Type 1 Diabetes Mellitus Associated With Autoimmune Thyroid Disorders in Iranian Children: A Review

Daniel Zamanfar 1; Mohsen Aarabi 2,*; Iman Sadeghian 3

1 Diabetes Research Center, Mazandaran University of Medical Sciences, Sari, IR Iran
2 Health Sciences Research Center, Mazandaran University of Medical Sciences, Sari, IR Iran
3 Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, IR Iran
*Corresponding author: Mohsen Aarabi, Health Sciences Research Center, Mazandaran University of Medical Sciences, Sari, IR Iran. Tel: +98-1133342331, Fax: +98-1133344506, E-mail: aarabi@mazums.ac.ir

Received: November 8, 2014; Accepted: December 30, 2014

Context: Type one diabetes mellitus (T1DM) is an autoimmune disorder that is yet the most common type of diabetes in children and adolescents. Several genetic risk factors have been associated with T1DM, auto immune thyroiditis and other autoimmune disorder. Among autoimmune disorders, autoimmune thyroid disease (ATD) is the most frequent disorder associated with T1DM. Its prevalence varies depending on age, sex and ethnic origin of the subjects and is considerably higher than the general population and increases with duration of T1DM. The aim of this study was to review the prevalence of ATD in Iranian children with T1DM compared with other countries.

Evidence Acquisition: We conducted a review on all papers published on the association between autoimmune thyroiditis and T1DM, which was available on Google Scholar, Scientific Information Database (SID), Magiran and Iran Medex databases up to June 2014. Both Persian and English articles were checked. The searched terms were: diabetes mellitus, autoimmune thyroiditis, prevalence, frequency, Iranian children and adolescents. All papers which were done on patients with age under 20 years old and have used Anti-TPO and Anti-TG to evaluate patients were included.

Results: Six papers met all the criteria. A total of 736 participants were included in this review. After review of all the papers, the prevalence of Anti-TPO was reported between 8% and 30% and Anti-TG was reported 6.06% to 23.6% in diabetic children in Iran.

Conclusions: Autoimmune thyroid disorders are the most prevalent immunological diseases in patients with type 1 diabetes. All these studies have shown a higher prevalence of the disorder in patients with T1DM compared to the Iranian healthy population. Anti-TPO reported between 8% and 30% and Anti-TG reported 6.06% to 23.6% in diabetic children in Iran that was similar to the studies in other countries.

Keywords: Diabetes Mellitus; Autoimmune Thyroiditis; Prevalence; Frequency; Child; Adolescent; Iran

1. Context

Type one diabetes mellitus (T1DM) is an autoimmune disorder that is yet the most common type of diabetes in children and adolescents (1, 2). This disorder results from immune and non-immune destruction of β-cell islets of the pancreas (3). Therefore, children and adolescents with T1DM are at increased risk for developing other autoimmune diseases (3, 4). The most common autoimmune disorder that is associated with T1DM is autoimmune thyroiditis; however, its prevalence is dependent to age, sex and ethnic origin of the subjects and varies considerably (5). Several genetic risk factors have been associated with T1DM, autoimmune thyroiditis and other autoimmune disorder (12).

Several genes such as HLA-DQ alpha, HLA-DQ Beta, preproinsulin, PTPN22, CTLA-4, IL2 receptors and others have roles in increasing the risk of T1DM (13, 14). The major susceptibility gene for T1DM is in the HLA region of chromosome 6p, which contains the genes that code for major histocompatibility complex (MHC) Class II molecules (15, 16). The highest-risk human leukocyte antigen (HLA) genotype for T1DM are DR3-DQ2 and DR4-DQ8 (17). In fact, children with this genotype have a 5% risk for T1DM by 15 years of age (17). In other hand, the same HLA alleles such as DQA1*0102 and DQB1*0602 is associated with a low risk for T1DM and are protective for disease development (18). Also, MHC susceptibility genes are not sufficient to induce T1DM; so in most cases, the polygenic inheritance can be suggested (16). The MHC I related gene A (MIC-A) has been associated with autoimmune disease (12).

