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The Prevalence of Asthma in Children with Type 1 Diabetes Mellitus and Relationship between Control of Diabetes and Severity of Asthma

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Abstract

Background: Type 1 diabetes mellitus (T1DM) is by far the most common metabolic disease in children. Asthma is the most common chronic disease in pediatric population, and its prevalence has increased in the last decades. In this study, the prevalence of asthma among these children with T1DM has been described and its association with the demographic and clinical characteristics of Iranian children has been evaluated.

Materials and Methods: A cross sectional study was carried out on children with T1DM who referred to pediatric endocrinology clinics of Isfahan University of Medical Sciences. The participants were classified as a group with asthma and the second group as diabetic children without asthma. After selection and evaluation of the diabetic patients with asthma, their glycemic status was evaluated three times in the past year. All data were analyzed using the SPSS version 23.0 statistical software package.

Results: A total of 419 patients (49.4% male and 50.6% female) diagnosed with T1DM were included in the study. The mean age of patients at the time of recruitment was 12.65 ± 3.9 years with a range from 3.8 to 18 years. The mean of disease duration was 5.3 ± 2.7 years. Among all participants, asthma was detected in 24 children with T1DM (5.7%). Glycemic control was significantly poorer among asthmatic patients with diabetes compared with diabetic patients without asthma.

Conclusion: The study demonstrated a lower prevalence of asthma among T1DM children rather healthy than ones. Hence, diabetic child patients with asthma experience poorer glycemic control in comparison with T1DM patients without asthma.

Key Words: Asthma, Children, Diabetes Mellitus.

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1- INTRODUCTION

Type 1 diabetes mellitus (T1DM) is by far the most common metabolic disease in children. In 2004, its incidence was 13 to 14 new cases per 100 000 children each year and is progressing every year by more than 3% (1). Asthma is also the most common chronic disease in pediatric population, and its prevalence has increased in the last decades (2). T1DM and asthma are chronic inflammatory diseases mediated by opposite arms of the cellular immune system, called Type 1 T helper (Th1) and Type 2 T helper (Th2) cells, respectively (3). This view of T1DM and asthma as Th1 and Th2 restricted diseases is debatable. Recent evidence suggests that Th1 cytokines are also involved in the pathogenesis of T1DM, and that an increased secretion of a prototype Th1 cytokine, interferon gama gene (INFɣ), is associated with severe asthma exacerbations (4). Epidemiological studies which have examined the co-existence of asthma and T1DM show conflicting results (5).

For diabetic microangiopathy the lung is one of the target organs in patients with diabetes from previous studies. A retrospectively longitudinal cohort study in North California shows that patients with diabetes an increased risk of several pulmonary disease like asthma, pulmonary fibrosis, etc. (6). Furthermore a previous European study showed that the risk of asthma significantly decreased in diabetic children (7). Limited clinical data is available regarding the phenotypic features of patients with both T1DM and asthma and we had not found any study focused on the prevalence of asthma in diabetic children in Iran. So in this study, the prevalence of asthma is described among these children with T1DM, and its association with the demographic and clinical characteristics of Iranian children is evaluated. Also, the association between severity of asthma and glycemic control among children with type 1 diabetes and asthma was surveyed.

2- MATERIALS AND METHODS

2-1. Participants and data source

A cross-sectional study was carried out on children with T1DM who referred to pediatric endocrinology clinics of Isfahan University of Medical Sciences. All participants were visited by the study physician (pediatric resident) within fifteen months from October 2014 to march 2015). All children with T1DM were included in the study. Exclusion criteria included a history of diabetic ketoacidosis (DKA) attack the previous month, history of chronic disorders such as congenital heart disease, and no tendency to participate in the study. At first, informed consent was obtained; check list were given and demographic data, Hemoglobin A1c (HbA1c) levels, diabetes treatment, duration of disease, parenteral education, asthma suffering are obtained in these check lists, and physical examination including cardiovascular and respiratory examination and measurement of height, weight, body mass index, and blood pressure were performed through pediatric resident. Then, blood samples were obtained from metabolically stable participants (no episodes of diabetic ketoacidosis during the previous month)

