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Review article

Type 1 diabetes mellitus and atopic diseases in children.

Nancy S. Elbarbary
Assistant Professor of Pediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Background

Diabetes mellitus type 1 (T1DM) is a complex disease resulting from the interplay of genetic, epigenetic, and environmental factors.[1] Worldwide, T1DM epidemic represents an increasing global public health burden, and the incidence of T1DM among children has been rising[2] with an overall incidence of ∼3% to 5% per year, and it is estimated that there are ∼65. 000 new cases per year in children under 15 years old.[3] This significant worldwide increase in the incidence of T1DM suggests the importance of interactions between genetic predisposition and environmental factors in the multifactorial etiology of T1DM.[4]

Pathophysiology of type 1 diabetes mellitus: role of pro-inflammatory cytokines

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by the destruction of insulin-producing β-cells in the pancreatic islets of Langerhans (Fig.1), which is mediated by autoreactive T cells, macrophages and pro-inflammatory cytokines (Fig.2). This leads to an inability to produce sufficient insulin resulting in elevated blood glucose levels and pathological effects[5].

T1DM is believed to be initiated by physiological β-cell death or islet injury triggering the homing of macrophages and dendritic cells that in turn launch an inflammatory reaction.

The infiltrating macrophages secrete pro-inflammatory cytokines, namely interleukin-1β (IL-1β) and tumour necrosis factor α (TNF α) as well as various chemokines that attract immune cells such as dendritic cells, macrophages and T lymphocyte. T cells recognizing β-cell-specific antigens become activated, infiltrate the inflamed islets and attack the β-cells[6,7].

In a normally functioning immune system, T cells with a high affinity for self-antigens are eliminated during their differentiation resulting in immune ‘tolerance’. Autoreactive cells that have escaped these mechanisms are subject to ‘peripheral immune regulation’ that blocks their activation and clonal expansion, preventing development of an autoimmune disease[8]. For reasons we do not fully understand, these immune regulatory mechanisms either fail to launch, or are ineffective in stopping the immune attack against the β-cells in T1DM, and a positive feedback cycle is established[8]. This forward-feeding process of T cell- and cytokine-mediated β-cell killing can be ongoing for years progressively destroying the β-cells. When over 80 % of the β-cells are deleted by this continuous T lymphocyte and inflammatory cytokine-driven attack the insulin secretory capacity falls below a certain threshold and the disease manifests itself.

Activated T cells induce death of a target cell by (1) secreting perforin and granzymes, (2) releasing pro-inflammatory cytokines including interferon-γ (IFN γ) and TNFα or (3) activation of Fas receptors on the surface of target cells. All these factors have also been described to contribute to β-cell killing in T1DM[9]. In particular, recent evidence suggests that the cause stress in β-cells which eventually activates the cell’s death machinery. The signal transduction pathways activated by these pro-inflammatory cytokines leading to chemokine secretion, β-cell stress and death are detailed below. It is very important to note that any of the above pro-inflammatory cytokines alone has limited effects in terms of cell stress or death, on β-cells. However, combinations of IL-1β/ or TNF α/IFN γ have very strong, synergistic effects that trigger serious levels of stress culminating in cell death.

Atopy is the development of adverse hypersensitivity immune reactions against environmental antigens, usually associated with immunoglobulin E, and includes atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis and food allergy[10]. The prevalence of allergic diseases has increased in the world as a whole, particularly in developing countries[11].

The relationship between the expression of allergic and autoimmune diseases

There has been considerable interest in defining the relationship between the expression of allergic and autoimmune diseases in populations of patients (Fig.3). Are patients with autoimmune disease ‘protected’ from developing allergic [immunoglobulin E (IgE)-mediated] diseases? Does the establishment of an atopic phenotype reduce the risk of the subsequent development of autoimmune diseases? Although there are clinical studies addressing this question, methodological problems, particularly in identification of atopic subjects, limits their usefulness. Moreover, an immune-based explanation of the observed epidemiological findings has relied on a paradigm that is currently undergoing increased scrutiny and modification to include genetic predisposition and its interaction with environmental factors, such as early endotoxin or mycobacterial exposure[12,13].