Polymorphism of MIC-A associated with T1D and polymorphism in other genes are associated with many autoimmune diseases, suggests that these genes may play roles in susceptibility to autoimmunity (19, 20). Several auto antigens within the pancreas β-cells may play important roles in the initiation and/or progression of autoimmune islet injury (21-23). These auto antigens are proinsulin/insulin, islet-specific glucose-6-phosphatase catalytic-subunit-related protein (IGRP), glutamic-acid...
decarboxylase (GAD), insulinoma associated protein 2 (IA-2 and IA-2 beta) and the auto antigen Zn T8, a zinc transporter of islet beta cells (24-27). It has been appeared that auto antibodies against these antigens develop sequentially (12), especially in young children often insulin autoantibodies are the first to appear that followed from birth and progressing to diabetes and are the highest in whom developing diabetes (28).

Antibodies to GAD-65 are found in about 70%, antibodies to insulinoma associated proteins were found in 58% and also auto antibodies to Zn T8 were founded in 60-80% of patients with T1DM at the time of diagnosis (29-32). Thus, one of the best predictors of progression to T1DM is an expression of two or more of these auto antibodies (33). In fact, family members who expressed these three auto antibodies have a 75% of five-year risk of diabetes compared with a 25% of five-year risk in relatives who expressed one of them (33). These auto antibodies may be present for years before the diagnosis of diabetes and the risk for diabetes does not decline over time (34-37). Among the genes mentioned above, CTLA-4 genes may play an important role in synergy with HLA for the development of both T1DM and auto immune thyroiditis (38, 39).

It is appeared that children with β-cell auto antibodies such an Anti-GAD and also specific HLA subtypes such as HLA-DQBI*0302 are associated with greater risk of developing anti-thyroid antibodies (40-43). Indeed, there is a close association between specific thyroid auto antibodies such as microsomal and peroxidase antibodies and anti-pancreatic β-cells auto antibodies and an increased prevalence of thyroid antibodies occur in T1DM patients with ATD, but the reasons for this increased frequency remained obscure (44-47).

Among auto immune disorders, autoimmune thyroid disease (ATD) is the most frequent with T1DM and prevalence of it that varies depending on the age, sex and ethnic origin of the subjects is considerably higher than the general population and increase with duration of T1DM (7, 48, 49). High titers of anti-TPO are highly suggestive of ATD and correlated well with thyroid dysfunction. Patients with circulating antibodies may be euthyroid, hypothyroid or rarely hyperthyroid (50-52). The presence of autoimmune thyroid disorder in patients with T1DM - even in subclinical hypothyroidism - can be associated with an increased risk of hypoglycemia, reduced linear growth and lower weight, better diabetes control, menstrual regularity and overall well-being (17, 53, 54). Current recommendations from the American Diabetes Association (ADA) are for screening TSH after stabilization at onset of diabetes, and every one to two years thereafter (53). It is also recommended that subjects with positive TPO auto antibodies and normal thyroid function should be screened on a more frequent basis, such as every six months to a year. The aim of this study was to review the prevalence of autoimmune thyroid disorders in Iranian children with T1DM and compare it with other areas, and also present the importance of screening in this group of patients.

2. Evidence Acquisition

We conducted a review of all papers published on association between autoimmune thyroiditis and T1DM that was available on Google Scholar, Scientific Information Database (SID), Magiran and Iran Medex databases up to June 2014. Both Persian and English articles were checked. The searched terms were: diabetes mellitus, autoimmune thyroiditis, prevalence, frequency, Iranian children and adolescents. References of the found articles were used for finding more appropriate papers. Moreover, relevant national and regional conference proceedings were checked. All the studies that contained prevalence of autoimmune thyroiditis disease in children and adolescents who had T1DM were included. Articles with no information about autoantibody titer were excluded. The total number of participants with T1DM and the number of them with autoimmune thyroiditis were extracted from all papers.

