ORIGINAL ARTICLE

Hypothyroidism and Celiac among Patients with Diabetes Mellitus Type I in Yazd, Iran; a Descriptive Study

Mahtab Ordooei[1], Seyed Mohammad Mohammadi[2], Golnaz Malekzadeh[3*], Marzieh Ordooei[4]

1- Pediatric Endocrinologist, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
2- Yazd Diabetes Research Center, Shahid Sadoughi University of Medical Science, Yazd, ran.
3- Medical Student of Shahid Sadoughi University of Medical Sciences, Yazd, Iran
4- Medical Doctor, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

[*]**Correspondence:**
Golnaz Malekzadeh, Medical Student of Shahid Sadoughi University of Medical Sciences, Yazd, Iran
Email: golnaz_malek_zade@yahoo.com
Tel: (98) 913 253 6332

Received: 10 January 2015
Accepted: 02 March 2015
Published in June 2015

Abstract

Objective: The autoimmune diseases tend to coexist with diabetes mellitus type I (T1DM). The concomitance of these two types of diseases will lead to poor glycemic control beside their own complications. In this study the prevalence of thyroid disorder and celiac disease among T1DM patients in Yazd, Iran was evaluated.

Materials and Methods: all the patients diagnosed as T1DM in Yazd younger than 18 years old were investigated for the presence of thyroid disorders and celiac by measuring T3, free T4, TSH, Anti TPO and anti-tTG IgA. In positive celiac disease laboratory tes, intestinal biopsy was done to confirm the presence of this disease. Data gathered from all patients were analyzed using SPSS software version 18th.

Results: Eighty one patients consist of 38 boys and 43 girls involved in our study. Six patients (7.4%) consist of 4 girls and 2 boys presented hypothyroidism with positive Anti TPO. Two patients (2.4%) presented positive anti-tTG IgA that both were confirmed by intestinal biopsy.

Conclusion: due to the considerable prevalence of thyroid disorders and celiac disease among T1DM patients, serologically screening for autoimmune diseases and then annually for any new onset is suggested.

Keywords: Diabetes mellitus type I, Celiac disease, Thyroid disorder, Auto immune disease

Introduction

Diabetes mellitus type 1 (T1DM) is characterized by decreased endogenous insulin due to autoimmune destruction of pancreatic beta cells. The T1DM prevalence is growing worldwide and turned out as a health system concern (1).

It has been shown that other autoimmune diseases such as hypothyroidism, Celiac, Addison's disease, pernicious anemia and etc are more prevalent among T1DM patients (2-3). The underlying cause of this coincidence is still unclear, but it has been related to the cross reaction of auto anti bodies that predispose these patients to various autoimmune diseases. There is a close relation between thyroid antibodies especially microsomal and peroxidase and auto antibodies against pancreatic beta cells. (4) The positivist antibodies against thyroid among newly

diagnosed diabetic type I patients is reported 10 to 30% that can't be ignored.(5-8) Untreated hypothyroidism in patients with T1DM can lead to growth retardation, infertility, cardiovascular complications, dyslipidemia and etc.(9)Celiac is also an autoimmune disease that coexist with T1DM and affects the small bowel mucosa. Malabsorption is the Celiac consequence due to the inflammation in small bowel tissue which causes failure to thrive in children. (10)
The growing prevalence of diabetes type I, the complications of hypothyroidism and celiac and their coincidence with T1DM bring the idea of screening to the fore. The aim of this study was to evaluate the prevalence of thyroid disorders and celiac in diabetes type I patients in Yazd, Iran to have a scheme for future planning.

Materials and Methods

In this observational study all the patients with diabetes type I younger than 18 years old who admitted to pediatrics endocrinology clinic of Shahid Sadoughi University of medical sciences, Yazd, were involved. Inform consent was taken from all the patients' parents. Celiac disease was screened by blood level of transglutaminase (anti-tTG IgA) (Orgentec Diagnostika GmbH, Mainz, Germany).The blood level of transglutaminase more than 10 U/ml was assumed to be celiac. In patients who had positive serology the second part of duodenum intestinal biopsy was done as gold standard to confirm the celiac disease. The biopsies were evaluated by a pathologist and classified the patients according Marsh classification. In addition all the patients were previously checked for IgA deficiency.
Serum level of T_3, FT_4I , and TSH were measured in all patients to evaluate any thyroid disease(immune fluoro metric assay TSH ultra, Perkin Elmer Italia SP, Monza, Italy was used to measure TSH and Auto analyzer Immulite 2000 or Centaurus CDPC limited, San Jaun Capistranto, CA were used to measure $T_3$and FT_4I)
Anti thyroid peroxidase antibody (Anti TPO) was measured to rule out the autoimmune base.(RIA kit, Becton Dickinson and Co., Franklin Lakes, NJ, USA was used to measure Anti TPO level). Normal lab tests ranges according to the age are showed in Table1.
If the serum level of TSH was higher than its normal range and thyroid hormones were lower than their normal range it was reported as hypothyroidism but if the thyroid hormones were normal it was reported as subclinical hypothyroidism. In the case of decreased TSH and elevated hormones hyperthyroidism was reported. Increased Anti TPO (more than 15) level was assumed as autoimmune thyroid disease.
The result of lab tests of each patient was compared to the normal ranges reported by laboratory references to decide for presence of thyroid dysfunction or celiac. Also all the patients were interviewed for any positive family history of thyroid disease or celiac. Data gathered from the patients were analyzed using SPSS software version 18 and univariate analyses were used toreport the prevalence and distribution of study variables.

