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Prevalence of Celiac Disease in children with Type 1 Diabetes Mellitus: A review of literatures in the Islamic Republic of Iran

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ABSTRACT

Type 1 Diabetes Mellitus is the most common chronic metabolic disorder in children. Celiac disease or gluten-sensitive enteropathy is a genetic and autoimmune disease which results from immune reaction to gluten. Therefore like type 1 diabetes mellitus, celiac disease is triggered by an environmental exposure in genetically susceptible individuals. The aim of this study was to review the articles reporting the prevalence of celiac disease in patients with type 1 diabetes in Iran. The results can be used for comparison with other countries, and also emphasizes the importance of screening for this disease in these patients. In this study, the articles published in PubMed, Google Scholar, Scientific Information Database (SID), Magiran and Iranmedex databases were reviewed. Three published studies (1 cross-sectional and 2 case-control) had been found and described the prevalence of celiac disease in patients aged 2-18 years with type 1 diabetes in Iran. The reported prevalence was between 3.4% and 6.8%. This is similar to reports from other countries however more studies are warranted.

Introduction

Type 1 Diabetes Mellitus (T1DM) is a chronic metabolic disorder in children which remains the most common form of diabetes in children and adolescents. However, there is an increasing rate of type 2 diabetes mellitus.[1-4] that varies around the globe.[5,6] This disorder is caused by insulin deficiency resulting from the autoimmune and non-autoimmune destruction of pancreatic insulin-producing Beta-cells in the islets of Langerhans.[7] It occurs in genetically susceptible subjects when triggered by environmental

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exposures or events.[8] The important point is that the lifetime risk of the development of T1DM in close relatives of type 1 diabetic patients is increasing significantly (Table 1).[9, 10]

Table1. Incidence risk of Diabetes disease in relatives of the patients with type I DM [11,12]

Risk factor	Incidence
No family history	0.4%
Offspring of an affected mother	1-4%
Offspring of an affected father	3-8%
Offspring with both parents affected	Up to 30%
Non-twin siblings of affected patient	3-6%
Dizygotic twin	8%
Monozygotic twin	30-65%

Moreover, multiple genes are reported to have a role in increasing the risk of T1DM such as; HLA-DQalfa, HLA-DQBeta, preproinsulin, PTPN22, CTLA-4, interferon induced helicase, IL2 receptor, a listing like gene and ERBB3e.[13,14] The major susceptibility gene for type 1 diabetes mellitus is in the HLA region of chromosome 6p, which contains the genes that code for major histocompatibility complex (MHC) class II molecules.[15, 16] Substitutions of amino acid composition of their alpha and beta chains at one or two critical positions can markedly change the susceptibility to type 1 diabetes by the increase or decrease of binding of autoantigenes.[17, 18] The prevalence of these genotypes is remarkably high in some populations.[18, 19]

In fact, the children and adolescents with T1DM are at an increased risk of developing other endocrinopathies and autoimmune diseases especially those expressing HLA-DR3.[20] One of the most common associated diseases with type 1 diabetes is celiac disease. Celiac disease or gluten-sensitive enteropathy is a genetic and autoimmune disease which results from immune reactions to gluten.[21, 22] Similar to the T1DM, celiac disease is triggered by an environmental agent in genetically susceptible individuals.[23,24] Some loci of genes are conferring the associated risk for type 1 diabetes mellitus and celiac disease (RGS1, IL18RAP, CCR5, TAGAP, SH2B3, PTPN2).[25] In high risk infants, the timing of initial exposure to gluten-containing or rice-containing cereals may affect the risk of developing islet cell autoantibodies with the introduction of gluten before the age of 3 months increasing the risk of celiac disease. [26], [27]

Celiac is a common disease that occurs in 0.5-1% of the general population in most countries[28] and by sensitive and specific screening tests, its prevalence estimates have increased.[29] The prevalence of celiac disease has substantially increased in some groups as compared to general population such as the patients with type 1 diabetes mellitus.[30- 33] A causal relationship between celiac disease and T1DM is suggested, however not established, with several studies suggesting that the celiac disease may trigger autoimmune processes that lead to diabetes,[34-35] but other observations do not support this hypothesis Larger studies, [36] especially prospective clinical studies, are required to clarify the relationship between autoimmune diseases such as celiac, T1DM etc.[37]

Only a minority of children with type 1 diabetes mellitus and celiac show the symptoms of celiac disease such as abdominal bloating and pain, chronic diarrhea, vomiting, weight loss and constipation. More common initial findings include unpredictable blood glucose measurements, recurrent episodes of hypoglycemia, poor glycemic control and growth failure.[38-40]

Early diagnosis and treatment of celiac disease in patients with T1DM can help to control and manage their insulin intake needs to maintain their HbA1C and also monitor their growth. It also affects the incidence of complications including hypoglycemia, diabetic neuropathy, diarrhea, failure to thrive, osteomalacia and anemia .[44-46] As a result, early diagnosis and treatment of celiac in type 1 diabetic patients is important for achieving the favorable treatment outcomes.[47] On the other hand, whether a gluten free diet can improve diabetes in diabetic patients with obvious or silent celiac disease is not clear and only a few studies are investigating these effects.[48-50]

Table 2. Prevalence of celiac disease in Iranian diabetic patients

Study	Population	Method	Confirmation by intestinal biopsy	Result (prevalence)
Ghergherehchi [41]	135	AEA tTG	Yes	6.8%
Moayeri[42]	87	AEA	Yes	3.4%
Fallahi[43]	96	tTG	Yes	6.25%

The aim of this study was to review the prevalence of celiac disease in Iranian type 1 diabetic patients and compare it with other areas, and also present the importance of screening in this group of patients.