3. Results

From all papers done in T1DM patients with age under 20 years old and used anti TPO and anti TG to evaluate patients, six papers met the all criteria. But in our research, we found three studies that the studied population was contained both adults and children. Three of which were published in English and three of them in Persian language. Three studies done in case control methods and other studies performed in cross sectional method. A total of 736 participants were checked in this review. After reviewing all the papers, the prevalence of anti-TPO was found between 8% and 30% and anti-TG was found between 6.06% and 23.6% in diabetic children in the Iran. Table 1 demonstrates the prevalence of autoimmune thyroid disorders in Iranian diabetic children derived from the selected papers.

Table 1. Prevalence of Autoimmune Thyroid Disorders in Iranian Diabetic Children a

| Study       | Population Method | Anti-TPO Anti-TG |
|-------------|-------------------|------------------|
| Shiva (55)  | 99 Cross-sectional | 8.08 (6.06)      |
| Sharifi (56) | 55 Case control   | 16 (29) 12 (21.6)|
| Bahrami (57)| 386 Cross-sectional | 115 (30)         |
| Saffari (58)| 65 Case control   | 7 (10.8) 11 (16.9)|
| Vakili (59) | 48 Case control   | 9 (19) 10 (21)   |
| Ardestani   | 83 Cross-sectional | 16 (9.3) 9 (11)  |

a Data are presented as No. or No. (%).

4. Conclusions

Autoimmune thyroid disorders are the most prevalent immunological diseases in patients with T1DM. In general population, this condition is affecting approximately 2% of the female population and 0.2% of the males (61).
Using case-control studies in Iranian healthy children, the prevalence of autoimmune thyroid disorders was approximately 5.7% (56, 58). According to Boelaert et al. study, the prevalence of autoimmune thyroid disease in United Kingdom population was estimated about 1.5% (62). Munteis et al. reported 2.24% in healthy Spanish people (63). Shiva et al. demonstrated that the prevalence of anti-TPO and anti-TG antibodies are 8 (8.08%) and 6 (6.06%) (55) in 2013, in a cross sectional study about thyroid autoimmunity at the onset of TIDM on 99 Iranian children patients. Bahrami just used the anti-TPO, but other researchers used both antibodies (57). In Bahrami et al. study, 386 diabetic patients screened for autoimmune thyroiditis, but they just used anti-TPO to investigate patients. The patients underwent follow up about 9.8 ± 4 years. Anti-TPO checked for all participants every two years. At the end of this research, 115 (30%) patients were positive for anti-TPO (57). Sharifi et al. screened diabetic patients to determine antithyroid antibodies; although this research was done in all ages, the results included information of patient who had aged less than 20 years. Ninety one diabetic patients screened in this study, but 55 patients enrolled in our review (56).

Saffari et al. and Vakili et al. in case control studies checked the prevalence of Antithyroid Antibodies (58, 59). In Saffari et al. study, 65 diabetic patients screened for autoimmune thyroiditis along with 65 healthy children. Prevalence of anti-TPO was estimated about 16.9% and anti-TG was 10.8% (58). In Vakili et al. study, 48 diabetic children and 48 healthy children were enrolled and the prevalence of anti-TPO was estimated about 19% and anti-TG was 21% in diabetic children (59). In Ardestani et al. study on 83 children and adolescents with TIDM in Isfahan, the prevalence of anti-TPO and anti-TG antibodies was reported 19% and 12%, respectively (60). All these studies have shown higher prevalence in Iranian healthy population. Based on studies, 15-30% of TIDM patients had autoimmune thyroid disorders (ATD) (12, 60, 64-66).

ATD is a more prevalent autoimmune disorder associating with TIDM that is often clinically silent, but it may progress to obvious autoimmune thyroid disease (AITD), identified as overt or subclinical hypothyroidism and hyperthyroidism by prevalence of 1.5% and 0.5-7% for in young diabetic patients, respectively (67-69). Thyroid autoimmunity is increased in females and with longer duration of diabetes (2, 12, 37, 54). Prospective follow-up showed that the development of thyroid disease was related to the female gender and the presence of TPO antibodies, and measuring of circulating antibodies against thyroid peroxidase (anti-TPO Ab) and thyroglobulin (anti-Tg Ab) can be made easily (70).