Results

All the patients with diabetes type I younger than 18 years old in Yazd were 81patients which 38 (46.9%) were boys and 43 (53.1%) girls. The mean age of patients was 13.42±4.67 years old. The mean age of T1DM onset among them was 8.6±2.5 years old.
The laboratory results showed increased TSH and decreased thyroid hormones in 6 (7.4%) patients which were compatible with hypothyroidism. All 6 patients had positive Anti TPO which indicates the autoimmune base. The patients' characteristics are shown in table 2. None of the patients showed subclinical thyroidism or hyper thyroidism, moreover none of the other patients had positive Anti TPO. The thyroid disease family history was positive in 22 patients (27.2%).
Among these 81 patients only 2 had positive Anti tTG IgA which is equivalent to 2.4%. One of them was a girl which was also

afflicted with autoimmune hypothyroidism (patient number 1 in Table2) and the other one was a14 year old boy. The results of intestinal biopsies of both patients were positive for celiac and compatible with Marsh II lesions but none of them were symptomatic. Meanwhile none of the patients had any positive family history for celiac.

Discussion

In this study we evaluate the prevalence of thyroid disorders and celiac as the most important and prevalent autoimmune diseases in patients with T1DM younger than 18 years old in Yazd, Iran. Our results showed 7.4% of them were afflicted by hypothyroidism and 2.4% had celiac.

In previous studies the coincidence of thyroid disorders and T1DM was reported two to four times more than general population (11-12). The positivism of Anti TPO among T1DM patients was reported 10 to 23.4% whilst it is 6.6 to 13.9% in general population (13) in our study this number was 7.4%.

Michele et al study showed, the prevalence of hypothyroidism was about 7.3% between diabetic type I patients(14) that goes along with our result (7.4%) but another study by Ardestani et al in Isfahan, Iran with respecting Isfahan geographical location, it is a suitable population to be compare with Yazd and the reported prevalence was 19.3%(15).In the study of Ayca Torel Erguret al autoimmune thyroid disease was detected in 31.5%.The celiac frequency was 7.8% but none of them were symptomatic (16).The prevalence of autoimmune thyroid disorders was 38.6% and 18.75% among T1DM in Turkey and Greece respectively (13,17). In these countries the prevalence of hypothyroidism among patients with T1DM is reported much more higher than our country.

In the study of Kordonouri et al. 15.4% of patients with T1DM had raised anti-TPO and 14.4% raised anti-tTG which was more prevalent among girls (18). In some other studies also showed that autoimmune diseases among T1DM patients was more prevalent in girls than boys that is related to preservation of male hormones towards autoimmunity (19-22). In our study also it was more prevalent among girls (66.6%) against boys. In this study also patients were recommended to regular measurement of thyroid hormone even in the absence of thyroid disease particularly in puberty period. The majority onset of their disease was after 15years old or approximately 3.5 years after the initiation of T1DM (18), but all our patients afflicted by thyroid disorder were under this age.

In a study hypothyroidism in T1DM patients is introduced as a factor lead to growth falter, short stature and pubertal delay. Diagnosis that is to the time can prevent all of them (23). Fortunately none of our diabetic patients had failure to thrive. In Kostas Kakleas study the risk factors for development of thyroid autoimmune disease among T1DM patients were reported as following: female gender, long duration of T1DM, older age and the level of TSH. In contrast the occurrence of

Table 1. Normal ranges of laboratory tests according to the age.

