

## ALLERGIC DISEASES IN TYPE 1 DIABETIC PATIENTS: A BRIEF REVIEW

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### ABSTRACT

Type 1 diabetes mellitus is considered an autoimmune disease mediated by Th1 lymphocytes, while allergic diseases are characterized by Th2-mediated immune response. Their incidence is rising in developed countries and the interaction between autoimmune and atopic diseases has been a subject of interest for decades. There are many controversies about the association or mutual exclusion of these diseases, but classical paradigm based on the assumption that diseases mediated by Th1 and Th2 should be mutually exclusive, has been revised considering both the role of regulatory T cells Threg, and the environmental factors involved. The aim of this review is to investigate the association of allergic diseases (rhinitis, asthma, dermatitis) in patient diagnosed with type 1 diabetes mellitus. The studies that attempted to shed light on this topic had surprisingly varied results. These ranged from statistically significant proof of an inverse association between an autoimmune disease and one or several atopic ones to other implying positive associations. Although up to now studies on this subject present seemingly discordant results, each attempt raises new questions and sheds light on new factors involved in the interaction of these diseases. They present much needed stepping stones for future studies to learn from and adapt.

**Keywords:** allergy, diabetes mellitus type 1, atopic disease, rhinitis

### INTRODUCTION

The interaction between autoimmune and atopic diseases has been a subject of interest for decades. Their incidence is rising in developed countries and both types of conditions will, most often, affect the patients for all of their lives. The mechanisms governing these diseases are immunological in nature but are still insufficiently understood. As a result, an effective etiologic treatment is still a work in progress. These are just some of the reasons that justify the interest in studying these diseases and their interaction. (1-5)

Initial observations seemed to indicate that sufferers of autoimmune diseases, like type 1 diabetes mellitus (T1DM), were under lower risk of acquiring

atopic diseases such as allergic rhinitis or asthma. The paradigm states that types 1 and 2 T-helper lymphocytes (Th) inhibit each other's development from naive Th cells. The emergence of the Th1/Th2 paradigm offered a possible explanation to these observations and further increased the interest in the topic. Since Th1 lymphocytes are involved in the inflammatory processes of autoimmune diseases and Th2 lymphocytes in the ones of atopic diseases it was supposed that the two categories of conditions could inhibit each other to some degree. This opened the possibility of not only getting more insight in the mechanisms of these widely encountered diseases, but also of a better understanding of the inner workings of the immune system as a whole. (4,5)

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The studies that attempted to shed light on this topic had surprisingly varied results. These ranged from statistically significant proof of an inverse association between an autoimmune disease and one or several atopic ones to other implying positive associations. These results are even harder to interpret because of the low statistical power or because of the high risk or bias through procedural difficulties of some of the studies. For example, a patient's history of atopic episodes can be difficult to compile since memory is not always exact and a mild episode might not figure on any hospital records. (2)

The review will follow the results involving type 1 diabetes mellitus since this autoimmune disease was the focus of many of the mentioned articles and is a disease of great importance in healthcare. This review aimed to highlight the results of the significant recent works on this topic and to attempt to come to a conclusion from their combined insight.

### **Relevant physiopathological mechanisms in T1DM, atopic diseases and the Th1/2 paradigm**

Type 1 diabetes mellitus starts in childhood and requires lifelong insulin treatment. The incidence of this disease is rising in developed countries, the highest incidence rates is in Finland (approximately 65 per 100,000 person-years), Northern Europe and Canada, while in Asia the incidence of T1DM is very low (approximately 3,1 per 100,000 person-years in China). (7)

The clinical manifestations of T1DM originate in the lack of insulin, the major hypoglycemic factor in the human body. The absence of insulin is due to the destruction of its producer cells, the  $\beta$  cells of the pancreatic Langerhans islets. In T1DM these cells are the target of an autoimmune reaction orchestrated by Th1 lymphocytes. At their direction the  $\beta$  cells are targeted by cytotoxic T lymphocytes and destroyed. Several molecules located in the  $\beta$  cells have been proven to act as self-antigens in this disease, an example being the enzyme glutamic acid decarboxylase (GAD). (3,4,6)

The exact causes for this autoimmune reaction are unknown but contact with certain viruses or foreign substances is speculated to be the trigger. A powerful genetic predisposition for T1DM has also been proven. (3,4,6)