Thyroid antibodies are more prevalent in TIDM patients compared with the general population with varying prevalence reported between 3% and 50%, based on the methodology of the study and patient’s characteristics such as age, sex, ethnicity, and genetic background (68, 71). Laboratory result showed that 80% have elevated TSH level and between 10% and 20% in those diabetic individuals having normal TSH levels. Anti-TPO reported between 8% and 30% and anti-TG reported 6.06% to 23.6% in diabetic children in Iran that was similar to other studies.

Acknowledgements

We would like to acknowledge Mrs. Soheila Shahmohammadi, CRNA, Research Fellow for her insightful comments on the draft of the manuscript and Dr. Leila Sarparast; the staff of Clinical Development Research Center at Bou Ali Sina Hospital providing software facilities for searching articles.

References

1. American Diabetes A. Diagnosis and Classification of diabetes mellitus. Diabetes Care. 2010;33 Suppl 1:S62-9.
2. Ghawil M, Tonutti E, Abusrewil S, Vinti B, Hadeed I, Motti V, et al. Autoimmune thyroid disease in Libyan children and young adults with type 1 diabetes mellitus. Eur J Pediatr. 2011;170(8):988-7.
3. Li J, Shen S, OuYang J, Hu Y, Hu L, Cui W, et al. Auto logical hematopoietic stem cell transplantation modulates immune competent cells and improves beta-cell function in Chinese patients with new onset of type 1 diabetes. J Clin Endocrinol Metab. 2012;97(5):1729-36.
4. Black MM, Quigg AM, Hurley KM, Pepper MR. Iron deficiency and iron-deficiency anemia in the first two years of life: strategies to prevent loss of developmental potential. Nutr Rev. 2011;69 Suppl 1:S64-70.
5. Riley WJ, Maclaren NK, Leoetz DC, Scillari RP, Rosenbloom AL. Thyroid autoimmunity in insulin-dependent diabetes mellitus: the case for routine screening. J Pediatr. 1991;99(3):350-4.
6. Radaideh A, EL-Khatteeb M, Batieha AM, Nasser AS, Ajlouni KM. Thyroid function and thyroid autoimmunity in patients with type 1 diabetes mellitus. Saudi Med J. 2003;24(4):352-5.
7. Przyni M, Skhra J, Limanowa Z, Vanickova Z, Hilgertova J, Prazna J, et al. Screening for associated autoimmunity in type 1 diabetes mellitus with respect to diabetes control. Physiol Res. 2005;54(1):41-8.
8. Hawkins BR, Cheah PS, Dawkins RL, Whittingham S, Burger HC, Patel Y, et al. Diagnostic significance of thyroid microsomal antibodies in randomly selected population. Lancet. 1980;2(8183):1057-9.
9. Menon PS, Vaidyanathan B, Kaur M. Autoimmune thyroid disease in Indian children with type 1 diabetes mellitus. J Pediatr Endocrinol Metab. 2001;14(3):279-86.
10. Holl RW, Bohm B, Loos U, Grabert M, Heinze E, Homoki J. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. Effect of age, gender and HLA type. Horm Res. 1999;52(3):183-8.
11. Chikuba N, Akazawa S, Yamaguchi Y, Kawasaki E, Takino H, Takao Y, et al. Type 1 insulin-dependent diabetes mellitus with coexisting autoimmune thyroid disease in Japan. Intern Med. 1992;31(9):1076-80.
12. Barker JM. Clinical review: Type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. J Clin Endocrinol Metab. 2006;91(4):1320-7.
13. Tuomilehto J, Pedar T, Tuomilehto-Wolf E, Virtala E. Evidence for importance of gender and birth cohort for risk of IDDM in offspring of IDDM parents. Diabetologia. 1995;38(8):795-82.
14. Concannon P, Rich SS, Nepom GT. Genetics of type 1A diabetes. N Engl J Med. 2009;360(16):1646-54.
15. Barker J, Barriga K, Yu L, Miao D, Erlich HA, Norris JM, et al. Prediction of autoantibody positivity and progression to type 1 diabetes: Diabetes Autoimmunity Study in the Young (DAISY). J Clin Endocrinol Metab. 2004;89(5):1896-902.
16. Davies JL, Kawaiuchi Y, Bennett ST, Copeman JB, Cordell HJ, Pritchard LE, et al. A genome-wide search for human type 1 diabe-
tes susceptibility genes. *Nature*. 1994;374(6523):330-6.