Until recently, the adaptive cellular immune response has been characterized broadly as being polarized in one of two directions: type 1 or type 2[14]. Type 1 responses, directed by T helper type 1 (Th1) CD4+ T cells and identified by the signature cytokine interferon (IFN)-g, are considered to protect against infections by intracellular pathogens[15], and have been incriminated in the pathogenesis of autoimmune diseases such as rheumatoid arthritis (RA), multiple sclerosis (MS) and type 1 diabetes mellitus[16,17]. By contrast, type 2 responses, directed by Th2 CD4+ T cells and identified by the signature cytokines interleukin (IL-4), IL-5 and IL-13, are considered to protect against helminthic infections[18] and to play major pathogenic roles in allergic diseases and asthma[19]. Reciprocal counter-regulation of Th1 and Th2 cells[20] predicted that Th1-type autoimmune diseases and Th2-mediated allergic diseases would occur in mutually exclusive populations of patients. However, recent observations have challenged the validity of the long-standing Th1/Th2 paradigm[21], and a far more complex story explaining the immunological basis of cellular immune-mediated host defense and the pathogenesis of autoimmune and allergic diseases is emerging. The new paradigm identifies additional lymphocyte subsets, such as Th17 T cells, regulatory T cells (Treg) and novel soluble factors. These help to explain experimental observations not predicted by the Th1/Th2 paradigm, and provide a new prism through which to examine the intersection of autoimmune and allergic disease[21]. In this review, we first take a critical look at the epidemiological literature bearing on the relationship between allergic diseases and type diabetes, and then examine the findings in the context of current principles that underlie immune mediated tissue damage.