Lab test	Newborn	2-12 month	1-6 year	7-12 year	13-16 year	>16year
FT_4I(µg/dl)	6.2-18.7	4.3-16.4	5.5-17.2	5.0-12.5	5.4-11.7	4.4-11.6
T_3(ng/dl)	80-300	80-300	90-380	80-270	120-240	52-185
TSH(µIU/ml)	0.9-7.7	0.8-6.3	0.6-5.9	0.6-5.9	0.5-4.8	0.44-4.6

Table 2. Details of DMTI patients who were also afflicted with autoimmune hypothyroidism

Age(year)	Gender	TSH (µIU/ml)	T_3 (ng/dl)	FT_4I (µg/dl)	Anti TPO
10	Female	0.02	401.0	38.8	211.4
14	Female	0.12	286.0	18.9	126.2
8	Female	0.08	305.0	17.5	159.1
9	Female	0.05	380.0	21.6	98.5
12	Male	0.10	356.0	21.8	186.5
10	Male	0.25	335.0	25.0	127.4

celiac is related to younger age and short diabetes duration. (13,10)

The prevalence of celiac disease among T1DM patients is reported between 0.97 % to 16.4% in previous studies.(24)the prevalence of celiac in healthy blood donors in Iran is about 0.6% (25) In our study this number was 2.4% which is four times more frequent in patients with T1DM. The gold standard for diagnosing celiac is intestinal biopsy (26) that both our patients were prompted with intestinal biopsy and compatible with Marsh II lesions.

In Rozsai et al study the positivism of antiendomysium antibody (EMA) among 196 T1DM patients was reported 6.6% which only 1.5% of them were symptomatic (27).None of our patients were symptomatic. The other studies also showed that the symptoms of celiac can be subtle. (28,29)

In Karaguzel study EMA was positive only in 3.5% of T1DM patients.(17) Franjka*'s* study showed the frequency of Celiac between 3 to 6 % which about 60% of them were diagnosed upon the diagnosis of T1DM.(30) The result of Sinan and Erninian studies indicated 7% and 5.79% celiac disease in T1DM (31-32). In Barera study celiac frequency among T1DM patients was 16.4% which was higher than the result of other studies. (29)

In study of Cherubini et al despite T1DM patients, their siblings were also screened for celiac and the result was 6.6% among T1DM and 5.2% among their siblings. (33) Our patients did not have any positive family history for celiac but they had 27.2% positive family history for thyroid disorders.

Some studies administered gluten free diet for the T1DM patients affected by celiac to overcome failure to thrive and hypoglycemic attacks that lead to dramatic recovery. In contrast it has been also reported no change in the rate of ketoacidosis and hypoglycemic attacks (13,16) fortunately none of our patients had failure to thrive.

In conclusion thyroid disorders and celiac tend to coincidence with diabetes mellitus, moreover they mutually influence each other and glycemic control without treatment of these diseases is not beneficial, so it is suggested that children at the time they are diagnosed to be afflicted by diabetes mellitus be screened for other autoimmune disorders mostly thyroid ones and celiac for better glycemic control and as a result a better prognosis. It is also suggested to be screened annually for any new onset of these diseases.

Acknowledgment

The authors want to thank the staff of pediatrics endocrinology clinic of Shahid Sadoughi University of medical sciences, Yazd, Iran for their highly appreciated cooperation.

References

1. Smyth DJ, Plagnol V, Walker NM, Cooper JD, Downes K, Yang JH, et al. Shared and distinct genetic variants in type 1 diabetes and celiac disease. N Engl J Med 2008;359(26):2767-77.
2. Davidson A, Diamond B. Autoimmune diseases. N Engl J Med 2001;345(5):340-50.
3. Dretzke J, Cummins C, Sandercock J. Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus. Health Technol Assess 2004;8(22):1-183.
4. Rattarasarn C, Diasdado MA, Ortego I, Lee Lawattana R, Soonthornpun S. Thyroid autoantibodies in thai type1 diabetic patient: clinical significance and their relationship with glutamic acid decarboxilase antibodies. Diabetes Research and Clinical Practice, 2000;49:107-11.
5. Perros P, McCrimmon RJ, Shaw G, Frier BM. Frequency of thyroid dysfunction in diabetic patients: value of annual screening.Diabet Med 1995;12(7):622-7.
6. 6. Umpierrez GE, Latif KA, Murphy MB. Thyroid dysfunction in patients with type 1 diabetes: a longitudinal study. Diabetes Care 2003;26(4):1181-5.
7. Barker JM, Yu J, Yu L, Wang J, Miao D, Bao F, et al. Autoantibody "subspecificity" in type 1 diabetes: risk for organ specific autoimmunity clusters in distinct groups. Diabetes Care 2005;28(4):850-5.