2-2. Asthma diagnosis

Study participants were classified as (1) having asthma if a diagnosis of asthma was present in their medical record, or if asthma was reported on the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire accomplished at the time of the study; (2) diabetic patients with no asthma (8). A comprehensive checklist including patients' information, age, gender, height, weight, body mass index (BMI), disease duration, and parenteral education was registered by the study physician. All other

participants were classified as not having asthma, including those who reported on the health questionnaire having asthma but no corresponding diagnosis or prescription for asthma medications in the medical record, nor any indication of asthma-specific medications on the health questionnaire. Severity of asthma was assessed based on EPR3 reference (Expert panel report 3; Guideline for the diagnosis and management of asthma) (9), categorized into intermittent and persistent (mild, moderate, and severe) subtypes.

2-3. Diabetes control

After selection and evaluation of the diabetic patients with and without asthma, their glycemic control with measurement of HbA1c had been evaluated three times in the previous year with duration of every four month. HbA1C was checked every three or four months in all diabetic patients and these data are available in clinical records of all of the diabetic patients. Mean level of hemoglobin A1C was used to categorize glycemic control in accordance with the American Diabetes Association recommended age-specific cutoff points for a good control (7.5%–8.5% at younger than 6 years, 8.0% at 6–12 years, 7.5% at 13–18 years, and 7.0% at 19 years and older) (10). Values of hemoglobin A1C 9.5% at any age were classified as "poor" control and "intermediate" control, including values between the definitions of "good" and "poor" control (10). Finally, in the group of children affected by both asthma and T1DM, asthma severity was evaluated through visiting pediatric asthma and allergy specialist and then it was compared with glycemic control.

2-4. Statistical analysis

All data were analyzed using the SPSS version 23.0 statistical software package. Quantitative demographic characteristics are expressed as mean ± standard deviation (SD), and qualitative data are shown in percentages. For non-normally distributed data, the Mann–Whitney U-test was used. For comparisons of the correlations between the two groups, the chi-square and Fisher's exact tests were used. P-value of <0.05 were considered statistically significant.

3- RESULTS

A total of 419 patients (49.4% male and 50.6% female) diagnosed with T1DM were included in the study within fifteen months from October 2014 to March 2015). The mean age of patients at the time of recruitment was 12.65 ± 3.9 years, ranging from 3.8 to 18 years. The mean disease duration was 5.3 ± 2.7 years. The majority of participants (81.1%) were treated with Glargine (long acting analog of insulin), and Aspart (short acting analog of insulin). Detailed demographic data are demonstrated in **Table.1**.

The prevalence of asthma in diabetic patients was 5.7% and asthma was detected in 24 children with T1DM (5.7%). Of 24 asthmatics with T1DM, 16 (3.8%) patients suffered from intermittent asthma and 8 (1.9%) patients suffered from persistent asthma, respectively. All diabetic patients with persistent asthma were mild to moderate ones. Altogether, comparing T1DM patients without asthma, a higher significant proportion of diabetics with asthma was male (18 males vs. 6 females), which is similar to the predominance of asthmatic males among healthy children. There was no correlation between being asthmatic and age at examination, parental education, diabetes duration, and BMI status ($P>0.05$).

Distribution values of glycemic control were good control 33.9%, moderate control 53.5%, and bad control 12.6%, correspondingly, among T1DM participants. Considering 24 asthmatics with T1DM, prevalence of control was good control 25%, moderate control 50%, and bad control 25%, respectively.

Glycemic control was significantly poorer among asthmatic patients with diabetes compared with patients who just suffered from diabetes. **Table-2** demonstrates comparisons between T1DM patients with and without asthma. Although there was no correlation between glycemic control and gender; also a significant correlation was demonstrated between parental education and diabetes control. Also, the results demonstrated that higher parenteral education was associated with better glycemic control.

Table-1: Characteristics of children with T1DM according to asthma status.