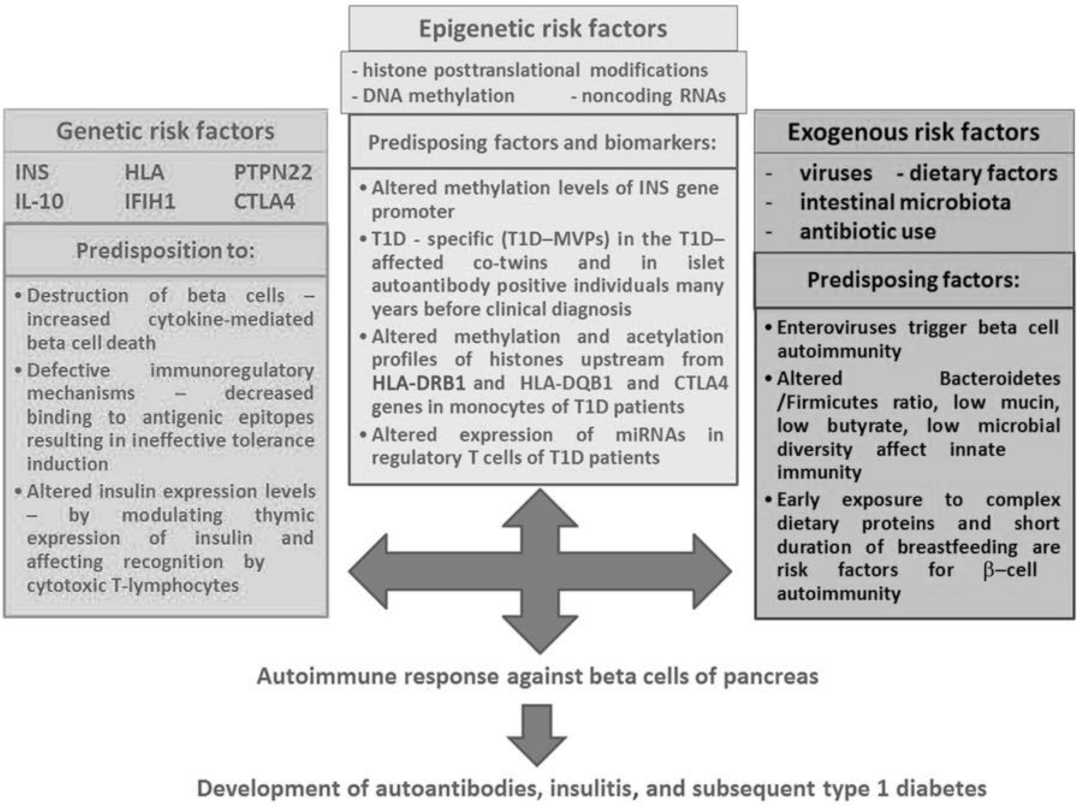

Figure 1. Genetic, exogenous, and epigenetic predisposing factors and biomarkers in T1DM.
Adapted from: Stankov K, Benc D, Draskovic D. Genetic and epigenetic factors in etiology of diabetes mellitus type 1. Pediatrics. 2013 Dec;132(6):1112-22.

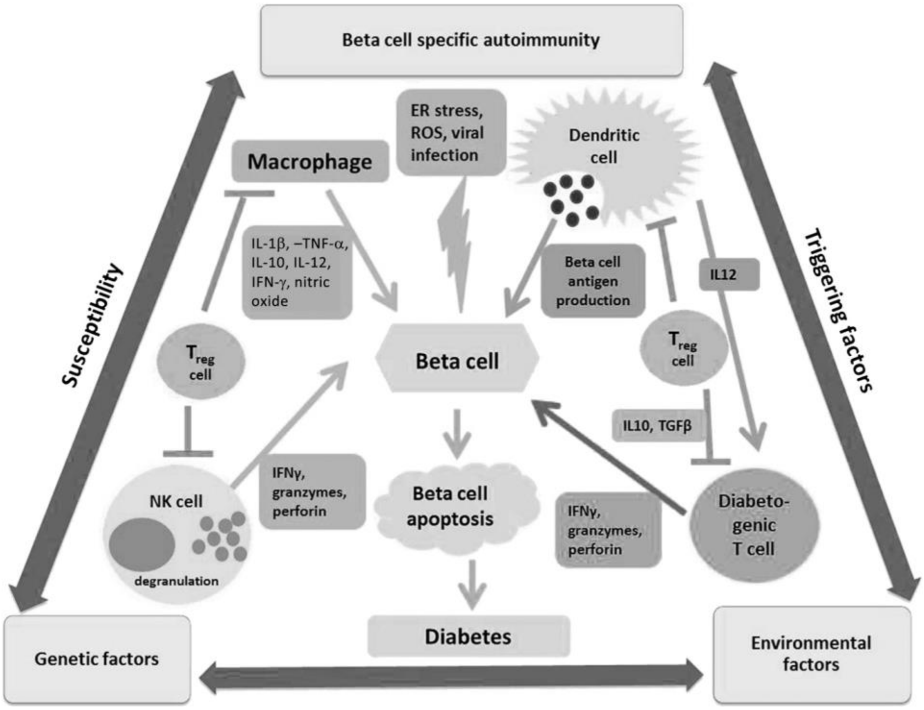

Figure 2. Pathogenic mechanisms and environmental factors that trigger T1DM onset in genetically susceptible people, resulting in b-cell apoptosis and diabetes. ROS, reactive oxygen species.

Adapted from: Stankov K, Benc D, Draskovic D. Genetic and epigenetic factors in etiology of diabetes mellitus type 1. Pediatrics. 2013 Dec;132(6):1112-22.