Materials and Methods

In this review, the articles published in PubMed, Google Scholar, Scientific Information Database (SID), Magiran and Iranmedex databases up to June 2013 were reviewed. The following terms were used for searching: celiac disease, diabetes mellitus, prevalence, frequency, Iranian children and adolescents and data was obtained from published English or Persian language studies. National and regional conference abstracts were also checked. All articles that reported prevalence of celiac disease among diabetic children were included. The total number of participants with T1DM and the number of them with celiac disease were extracted from all included papers.

Results

Three papers that estimated the prevalence of celiac disease in Iranian children with T1DM were included, [51-53] two of which were published in English and the other in Persian language (Table 2).

A total of 318 participants, 151 females and 167 males were studied in the three papers aged 2 to 18 years. The celiac disease was confirmed by biopsy in 18 patients. One study was a case-control that compared the prevalence of celiac in T1DM patients with healthy children (altogether 87 patients, 43 girls and 45 boys),[52] and in another cross-sectional study, the prevalence of celiac disease was determined amongst 135 diabetic patients (71 boys, 64 girls).[51] The average age of patients with celiac disease was 7.29±1.23 years.

In Fallahi et al. study, 96 diabetic children (51 girls, 45 boys) were screened for celiac disease.[43] The screening tests carried out in the studies of Ghergherehchi et al., and Moayeri et al. were the same both in the screening of patients for the presence of celiac disease related marker [IgA –endomysial antibody (EMA)], and patients who were EMA positive were further investigated with an intestinal biopsy. But Fallahi et al. used anti-tissue transglutaminase (anti-tTG) to screen the patients.

Based on the gathered information from the studies carried out in Iran, the prevalence of celiac disease in T1DM patients is about 5.66%.

Ghergherehchi et al. divided the patients into 3 age groups; <4, 5-9, >10 years which had no significant difference in terms of celiac disease prevalence. The patients with celiac disease in the Moayeri et al. study had significantly shorter height, weighed less and higher blood glucose and HbA_1C than the T1DM patients without celiac disease.

Discussion

This study aimed to find out the prevalence of celiac disease in type 1 diabetes mellitus in Iranian children. Based on three studies carried out in Iran, the prevalence of celiac disease was about 5.66% in children with T1DM.

It is estimated that about 7.0% of children with T1DM develop celiac disease within the first 6 years of diagnosis.[54] In addition, the incidence of celiac disease is higher in children under the age of 4 and females are affected twice as often as males.[55,-57] The prevalence of celiac disease amongst children with T1DM is significantly higher than non-diabetic children, [54] however, in the studies carried out in Sweden and India, the reported of celiac disease was around 10 to 11.1%.[54] As the prevalence of celiac disease depends on the distribution of HLA genotypes, a difference in prevalence in various countries is expected. Despite the estimates of about 7.0% of children with T1DM developing celiac disease,[57] a research in Egypt showed its occurrence being around 6.4% which is similar to the global estimates and studies from Iran. However, in a study carried out among 116 patients in Algeria, celiac disease was reported at 16.4%.[58]

Type 1 Diabetes Mellitus is associated with other autoimmune conditions with the most frequent like celiac disease.[51] The incidence of T1DM is highly variable amongst different races. The worldwide incidence of T1DM ranges between 0.7/100,000 per year in Karachi (Pakistan) to about 401/100,000 per year in Finland[57] and around 3.7/100,000 per year in Iran.[59]

The prevalence of celiac disease in non-diabetic children aged 2.5 to 15 years in Europe and North America is reported as 0.5% (ranging from 3 to 13/1000 children or 1/300 to 1/80 children).[57] Despite the high prevalence reports in the Saharawi population in North Africa,[57] regions such as the other North African countries, the Middle East, and Southern Asia are the same as the western countries. [61-64] The global distribution of the disease seems to be dependent on the distribution of HLA genotypes that could cause celiac disease.[41]

The classical celiac disease is often diagnosed around the age of 2-3 years, while the mean age of diagnosis of T1DM is 7-8 years with patients who had both diseases being younger than those with only T1DM.[42] In patients with T1DM, diabetes is usually diagnosed first, however, in 10-25% of cases, celiac disease was diagnosed first.[42,43] Generally celiac disease diagnosis in T1DM patients occur through the screening.[43]

Conclusion

According to this study, the prevalence of celiac disease in patients with diabetes mellitus in Iran is similar to the prevalence rates reported in other countries and regions such as the United States, Europe, Canada, and Asia.[6, 21, 23] Due to the lack of national and regional data on the estimation of the prevalence of celiac disease in Iranian children with T1DM, further multi-center studies with larger sample sizes are required. Furthermore, because of the occurrence of celiac disease in patients with T1DM, all of these children should be screened for celiac disease.

Conflict of Interest

The authors have no conflicts of interest to declare.

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