Variables	Sub-groups	No Asthma (n=395) Number (%)	Asthma (n=24) Number (%)	P-value
Age, year	< 5	11(2.8)	0(0)	0.34
	5-10	103(26.1)	12(50)	
	11-15	164(41.5)	3(12.5)	
	>15	117(29.6)	9(37.5)	
Gender	Male	189(91.3)	18(8.7)	0.01
	Female	206(97.2)	6(2.8)	
BMI status		19.4+-4.6	18.4+-4.4	0.19
Parental education	Less than or graduated high school	245(62)	14(58.3)	0.93
	B.S graduated	123(31.1)	10(41.7)	
	M.S or Ph.D graduated	27(6.7)	0(0)	
Diabetes duration (year)	< 5	185(46.8)	14(58)	0.19
	5-10	186(47)	5(20.8)	
	>10	24(6)	5(20.8)	
Glycemic control	Good	136(34.4)	6(25)	0.049
	Moderate	212(53.7)	12(50)	
	Bad	47(11.9)	6(50)	
Asthma medication	No medication		7(29.16)	*
	Short acting ß2 agonist		10(41.66)	
	Inhaled corticosteroid		3(12.5)	
	Leukotriene modifiers		2(8.33)	
	Oral corticosteroid		2(8.33)	

*****: Not applicable.

Table-2: Comparison of glycemic status in different groups of diabetic patients.

Variables	Sub-group	Good Number (%)	Moderate Number (%)	Bad Number (%)	P-value
Asthma status	No asthma	136(34.4)	212(53)	47(11.9)	0.02
	Intermittent	5(31.2)	8(50)	3(18.3)	0.03
	Mild and Moderate persistent	1(12.5)	4(50)	3(37.5)	
	Severe persistent	0(0)	0(0)	0(0)	
Gender	Male	65(31.4)	121(58.8)	21(10.1)	0.84
	Female	77(36.3)	103(48.6)	32(15.1)	
Parental education	Less than or graduated high school	57(29)	144(55.6)	40(15.4)	0.002
	B.S graduated	54(40)	68(51.1)	11(8.3)	
	M.S or Ph.D graduated	13(48.1)	12(44.4)	2(7.4)	

4- DISCUSSION

A total of 419 patients (49.4% male and 50.6% female) diagnosed with T1DM were included in the study. Twenty four individuals (5.7%) had asthma. The mean age of patients at the time of recruitment was 12.65 ± 3.9 years, ranging 3.8 to 18 years. In 2011, a similar study was conducted by Black et al. on 226 children, of whom 27 (12%) had asthma; the mean age of patients with both asthma and T1DM was 11.3 years compared to 11.5 years of those with diabetes alone (11).

The current study demonstrated that prevalence of asthma in T1DM patients is lower than the common population. The prevalence of asthma among children with diabetes type 1 was 5.7% and prevalence of asthma in general population is various from 9.5% to 12.3%. For example in one study in 2011, the prevalence of asthma was 10.0% among children with T1DM (12). Modaresi et al. showed that the prevalence of asthma among 1612 children in Isfahan was 12.3% (25). In 2002, Golshan et al. showed that the prevalence of asthma and related symptoms among 4,096 Junior high school children in Isfahan, Iran, was 9.5%, with a male to female ratio of 2:1.

A systematic review and meta-analysis revealed that the prevalence of asthma among Iranian children varied from 0.5 to 11.0% according to 27 articles which used the International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire (16). In 2011, a European study on 4,530 Danish twins presented that the risk of asthma significantly decreased in children with T1DM (17). Some factors might explain why T1DM patients might be protected from asthma development. The paradigm states that type1and 2 T-helper lymphocyte inhabit each other's development from naive Tcell. In reality this would translate in an inverse association between these 2 categories of disease. Previous studies demonstrate that sufferers of autoimmune disease like Type 1 DM. were under lower risk of acquiring atopic disease such as allergic rhinitis or asthma. For example Dutch study performed by Meervaldt and colleagues showed a lower prevalence of atopic dermatitis allergic rhinitis and asthma in Dutch children suffering of TIDM compared with control group (18). Furthermore an animal study on rats demonstrated that an autonomic nervous system dysfunction reduces sensory neuropeptide release in the airways related to an increased inhibitory neuronal M2 muscarinic receptors function(19). That has protective effects on developing asthma in diabetic patients. Likewise, animal diabetes models evidenced that insulin treatment was able to (a) normalize M2 receptor function (and therefore the vagal-mediated hyper-reactivity) (b) reverse the down-regulation of eosinophil accumulation in the airways following allergen challenge (c) re-establish the bronchial contraction associated with mast cell degranulation and histamine release (19). The current investigation revealed that a higher significant proportion of diabetic patients with asthma were male (18 males and 6 females). Similarly, a study conducted by Zhu et al. reported that the prevalence of asthma was more common in males than females in primary school children (13).