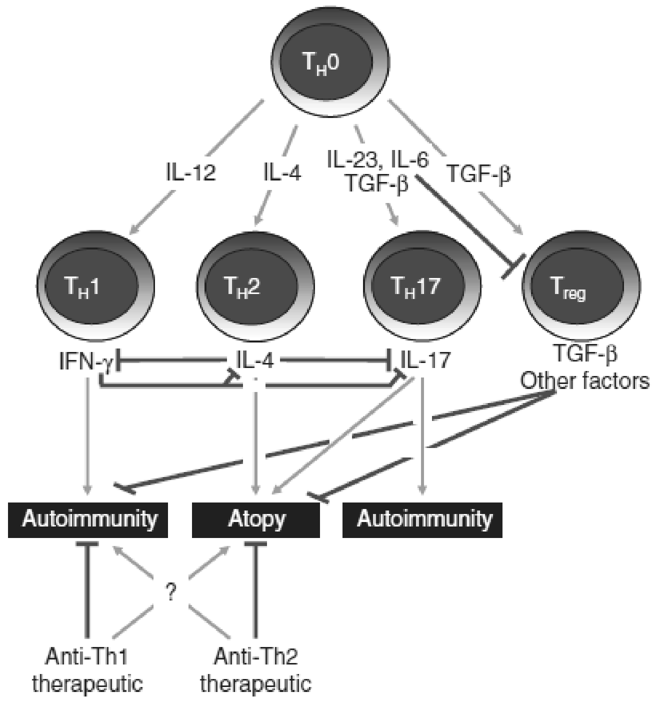

Figure 3. Differentiation of and nexus between CD4+ T cell subsets. The figure depicts the diversity of CD4+ T cell subsets and their multiple modes of interaction. Green arrows signify positive influences and red lines inhibitory influences. All lines represent the activity of individual cytokines except in the case of T helper type 17 (Th17) cell inhibition by interferon-g and interleukin-4 where both cytokines must act in concert. The crossed green arrows with the question mark below indicate the potential for a Th1-specific immunomodulatory agent to reveal or exacerbate a Th2 disease or vice versa.

IL, interleukin; TGF, transforming growth factor; IFN, interferon.

Adapted from: Rabin RL, Levinson AI. The nexus between atopic disease and autoimmunity: a review of the epidemiological and mechanistic literature. Clin Exp Immunol 2008; 153:19–30

Animal model hypothesis of association between childhood type 1 diabetes and atopic disease

In animal models, Th1 cytokines such as IFN-γ and IL-12 are associated with islet cell destruction[22,23], and Th2 cytokine-secreting T cells are protective[24]. Among many known autoantigens, only pro-insulin and insulin are islet cell specific[25]. Specific T cells stimulated with pro-insulin peptides secrete IFN-γ, while cells from many controls secrete the regulatory cytokine IL-10[26]. Type 1 diabetes mellitus is linked strongly with HLA class II haplotypes, some of which predispose to disease and others that protect[27]. While the HLA linkages are by far the strongest immunological risk factor, type 1 diabetes mellitus is also associated with polymorphisms in non-coding regions of two cytokine genes, IFN-γ[28] and IL-12 p40[29], and an amino acid substitution in cytotoxic T lymphocyte associated molecule 4, a co-stimulatory protein essential for attenuating cell-mediated immunity[30-32].

The earliest observations of an inverse association between diabetes mellitus and allergic diseases prompted many reports throughout the mid-20th century, those addressing subjects with type 1 diabetes mellitus are considered in this review.

The Hygiene Hypothesis

The hygiene hypothesis argues that early environmental stimulation by infections is necessary to achieve a mature and balanced repertoire of immune responses[33]. Epidemiological studies provide evidence that frequent exposure to infections early in life is protective for both diabetes[34] and asthma[35,36].

The protective mechanisms induced by infection are unknown but thought to be related to the production of regulatory T cells. Complex interactions between various components of the immune system control the production of Th1 cells, which are traditionally associated with autoimmune disease, and Th2 cells, which are traditionally associated with allergic disease[37]. Such interactions could explain an inverse relationship between autoimmune and allergic disease such that the hygiene hypothesis is consistent with an inverse association between atopic diseases and type 1 diabetes at the individual level, despite their simultaneously increasing incidence in the population. Such inverse associations have been reported for other autoimmune disorders[38]. However, the conclusion that the hygiene hypothesis provides the explanation for these inverse associations could be premature because there may be other shared environmental or genetic risk factors that predispose to one disease and protect against another .

Literature review

A meta-analysis concluded a ‘small but significant’ decrease in asthma prevalence in children with type 1 DM[39]. Studies of interest are discussed below. Douek and colleagues used the ISAAC questionnaire to compare 157 probands with type 1 diabetes mellitus to 173 unaffected siblings, and found that fewer type 1 diabetes mellitus subjects than controls had wheezed at all within 12 months of the study, or had multiple or speech-limiting episodes of wheezing[40]. Moreover, the frequency and severity of symptoms were also significantly lower among the children with T1D.