Atopy is a predisposition for acquiring allergic conditions like atopic dermatitis (eczema), allergic

asthma or allergic rhinitis (hay fever). It has a strong hereditary component but many environmental factors are also involved in ways that are not fully understood at this point. The „hygiene hypothesis“ proposes a possible explanation. Its premise is that the rise of the hygiene level in human society has led to children coming into contact with less and less antigens while they develop. (8) This lack of “immunological experience” could lead to improper immune responses to otherwise harmless exogenous molecules. This theory could explain the increase in the incidence of atopic and autoimmune diseases observed in recent times in developed countries. (9,10)

At a cellular level allergic reactions are coordinated by Th2 lymphocytes. After coming into contact with an antigen via antigen presenting cells, these lymphocytes secrete certain cytokines like IL4 which stimulates B lymphocytes to produce immunoglobulin E (IgE) molecules. The IgEs are specific for the encountered antigen and are bound on surface receptors of mast cells and basophils. Upon encountering the antigen these cells degranulate releasing many inflammatory mediators like histamine that cause the allergic reaction. (3,4,6)

From the above mechanisms it would seem that T1DM depends on the action of Th1 lymphocytes while atopy depends on Th2 cells. Following the Th1/Th2 paradigm this would imply that type 1 diabetes could offer some protection from atopic conditions.

Naive Th cells can further specialize into either Th1 or Th2 lymphocytes. At a molecular level, this implies that the 2 lymphocyte subpopulations inhibit each other's development from naive Th cells. (4,5)

Th1 lymphocytes develop under the influence of IL12. This leads to the activation of the interferon (IFN)- $\gamma$  gene by the transcription factor signal transducer and activator of transcription (STAT)4. The secreted IFN $\gamma$  helps maintain the cell's status by activating the gene for T-bet through another transcription factor, STAT1. T-bet is itself a transcription factor which keeps the IFN $\gamma$  gene active thus creating a positive feedback cycle between the two. However IFN $\gamma$  inhibits the gene for GATA3, a key molecule in the development of Th2 lymphocytes. (4,5)

Th2 cells typically start their development under the influence of IL4. As mentioned above the transcription factor GATA3 has a key role in this pro-

cess. However GATA3 inhibits the genes for IFN $\gamma$ , STAT4 and the receptor for IL12, all key molecules in the development of Th1 cells. (4,5)

However, recent discoveries have shown that the situation is not so clear cut. New lymphocyte classes have been identified and proven to participate in the inflammatory processes of autoimmune and atopic diseases. Examples would be the regulatory T cells (Treg), Th17 and the natural killer (NK) T lymphocytes. The classical Th categories have also been shown to behave differently in some situations hinting to possible subcategories among these. For example intestinal Th2 cells have a role in the immunological acceptance of the local flora by producing IL10 and not TNF, like the Th2 cells present in allergic reactions. (4,5)

In conclusion, the Th1/Th2 paradigm is not without merit and could explain many elements in the interaction between autoimmune and atopic conditions. But the participation of other less understood cellular elements must be taken into account as well when interpreting experimental evidence and could lead to other conclusions than those derived from the above mentioned paradigm alone.

### **Sources that support an inverse association between type 1 diabetes and atopy**

The Th1/Th2 paradigm would imply that atopic and autoimmune disorders inhibit each other and therefore should offer some measure of protection from one another. In practical terms this would translate in an inverse association between these 2 categories of diseases at an individual level.

Many studies have attempted to investigate this possibility and some have indeed shown an inverse association between autoimmune diseases like T1DM, multiple sclerosis or rheumatoid arthritis and atopic disorders such as allergic rhinitis, asthma and atopic dermatitis. However, the overall results were inconstant and variable with many studies failing to reach any statistically significant results, and some actually showing positive associations between atopic and autoimmune disorders.