17. Mohn A, Di Michele S, Di Luzio R, Tumini S, Chiarelli F. The effect of subclinical hypothyroidism on metabolic control in children and adolescents with type 1 diabetes mellitus. *Diabet Med*. 2002;19(9):709-3.
18. Frohlich-Reiterer EE, Kapers S, Hofer S, Schorer E, Kordonouri O, Pozza SB, et al. Anthropometry, metabolic control, and follow-up in children and adolescents with type 1 diabetes mellitus and biopsy proven celiac disease. *J Pediatr*. 2003;142(5):593-9.
19. Bottini N, Musumeci L, Alonso A, Rahmoni S, Nika K, Ros-tamkhani M, et al. A functional variant of lymphoid tyrosine phosphatase is associated with type 1 diabetes. *Nat Genet*. 2004;36(4):377-8.
20. Smyth D, Cooper JD, Collins JE, Heward JM, Howson JM, et al. Replication of an association between the lymphoid tyrosine phosphatase locus (LYP/PTPN22) with type 1 diabetes, and evidence for its role as a general autoimmune locus. *Diabetes*. 2004;53(10):3203-7.
21. Atkinson MA, Maclaren NK. The pathogenesis of insulin-dependent diabetes mellitus. *N Engl J Med*. 1994;331(21):1428-36.
22. Boitard C. The differentiation of the immune system towards anti-islet autoimmunity. Clinical prospects. *Diabetologia*. 1994;37(10):1238-49.
23. Lendrum R, Walker G, Gamble DR. Islet-cell antibodies in juvenile diabetes mellitus of recent onset. Lancet. 1975;2(7982):880-2.
24. Wenzlau JM, Julii K, Yu L, Mousa O, Sarkar SA, Gottlieb P, et al. The cation efflux transporter ZnT8 (Slc30A8) is a major autoantigen in human type 1 diabetes. *Proc Natl Acad Sci U S A*. 2007;104(43):17040-5.
25. Nakayama M, Abiru N, Moriyama H, Babaya N, Liu E, Miao D, et al. Prime role for an insulin epitope in the development of type 1 diabetes in NOD mice. *Nature*. 2005;438(7069):220-3.
26. Greenbaum CJ, Wilkin TJ, Palmer JP. Fifth International Serum Exchange Workshop for Insulin Autoantibody (IAA) Standardization. The Immunology and Diabetes Workshops and participating laboratories. *Diabetologia*. 1992;35(8):788-800.
27. Rabin Dd, Pleasac SM, Shapiro JA, Yoo-Warrren H, Oles J, Hicks JM, et al. Islet cell antigen 512 is a diabetes-specific islet autoantigen related to protein tyrosine phosphatases. *J Immunol*. 1994;152(6):3183-8.
28. Achenbach P, Koczvara K, Knopfl A, Naserke H, Ziegler AG, Bonifacio E. Mature high-affinity immune responses to (pro)insulin anticipate the autoimmune cascade that leads to type 1 diabetes. *J Clin Invest*. 2004;114(4):589-97.
29. Baekkeskov S, Aanstoot HH, Christgau S, Reest A, Solimena M, Cascalho M, et al. Identification of the 64k autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. *Nature*. 1999;347(6303):535-6.
30. Bonifacio E, Atkinson M, Eisenbarth G, Serretze D, Kay TW, Lee-Chan E, et al. International Workshop on Lessons From Animal Models for Human Type 1 Diabetes: identification of insulin but not glutamic acid decarboxylase or IA-2 as specific autoantigens of humoral autoimmunity in nonobese diabetic mice. *Diabetes*. 2001;50(11):2431-8.
31. Ellis TM, Schatz DA, Ottendorfer EW, Lan MS, Wasserfall C, Salis bury PJ, et al. The relationship between humoral and cellular immunity to IA-2 in IDDM. *Diabetes*. 1998;47(4):566-9.
32. Wenzlau JM, Walter M, Gardner TJ, Frisch LM, Yu L, Eisenbarth GS, et al. Kinetics of the post-onset decline in zinc transporter 8 autoantibodies in type 1 diabetic human subjects. *J Clin Endocrinol Metab*. 2010;95(1):472-9.
33. Verge CF, Giannelli R, Kawasaki S, Kupila A, Simell S, Veijola R, et al. Dynamics of diabetes-associated autoantibodies in young children with human leukocyte antigen-conferred risk of type 1 diabetes recruited from the general population. *J Clin Endocrinol Metab*. 2005;90(5):2717-2.
34. Bingley PJ, Christie MR, Bonifacio E, Bonifanti R, Shattock M, Fonte MT, et al. Combined analysis of autoantibodies improves prediction of IDDM in islet cell antibody-positive relatives. *Diabetes*. 1994;43(4):1304-10.