8. Barker JM. Clinical review: Type 1 diabetesassociated autoimmunity: natural history, genetic associations, and screening. J ClinEndocrinolMetab 2006;91(4):1210-7.
9. Hakanen M, Luotola K, Salmi J, Laippala P, Kaukinen K, Collin P. Clinical and subclinical autoimmune thyroid disease in adult celiac disease. Dig Dis Sci 2001;46:2631-5.
10. HolmesG KT. Screening for coeliac disease in type 1 diabetes.Arch Dis Child 2002;87:495-9
11. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. ClinEndocrinol (Oxf). 1995;43:55-68.
12. Zamrazil V, Pohunkova D, Vavrejnova V, Nemec J, Vana S. Prevalence of thyroid diseases in two samples of Czech population. A preliminary study.Endocrinol Exp. 1989;23:97-104.
13. Kakleasi K, Paschali E, Kefalas N, Fotinou A, Kanariou M, Karayianni CH, Karavanaki K. Factors for thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus, Upsala Journal of Medical Sciences. 2009;114:214-20.
14. Michele S, Mohn A, Faeicelli R, Martioti S. Increase frequency of subclinical hypothyroidism and thyroid-associated antibodies in siblings of children and adolescents with type 1 diabetes mellitus. European journal of endocrinology.2005;(153):717-8
15. Ardestani S, Hassanzadeh A, Khalili N. Thyroid disorders in children and adolescence with ytpe 1 diabetes mellitus in Isfahan .Iran journal pediatrics.2011;21(4):502-58
16. Ergur AT, Ocal G, Berberoglu M, Adiyaman P, Siklar Z, Aycan Z, et al. Celiac Disease and Autoimmune Thyroid Disease in Children with Type 1 Diabetes Mellitus: Clinical and HLA-Genotyping Results, J Clin Res Ped Endo 2010;2(4):151-4
17. Karagüzel G, Simşek S, Değer O, Okten A. Screening of diabetes, thyroid, and celiac diseases-related autoantibodies in a sample of Turkish children with type 1 diabetes and their siblings. Diabetes Res ClinPract. 2008;80(2):238-43.
18. Kordonouri O, Hartmann R, Deiss D, Wilms M, Gru¨ters-Kieslich A. Natural course of autoimmune thyroiditis in type 1 diabetes: association with gender, age, diabetes duration, and puberty, Arch Dis Child 2005;90:411-4.
19. Holl RW, Bohm B, Loos U, Grabert M, Heinze E, Homoki J. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. Hormone Research in Paediatrics 1999;52(3):113-8.
20. Hansen D, Bennedbaek FN, Hansen LK, Hoier-Madsen M, Jacobsen BB, Hegedus L. Thyroid function, morphology and autoimmunity in young patients with insulin-dependent diabetes mellitus. European journal of endocrinology 1999;140(6):512-8.
21. Kordonouri O, Klinghammer A, Lang EB, Grters-Kieslich A, Grabert M, Holl RW. Thyroid Autoimmunity in Children and Adolescents With Type 1 Diabetes A multicenter survey. Diabetes care 2002;25(8):1346-50.
22. Kordonouri O, Deiss D, Danne T, Dorow A, Bassir C, Grters-Kieslich A. Predictivity of thyroid autoantibodies for the development of thyroid disorders in children and adolescents with Type 1 diabetes. Diabetic medicine 2002;19(6):518-21.
23. CourtS, Parkin J M, Hypothyroidism and growth failure in diabetes mellitus, Archives of Disease in Childhood, 1982;57:622-4.
24. Bhadada SK, Kochhar R, Bhansali A, Dutta U, Kumar PR, Poornachandra KS, et al. Prevalence and clinical profile of celiac disease in type 1 diabetes mellitus in north India.J GastroenterolHepatol. 2011;26(2):378-81.
25. Shahbazkhani B, Malekzadeh R, Sotoudeh M, Moghadam KF, Farhadi M, Ansari R, et al. High prevalence of celiac disease in apparently healthy Iranian blood donors. Eur J GastroenterolHepatol 2003;15(5):475-8.
26. Husby S, Murray JA. Defining thresholds of antibody levels improves diagnosis of celiac disease: replacing the gold standard.ClinGastroenterolHepatol. 2013;11(4):404-5
27. Rozsai B, Kozari A, Hermann R, Soltesz G. Associated autoimmunity in Type I Diabetes. JPEM 2002;15:1067.
28. Lughetti L, Bulgarelli S, Forese S, Lorini R, Balli F, Bernasconi S. Endocrine aspects of coeliac disease. J PedEndocrinolMetab.2003;16:805-18
29. Barera G, Bonfanti R, Viscardi M, Bazzigaluppi E, Calori G, Meschi F, et al. Occurrence of celiac disease after onset of type 1 diabetes: a 6-year prospective longitudinal study. Pediatrics 2002;109(5):833-8.
30. Franjiko P, Metelko Z. Celiac disease and diabetes mellitus. Diabetologia croatica 2003;32(4):157-60
31. Sinan S, Esilkaya E, Egritas D. Prevalence of celiac disease in Turkish children with type 1 diabetes mellitus and their non-diabetic first-degree relatives. Turk journal gastroentrol 2010;21(1):34-8
32. Erminia M, MozzilloE, Nugnes R. Celiac disease in type 1 diabetes mellitus .Italian journal of pediatrics 2012;(38):10
33. Cherubini V, Fabiani PE, Scalari PA. High prevalance of Celiac Disease in siblings of Type 1 Diabetic Children. JPEM 2002;15:1075.