in 65 (21.3%) patients. Of those, 26 (8.5%) patients had evidence of overt hypothyroidism, 39 (12.8%) patients had subclinical hypothyroidism, and none of our patients had either overt or subclinical hyperthyroidism. Thyroid Microsomal Peroxidase (TPO) and Thyroglobulin (TG) antibodies were done in the

sera of 114 (37.4%) patients (Table 1), 76 (66.7%) patients euthyroid, 20 (17.5%) patient with overt-hypothyroidism, and 18 (15.8%) patients with sub-clinical hypothyroidism. Interestingly, in 16 (80%)

patients, with overt hypothyroidism were positive for both TPO and TG antibodies, while in the majority of the euthyroid patients (93.2%) both TPO and TG antibodies were negative.

Table 1. Thyroid status, and antibodies (TPO and TE) in 305 children and adolescent with type 1 DM

| Thyroid status (No.) | No. of patient (%) Antibodies done | -ve antibodies No. of patient (%) | +ve antibodies | |
|---------------------------------|---------------------------------------|--------------------------------------|----------------|----|
| | | | TPO | TG |
| Normal (240) | 76 (31.7%) | 71 (93.4%) | 5 | 3 |
| Subclinical hypothyroidism (39) | 18 (46.2%) | 13 (72.2%) | 5 | 5 |
| Overt hypothyroidism (26) | 20 (76.9%) | 4 (20%) | 16 | 16 |

TPO – thyroid-microsomal-peroxidase; TG – thyroglobulin.

Discussion

Type 1 Diabetes Mellitus is the most common endocrinopathy to have clinical onset in childhood and adolescence, with varied pathogenesis, clinical appearance and outcome, and seriously affects patients and families life. A combination of genetic, environmental and immunological factors over to a T-cell mediated autoimmune process targeted against insulin producing β -cells in the pancreatic islet of Langerhans (Daneman, 2006). It is increasing in incidence world-wide (Vehil and Dabelea, 2011). Fifteen to 30% of individuals with type 1 diabetes have autoimmune thyroid disease (AID), 5-8% has celiac disease, and 0.5% has Addison’s disease (AD). The risk for autoimmune disease is increased in relatives of patients with type 1 diabetes mellitus. Eighty percent of first-degree relatives have AID and up to 6% have CD (Perros et al., 1995; Hanukeglu et al., 2003; Umpierrez et al., 2003).

These diseases are associated with organ-specific autoantibodies: thyroid microsomal peroxidase (TPO) and thyroglobulin (TG) with AID. Endomysial (EMA) autoantibodies and transglutaminase (TTG) autoantibodies with CD. Using these autoantibodies organ-specific autoimmunity may be detected before the development of clinical disease. Early detection has the potential to prevent significant morbidity related to unrecognized disease (Perros et al., 1995). The association between type 1 diabetes and autoimmune thyroid disease has long been recognized. A high prevalence of thyroid antibodies has been found (8-44%) in several studies (Menon et al., 2001; Kordonouri et al., 2002; Umpierrez et al., 2003;

Kordonouri et al., 2005; Araujo et al., 2008; Mantovani et al., 2009; Shiva and Behbahan, 2009; Ghawil et al., 2011; Piatkowska and Szalecki, 2011).

This is the first study from Saudi Arabia looking into the prevalence of thyroid dysfunctions and autoimmunity in children and adolescents with type 1 diabetes mellitus. No similar studies have been conducted in Saudi Arabia, inspite of the high prevalence of type 1 diabetes mellitus. Few studies, were reported from other neighboring Arab countries, where Ghawil et al. (2011) from Libya, and Radaidah et al. (2003) from Jordan, reported almost a similar results of about 20%, i.e. higher than that reported from patients with type 2. Akbar et al. (2006) from Saudi Arabia, and Radaidah et al. (2004) from Jordan, reported a prevalence of 12-16%.