In addition, the EURODIAB ACE Substudy 2 study group 34 was comprised of eight centers in eastern and western Europe and reported data collected by interviews from five of the centers and by questionnaire from the other three. Probands with type 1 diabetes mellitus were compared with population-based controls. Atopic Dermatitis (AD), and asthma in particular, were decreased in children with type 1 diabetes mellitus. The risk reductions associated with the atopic diseases were marked in children in the 10-14-year age group.

Two sites in the United Kingdom, where the incidence of atopy was the highest, accounted for 40% of the diabetics and may have contributed disproportionately to the study as a whole. Furthermore, only the western European centers demonstrated the inverse relationship between type 1 diabetes mellitus and atopy, and the incidence of atopy was higher in the type 1 diabetes mellitus than controls in the Bulgarian cohort. Because atopy preceded type 1 diabetes mellitus, the authors’ inference that atopy may protect children from type 1 diabetes mellitus 34 may reflect the greater prevalence of atopy in western populations.

Stromberg and colleagues[41] compared 61 Swedish children with type 1 diabetes mellitus to age- and sex-matched controls, and did not find a significant difference in the prevalence of atopic disease as defined by history, clinical features, skin prick test results, serum immunoglobulin E (IgE), or circulating IgE antibodies to allergens.

Similarly, data from a 1987 Finnish registry[42], a British health and nutrition survey[43] and a Dutch cross-sectional survey[44] found no differences in the cumulative incidence of asthma between type 1 diabetes mellitus patients and controls.

Perhaps the most provocative report is a retrospective case–controlled comparison of 928

Danish children with type 1 diabetes mellitus to a random sample of 10.000 population-based controls that found a lower cumulative incidence of AD in the diabetics[45]. Uniquely, this report showed the inverse correlation only among those diabetics who had AD prior to the onset of type 1 diabetes mellitus.

Diabetics in whom the onset of AD followed type 1 diabetes mellitus were no different from controls. This study highlights a unique feature of type 1 diabetes mellitus relative to autoimmune diseases such as MS and RA: the pancreatic islet beta cells are diminished when type 1 diabetes mellitus presents[46], such that the inflammation, while not completely resolved, has diminished to a level insufficient to affect other responses. The concept of waned type 1 inflammation after clinical presentation of type 1 diabetes mellitus is supported by high serum levels of IL-18, IFN-g and CXCL9 (an IFN-γ inducible chemokine) in newly diagnosed diabetics compared with those with long-standing disease[47] and low-risk controls[48]. Alternatively, defective regulatory mechanisms may make those with active type 1 diabetes mellitus equally prone to subsequent atopic or autoimmune disease.

Consistent with the interpretation that active type 1 inflammation protects against clinical presentation of AD is a recent analysis of almost 500.000 Israeli adults at the time of their enrolment into military service between 1980 and 2003. The diagnosis of asthma was confirmed by spirometry.

Asthma prevalence and incidence were correlated inversely with a number of autoimmune diseases that were also diagnosed at enrolment[49], suggesting that those with newly diagnosed autoimmunity were less prone to have asthma.

Taken together, the studies that generalize the least and support the diagnoses with objective clinical and/or laboratory data suggest a model whereby Th1 inflammation suppresses the development of atopy[45], while Th2 inflammation suppresses the severity and perhaps the onset of some autoimmune diseases[50].

In a study from Taiwan[51], the prevalence of atopic diseases was compared in children with T1D and an age-matched control group. The prevalence of asthmatic symptoms in the T1D group was clearly lower than in the control group. However, the overall prevalence of atopy was not significantly different in these two groups. Symptoms of allergic rhinitis, including “nose symptoms with itchy watery eye in the past 12 months”, and “hay fever or nasal allergy ever” were less prevalent in the T1D group. also in Taiwan study they compared data that aimed to determine whether occurrence of atopic diseases in T1D patients was associated with (passive) smoking, pet exposure, or breast feeding. They found no obvious association between atopy and these factors in T1D patients.

Hermansson et al.[52] reported a lower probability of atopy in children with T1D, and their siblings as well, compared with control subjects. Moreover, Caffarelli et al. did not succeed in demonstrating an inverse relation between Th1- and Th2-mediated diseases in children with IgE sensitization or an atopic genetic predisposition[53].