35. Bingley PJ, Bonifacio E, Williams AJ, Genovese S, Bottazzo GF, Gale EA. Prediction of IDDM in the general population: strategies based on combinations of autoantibody markers. *Diabetes*. 1997;46(1):701-7.
36. Gardiner SG, Gale EA, Williams AJ, Gillespie KM, Lawrence KE, Bottazzo GF, et al. Progression to diabetes in relatives with islet autoantibodies. Is it inevitable? *Diabetes Care*. 1999;22(12):2049-54.
37. Ueda H, Howson JM, Esposti L, Heward J, Snook H, Chamberlain G, et al. Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. *Nature*. 2003;423(6939):506-11.
38. Earnardt M, Soderstrom A, Holgren-Burstrom A, Haraldsson S, Nilsson-Arner S, Persson-Gonzales C, et al. The CTLA4 region as a general autoimmune factor: an extended pedigree provides evidence for synergy with the HLA locus in the etiology of type 1 diabetes mellitus, Hashimoto’s thyroiditis and Graves’ disease. *Eur J Hum Genet*. 2003;11(1):81-4.
39. Sumnik Z, Drevinek P, Snajdervis M, Kolosuova S, Sedilakova P, Pechova M, et al. HLA-DQ polymorphisms modify the risk of thyroid autoimmunity in children with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab*. 2003;16(6):831-8.
40. Karavanaki K, Kakkas E, Pasch S, Kas N, Konstantopoulos I, Petrou V, et al. Screening for associated autoimmunity in children and adolescents with type 1 diabetes mellitus (TIDM). *Horm Res*. 2009;72(1):201-6.
41. Kordonouri O, Charpentier N, Hartmann R. GADA positivity at onset of type 1 diabetes is a risk factor for the development of autoimmune thyroiditis. *Pediatr Diabetes*. 2011;12(1):83-1.
42. Katahira M, Maeda H, Tosaki T, Segawa S. The human leukocyte antigen class II gene has different contributions to autoimmune type 1 diabetes with or without autoimmune thyroid disease in the Japanese population. *Diabetes Res Clin Pract*. 2009;85(3):293-7.
43. Beaven DW, Nelson DH, Renold AE, Thorn GW. Diabetes mellitus and Addison’s disease: a report on eight patients and a review of 55 cases in the literature. *N Engl J Med*. 1959;261(4):43-54.
44. Okten A, Akcay S, Cakir M, Girisken M, Kosucu P, Deger O. Iodine status, thyroid function, thyroid volume and thyroid autoimmunity in patients with type 1 diabetes mellitus in an iodine-replete area. *Diabetologia*. 2006;49(4):422-3.
45. Kalicza-Kasparycz A, Dziatkowicki H, Bartnik-Mikutra A, Pittucz-Noworolska A, Kasparycz K, Nazim J, et al. [Thyroid peroxidase antibodies and thyroid diseases in children and adolescents with newly diagnosed type 1 diabetes]. *Przegl Lek*. 2002;59(1):509-13.
46. Norden G, Jensen E, Stilbo I, Bottazzo GF, Lernmark A. B-cell function and islet cell and other organ-specific autoantibodies in relatives to insulin-dependent diabetic patients. *Acta Med Scand*. 1988;213(6):671-7.
47. Mantovani RM, Mantovani LM, Dias VM. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus: prevalence and risk factors. *J Pediatr Endocrinol Metab*. 2007;20(6):669-75.
48. Gonzalez GC, Capell I, Rodriguez-Espinosa J, Mauricio D, de Leiva A, Perez A. Thyroid autoimmunity at onset of type 1 diabetes as a predictor of thyroid dysfunction. *Diabetes Care*. 2007;30(6):1616-21.
49. Leong KS, Wallymahmoudi M, Wilding J, MacFarlane I. Clinical presentation of thyroid dysfunction and Addison’s disease in young adults with type 1 diabetes. *Postgrad Med J*. 1999;75(886):467-70.
50. Kordonouri O, Deiss D, Danne T, Dorow A, Bassir C, Gruters-Kieslich A. Predictivitity of thyroid autoantibodies for the development of thyroid disorders in children and adolescents with type 1 diabetes. *Diabet Med*. 2012;29(6):518-21.
51. Kordonouri O, Klinghammer A, Lang EB, Gruters-Kieslich A, Grabert M, Holt RW. Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. *Diabetes Care*. 2002;25(3):646-50.
52. Silverstein J, Klingsensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care*. 2005;28(8):2186-212.
55. Shiva S, Ilkhchooyi F, Shiva S, Rezamand A. Thyroid autoimmunity at the onset of type 1 diabetes mellitus in children. *Open J Immun*. 2013;3(1):37-40.