The diagnosis of thyroid dysfunction in diabetic patients based solely on clinical manifestations can be difficult. Poor glycemic control can produce features similar to hyperthyroidism, such as weight loss despite increased appetite, and fatigue. On the other hand, severe diabetic nephropathy can be mistaken for hypothyroidism because patients with this condition may have edema, fatigue, pallor, and weight gain.

The availability of the highly sensitive immunoassay for serum TSH provides a major advance in the diagnosis of thyroid disorders. It is the most reliable and sensitive screening test for thyroid dysfunction and allows both hypothyroidism

and hyper thyroidism to be diagnosed with certainty. In addition, subclinical thyroid dysfunction can only be diagnosed by an abnormal TSH, because the serum FT₃ and FT₄ are normal. The patients are usually asymptomatic.

Physiological effects, sub-clinical hypothyroidism can elevate serum lipid, further increase the risk of atherosclerosis. Subclinical hyperthyroidism may increase the risk of cardiac arrhythmia (Wa, 2000).

In our study group, it was noted that 65 (21.3%) patients were having variety of thyroid dysfunctions. Twenty-six (8.5%) patients were treated for overt-hypothyroidism, 39 (12.8%) patients had subclinical hypothyroidism, while none of the patients had hyperthyroidism either subclinical or overt.

In conclusion, children and adolescents with type 1 diabetes have a significant increase risk of developing thyroid dysfunction with a high prevalence of 21.3%. A routine screening should be implemented annually with determination of anti-thyroid microsomal and anti-thyroglobulin antibodies and TSH. Patients who have positive thyroid antibodies and normal thyroid function, may need the assessment of thyroid function, even, at a shorter intervals to allow detection and treatment, hence, avoid the associated complication.

Acknowledgement

The authors would like to thank Ms. Loida M. Seseand Abdulbasit Jalal Alloulou for their secretarial assistance and would like to extend their thanks and appreciation to College of Medicine Research Centre, Deanship of Scientific Research, King Saud University, Riyadh, Saudi Arabia for funding the work.

References

- Akbar, D.H., Ahmed, M.M., Al Mughales, J., 2006. Thyroid dysfunction and thyroid autoimmunity in Saudi type 2 diabetic. *Acta. Diabetol.* 43(1), 14-18.
- Araujo, J., Brandao, L.A., Guimaraes, R.L., 2008. Prevalence of autoimmune thyroid disease and thyroid dysfunction in young Brazilian patients with type 1 diabetes. *Pediatr. Diabet.* 9(4), 272-276.
- Barova, H., Perusicova, J., Hill, M., 2004. Anti-GAD-positive patients with type 1 diabetes mellitus have higher prevalence of autoimmune thyroiditis than anti-GAD-negative patients with type 1 and type 2 diabetes mellitus. *Physic. Res.* 53(3), 279-286.
- Bilimoria, K.Y., Pescovitz, O.H., Di Meglio, L.A., 2003. Autoimmune thyroid dysfunction in children with type 1 diabetes mellitus: screening guidelines based on a retrospective analysis. *J. Pediatr. Endocrinol. Metab.* 16(8), 1111-1117.
- Cooper, D.S., 2001. Subclinical hypothyroidism. *New Engl. J. Med.* 345, 260-265.
- Daneman, D., 2006. Type 1 diabetes. *Lancet* 367(9513), 847-858.
- Feely, J., Isles, T.E., 1979. Screening for thyroid dysfunction in diabetics. *BMJ* 1(6179), 1678-1680.
- Ghawil, M., Tonutti, E., Abusrewil, S., 2011. Autoimmune thyroid disease in Libyan children and young adults with type 1 diabetes mellitus. *Eur. J. Pediatr.* 170(8), 983-987.
- Gray, R.S, Irvine, W.J., Clarke, B.F., 1979. Screening for thyroid dysfunction in diabetics. *BMJ* 2(6202), 1439-1440.
- Haket, A.E., Pols, H.A., Visser, T.J., Drexhage, H.A., Hofman, A., Willeman, C.M., 2000. Subclinical hypothyroidism is an independent-risk factor for atherosclerosis and myocardial infarction in elderly woman. The Rotterdam study. *Ann. Intern. Med.* 132, 270-278.
- Hanukeglu, A., Mizrachi, A., Dalal, I., 2003. Extra pancreatic autoimmune manifestations in type 1 diabetic patients and their first-degree relatives. *Diabet. Care* 26, 1235-1240.
- Kordonouri, O., Dess, D., Danne, T., Dorow, A., Bassir, C., Gruters-Kieslich, A., 2002. Predictivity of thyroid autoantibodies for the development of thyroid disorders in children and adolescents with type 1 diabetes. *Diabetic Med.* 19(6), 518-521.
- Kordonouri, O., Hartmann, R., Deiss, N., Wilms, M., Gruters-Kieslich, A., 2005. Natural course of autoimmune thyroiditis in type 1 diabetes: association with gender, age, diabetes duration and puberty. *Arch. Dis. Child.* 90(4), 411-414.
- Lindberg, B., Ericsson, U.B., Ljung, R., Ivarsson, S.A., 1997. High prevalence of thyroid autoantibodies at diagnosis of insulin-dependent diabetes mellitus in Swedish children. *J. Lab. Clin. Med.* 130(6), 585-589.