Other studies have demonstrated the same results, i.e. more males have asthma before puberty, and the development of asthma impact males to a greater degree than females (14). Golshan et al. showed that the prevalence of asthma and related symptoms among 4,096 Junior high school children in Isfahan, Iran, was 9.5%, with a male to female ratio of 2:1 (15). Lancet revealed a negative correlation between asthma symptoms and T1DM, and showed that nondiabetic siblings' susceptibility to the protective effect may be due to environmental factors encountered in early

life or genetic risk factors (20). The protective mechanisms induced by infection are unidentified but thought to be related to the production of regulatory T-cells. The complex interactions between the immune system components that balance the Th1/Th2-cell responses play a role in the development of either disease. The Th1 and Th2 secretory patterns of patients with T1DM and asthma combine features of both diseases, suggesting a unique Th1/Th2 balance of a lower Th1/Th2 ratio compared with patients with T1DM alone (21). It was demonstrated that there is a significant relationship between glycemic control and asthma in diabetic patients. Most diabetic patients with asthma had poor glycemic control. Black et al. in 2011 showed that children with asthma were also more likely to have poor glycemic control (12).

A possible explanation for this finding is the anti-inflammatory action of some asthma medications such as anti-lukotriene which may also ameliorate systemic inflammation present in diabetic patient; however, some of the patients received no medication (29.1%) at the time of the study; otherwise, some had oral steroids that negatively affected glycemic control (12). Assuming 24 asthmatics with T1DM, 16(3.8%) and 8(1.9%) patients suffered from intermittent and persistent asthma, respectively.

A study on patients with asthma in U.S.A demonstrated that 53% of children suffered from symptoms of intermittent asthma, 25% mild persistent asthma, 13% moderate persistent asthma, and 10% symptoms of severe persistent asthma (22). Most of the subjects with poor glycemic control were male, similar to the common asthmatic population. Black et al. reported that most patients with T1DM and asthma were older, male, black, Hispanic, or Asian/Pacific Islander, obese, and from single parent households, compared to those without asthma (12). Hayat et al. revealed an increase in the frequency and severity of bronchial asthma in boys, particularly, those at school age. Correlating demographic factors and clinical status can help the prediction of the severity of asthma and possibly of its outcome (23). Asthma is fairly common in pediatric age group, and the burden of disease due to asthma continues to increase despite excellent treatments available. It was demonstrated that the worst diabetes control in children is related to lower education in parents.

One of the four major components of asthma management is patient education and is critical to the success of asthma management. Reasons for continued suffering are due to the fact that our management strategies are not easily understood by the patient/parents without a simple and careful approach towards this step. Educating patients or their parents how to recognize asthma contributes to a long-term strategy to keep control over asthma with or without medications (24).

4-1. Limitations of the study

The limitation of our study is its small sample size in comparison with other studies. The study design is cross-sectional; hence, there is no similar study to be compared with.

5- CONCLUSION

The present study demonstrated a lower prevalence of asthma among T1DM children (5.7%) rather than healthy individual (12.3). Also, it is concluded that diabetic children with asthma experience poorer glycemic control rather than T1DM patients without asthma. Further investigations on the interactions of these two disorders regarding each management are required to understand more detailed information.

6- CONFLICT OF INTEREST: None.

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