Notably, the presence of T1D does not completely inhibit atopic diseases. In patients with multiple sclerosis, 4% had symptoms of atopic disease[54].

O'Driscoll et al also concluded that patients with rheumatoid arthritis had a normal prevalence of atopic diseases and there was no evidence that allergic factors contributed to the arthritis of the rheumatoid arthritis patients[55]. Therefore, the presence of a Th1-mediated disease was only one of the factors which influenced the presentation of atopic symptoms .

The variation of atopy symptoms in T1D patients may be explained by the influence of some factors such as (passive) smoking, having pets and ever breast-feeding. These factors are known to influence atopic symptoms[56-57].

A recent survey of almost 500,000 Israeli adults at the time of their enrollment into military service between 1980 and 2003 found that asthma prevalence was inversely correlated with a number of autoimmune diseases that were also diagnosed at enrollment[49]. Moreover, the prevalence of various atopic symptoms (Table 1) showed no significant difference in the prevalence of atopic dermatitis, allergic rhinitis, conjunctivitis, hay fever, food allergy and asthma between the two groups. Although the prevalence of drug allergy, visit to an allergist, skin-prick test or RAST (radioallergosorbent) test was lower among T1DM patients as compared to control patients, this difference was not statistically significant .

Cardwell et al.[39] performed a meta-analysis summarizing the association between T1DM and atopic diseases (asthma, eczema, allergic rhinitis) in children. The analysis suggests that there is a small but significant reduction in the prevalence of asthma in children with T1DM, but the findings for the other atopic diseases are less conclusive. However, most of the studies were epidemiological and relied on patients’ and/or physicians’ reports rather than objective laboratory investigations such as IgE levels and sensitivity to aeroallergens.

In addition to these epidemiological studies there is laboratory evidence that supports the Th1/Th2 paradigm. Rapaport and co-workers[58] reported that stimulated peripheral blood mononuclear cells of T1DM patients had early decreased secretion of Th2 cytokines and a late secretion of Th1 cytokines as compared to normal controls[58].

In contrast to the “traditional” concept of an inverse association between atopy and autoimmunity, some investigators have shown that autoimmune Th1 diseases such as thyroiditis, T1DM, celiac, psoriasis and rheumatoid arthritis in both adults and children could coexist with Th2-mediated diseases[41,43,59], suggesting that the Th1/Th2 paradigm is oversimplified. Furthermore, the increasing prevalence of atopic diseases worldwide is accompanied by a parallel rise in autoimmune Th1-mediated diseases such as T1DM[60]. Duran and colleagues[59] found that atopy frequencies were similar in an adult population of type 1 diabetic patients and controls based on questionnaire, skin-prick test, pulmonary function test and methacholine challenge test. These studies together with our study are based on objective parameters rather than subjective evidence alone.

In a Brazilian study[61] the prevalence of allergic symptoms reported in their patients with T1DM was elevated as follows: rhinitis in 52.1% (alone 20.8%; associated 31.8%), asthma in 22.9% and atopic eczema by 9.4%. Although there is no matched control group in this study, the prevalence of allergic rhinitis observed was higher than that documented among non-diabetic children (28.2%) and adolescents (27.4%) living in the south-central city of São Paulo, evaluated through the same instrument of evaluation, ISAAC WQ[62].

The prevalence of sensitisation (positive SPT) among T1DM patients identified as having allergic disease by ISAAC WQ was 72.6% distributed as follow: rhinitis 68.0%, asthma 59.1% ,and atopic eczema 44.4%. Among those with no allergic manifestation it was 20.6%. Analyzing the etiology between those with respiratory symptoms we observed higher frequency of sensitisation to dust mites (61.1%), followed by cat dander (27.8%) and Blattella germanica (16.7%).

Although food allergens -mainly cow’s milk- have been studied as possible triggers for autoimmune disorder in T1DM, this subject is still controversial[63,64]. In the same study we found that food allergens had less relevance in the sensitization of patients, particularly among those with eczema: one patient was sensitive to soy and egg white and two patients were sensitive to peanuts. The sensitisation to cockroach allergens is a marker of severe asthma, more acute attacks, more hospitalizations and more frequent nocturnal symptoms.