- Mantovani, R.M., Mantovan, L.M., Dias, V.M., 2009. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus: prevalence and risk factors. *J. Pediatr. Endocrinol. Metab.* 20(6), 669-675.
- Menon, P.S., Vaidyanathan, B., Kaur, M., 2001. Autoimmune thyroid disease in Indian children with type 1 diabetes mellitus. *J. Pediatr. Endocrinol. Metab.* 14, 279-286.
- Mohn, A., Di Michele, R., Di Luzio, R., Tumini, S., Chiarelli, F., 2002. The effect of sub-clinical hypothyroidism on metabolic control in children and adolescents type 1 diabetes mellitus. *Diabetic Med.* 19, 70-73.
- Mohn, A., Di Michele, S., Faricelli, R., Martinotti, S., Chiarelli, F., 2005. Increased frequency of Subclinical Hypothyroidism and Thyroid-associated antibodies in siblings of children and adolescents with Type I Diabetes Mellitus. *Eur. J. Endocrinol.* 153, 717-718.
- Perros, P., McCrimmon, R.J., Shaw, G., Frier, B.M., 1995. Frequency of thyroid dysfunction in diabetic patients: value of annual screening. *Diabetic Med.* 12(7), 622-627.
- Piatkowska, E., Szalecki, M., 2011. Autoimmune thyroiditis in children and adolescents with type 1 diabetes. *Pediatr. Endocrinol. Diabet. Metab.* 17(4), 173-177.
- Radaidah, A., El-Khateel, M., Batiha, A.M., Nasser, A.S., Ajlouni, K.M., 2003. Thyroid function and thyroid autoimmunity in patients with type 1 diabetes mellitus. *Saudi Med. J.* 24(4), 352-355.
- Radaidah, A., Nusier, M.K., Amari, F.L., 2004. Thyroid dysfunction in patients with type 2 diabetes mellitus in Jordan. *Saudi Med. J.* 25(8), 1046-1050.
- Shiva, S., Behbahan, A.G., 2009. Autoimmune thyroid disease in children and adolescents with type 1 diabetes mellitus in Northwest Iran. *Saudi Med. J.* 30, 673-676.
- Umpierrez, G.E., Latif, K.A., Murphy, M.B., 2003. Thyroid dysfunction in patients with type 1 diabetes: A longitudinal study. *Diabet. Care* 26(4), 1181-1185.
- Vehil, K., Dabelea, D., 2011. The changing epidemiology of type 1 diabetes : why is it going through the roof? *Diabet. Metab. Res. Rev.* 1(27), 3-13.
- Wa, P., 2000. Thyroid disease and diabetes. *Clin. Diabet.* 18(1), 38-39.