56. Sharifi F, Ghasemi L, Moussavinasab N. Thyroid function and anti-thyroid antibodies in Iranian patients with type 1 diabetes mellitus: influences of age and sex. *Iran J Allergy Asthma Immunol*. 2008;7(1):36-6.

57. Bahrami A. [Autoimmune Thyroid Disorders in Patients with Type 1 Diabetes Mellitus; Results of Long Term Follow up of a Large Cohort of Patients in Endocrine and Diabetes Clinics of Tabriz University of Medical Sciences]. *Med J Tabriz Univ Med Sci*. 2012;34:22-7.

58. Saflari F, Agari A, Sadeghi T, Hajmanouchehri F. [Comparison of Hashimoto thyroiditis in patients with type 1 diabetes and controls]. *J Qazvin Univ Med Sci*. 2013;15(2):86-93.

59. Vakili R, Mahmoudi M, Ghasemi A. Prevalence of thyroid autoantibodies in diabetic children and adolescents in mashhad. *Iran J Diabetes Metabol*. 2004;3(1):7-11.

60. Ardestani SK, Keshelti AH, Khalili N, Hashemipour M, Barekatain R. Thyroid disorders in children and adolescents with type 1 diabetes mellitus in isfahan, iran. *Iran J Diabetes Metabol*. 2004;3(1):7-11.

61. Boelaert K, Newby PR, Simmonds MJ, Holder RL, Carr-Smith JD, Heward JM, et al. Prevalence and relative risk of other autoimmune thyroid disorders in children and adolescents with type 1 diabetes. *Coll Antropol*. 2009;33(1):273-9.

62. Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burris A. Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus. *Health Technol Assess*. 2004;8(22):iii-xi.

63. International Society for Pediatric and Adolescent Diabetes. Consensus guidelines for the management of type 1 diabetes mellitus in children and adolescents. The Netherlands: ISPAD; 2000.

64. Roquer J. Prevalence of autoimmune thyroid disorders in a Spanish multiple sclerosis cohort. *Eur J Neurol*. 2007;14(9):1048-52.

65. Umpierrez GE, Latif KA, Murphy MB, Lambeth HC, Stentz F, Bush A, et al. Thyroid dysfunction in patients with type 1 diabetes: a longitudinal study. *Diabetes Care*. 2003;26(4):1181-5.

66. 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.