Table 1. Allergic symptoms among insulin dependent diabetes mellitus (IDDM) and control patients.

	IDDM n (%)	Control n (%)	*P*
Onset of atopy			
Infancy	18 (66.7)	17 (54.8)	NS
Childhood	9 (33.3)	12 (38.7)	NS
Adolescence	0 (0)	2 (6.5)	NS
Atopic dermatitis	5 (7.7)	9 (12.2)	NS
Persistent allergic rhinitis	2 (3.1)	4 (5.4)	NS
Allergic conjunctivitis	2 (3.1)	3 (4.1)	NS
Seasonal allergic rhinitis	4 (6.2)	6 (8.1)	NS
Asthma	15 (23.1)	22 (29.7)	NS
Food allergy	5 (7.7)	8 (11.1)	NS
Drug allergy	2 (3.1)	5 (6.8)	NS
Visit to allergist	4 (6.2)	9 (12.3)	NS
Prick or RAST test	3 (4.7)	7 (9.5)	NS
Any type of atopy	26 (40)	30 (40.5)	NS

Adopted from: Tirosh A, Mandel D, Mimouni FB, Zimlichman E, Shochat T, Kochba I. Autoimmune diseases in asthma. Ann Intern Med 2006; 144:877–83.

Laboratory support

Laboratory support for the previous findings came from two elegant studies published recently. Maier et al.[65] investigated whether the Th2-related phenotype (total circulating IgE) and a Th1-mediated disease (T1DM) share genetic loci. They found that allelic variation in the IL-13 gene is associated with IgE levels variance and atopic illness but has no detectable effect in type 1 diabetes[65]. Heaton et al.[66] reported that Th1 cytokine secretion and not Th2 was associated with the size of immediate hypersensitivity skin test to allergens and bronchial hyper-responsiveness in a large cohort of T1DM children, suggesting that Th1 cytokine secretion may either be pro- or anti-inflammatory in the same autoimmune disease[67,68]. It should be mentioned that the small size of our groups prevents us from any definite conclusions, and that a larger sample size might have demonstrated a significant difference in some atopic categories. It is also possible that atopic manifestations in children with chronic disease such as T1DM are more readily diagnosed because of frequent medical visits. However, such a bias is unlikely in our study since our findings include also objective laboratory parameters in both groups.

The “classical” Th1/Th2 paradigm is currently undergoing increased scrutiny and includes, besides cytokines, other shared environmental and genetic risk factors that determine the balance between Th1 and Th2 subsets and underlie the pathogenesis of atopy and autoimmune disorders. The parallel appearance of asthma and autoimmune conditions in the same patients may reveal aberrations of the immune system regulation instead of polarization towards Th1 or Th2 domination as a common pathophysiological mechanism. The new paradigm identifies additional lymphocyte subsets, such as Th17 T cells, which differentiate along a pathway that is totally independent of Th1 and Th2 cells, regulatory T cells (Treg), Th2-like natural killer T cells and novel soluble transcription factors[21,69,70]. Indeed the role of these cells in the pathogenesis of autoimmune as well as atopic diseases has been extensively studied[71].

Conclusion

This review shows a lower prevalence of atopic disease in children with T1D compared with the control group, especially asthma. The results are consistent with the study from Europe reporting that children with diabetes had fewer symptoms of asthma as well as atopic dermatitis compared with the background population. This suggests that the occurrence of Th1-mediated diseases may protect against the development of Th2-mediated atopic disease. Furthermore, investigation of the role of environmental factors is important in advancing understanding of the occurrence of atopic diseases in T1DM patients. It should be noted that environmental factors interacting with the genetic profile of each patient may be related to the natural history of both the T1DM as allergic diseases and, therefore, may be involved in some way in the coexistence of these diseases. Moreover, it seems interesting to study further the association between the two pathologies to enable us to better evaluate the possible interrelationships between T1DM and allergy in order to understand which are the regulatory mechanisms of the immune system which will allow us to prevent the occurrence of both diseases.

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