It is important to note that some studies produced results that pointed to an inverse association but the connection was not strong enough to be deemed statistically significant. For example, a Dutch study performed by Meervaldt and colleagues showed a lower prevalence of atopic dermatitis, allergic rhinitis and asthma in Dutch chil-

dren suffering of T1DM compared with control groups. This would seem to support the Th1/Th2 paradigm but the prevalence difference in the report was not wide enough to be significant from a statistical standpoint. (11)

EURODIAB substudy, which could be considered a landmark study, has caused numerous discussions. The study was conducted in eight centers in Eastern and Western Europe with access to population-based T1DM registries compared with age-matched controls and reporting data collected by questionnaire in 3 centers and by interview in 5 centers. The final results showed a decrease in the prevalence of atopic diseases in T1DM group, especially for asthmatics compared with control group. The centers of Western Europe showed an inverse relationship between T1DM and atopy while in the center of Bulgaria incidence of atopy was higher than in control group. It has to be noted that, in the age group 10-14 years an inverse relationship of association of DM with all 3 atopic entities (rhinitis, asthma, atopic dermatitis) has been found. (12)

Another source of confusion are the variable results concerning different atopic diseases. Following the Th1/Th2 paradigm, one would expect an inverse association between T1DM and all atopic conditions. However, most studies focused on several such disorders and produced different result for each. A meta-analysis conducted by Cardwell and colleagues exemplifies this well. They analyzed 25 studies on the topic of correlating T1DM with various atopic diseases. After a thorough selection process that eliminated those studies that had methodological flaws or lacked statistical power they proceeded to process the results of all the remaining studies. The conclusion was that there was a statistically significant, albeit small, inverse association between T1DM and allergic asthma. The same could not be said about other investigated atopic conditions such as allergic rhinitis or atopic dermatitis. The authors made special notice of the high degree of heterogeneity among the studies they explored. (2)

Another point of interest is the time of onset of the studied atopic condition in relation to the onset of T1DM. A 2001 Danish case-control study run by Olesen and colleagues has shown a significant inverse association between atopic dermatitis and T1DM. These results were obtained only when considering the timeframe *before* the onset of diabetes. If taking into account the cases of dermatitis

that debuted after the diabetes, there was no significant difference with the control group. This study also included cases of asthma and allergic rhinitis but didn't discern any significant associations between these diseases and T1DM showing again the varied results of these studies. (13)

A lack of inverse association between T1DM and atopic diseases after the onset of diabetes would not necessarily contradict the Th1/Th2 paradigm. It has been observed that after the clinical debut of type one diabetes, the Th1 based autoimmune reaction that causes it is diminished since the targeted  $\beta$  cells are already destroyed at this point.

Some researchers have addressed the issue in a reverse order. The studies performed in Norway by Stene (14), in Finland by Matilla (15), in Germany by Rosenbauer (16), in Italy by Tosca (17) have tried to determine whether atopic conditions reduce the risk of acquiring T1DM, taking into account other risk factors. These studies have also concluded that atopy would have a protective effect against the development of T1DM. Stene found that atopic dermatitis indeed significantly reduces the risk of diabetes, but the evidence for asthma and allergic rhinitis showed no significant association. (14)

Others authors have stated that the connection between T1DM and asthma might be independent of Th1/Th2 dynamics and could therefore complicate the interpretation of results. The lack of insulin can reduce airway hypersensitivity via a dysfunction of the local autonomic nervous system. This is further explained by the enhanced function of M2 muscarinic receptors in these conditions. The connection has been proven on animal models. However, human T1DM patients receive insulin treatment and it is unclear if this exogenous source of insulin can correct the above mentioned lowering in air way hypersensitivity. (17,18)

This last hypothesis was investigated in an Italian study in 2013 lead by Tosca and colleagues. Their premise was the established association between rhinitis and asthma. A group of T1DM patients also suffering of allergic rhinitis were compared with a control group of patients suffering of rhinitis but not of diabetes. Their aim was to observe the prevalence of subclinical asthma among these 2 groups. Spirometry tests were effectuated before and after bronchodilatation using  $\beta$  adrenergic drugs. A significant increase of forced expiratory flow  $FEF_{25-75}$  after bronchodilatation was interpreted as subclinical asthma. Such increase was primarily observed in non-diabetic patients and therefore enforcing the above theory. (17)

Since autoimmune and atopic conditions can undoubtedly exist in the same patient, it is clear that the Th1/Th2 paradigm is not an absolute rule. As shown above, studies have brought forth results that support the paradigm to some degree. However these results are not constant and sometimes are contradictory. Other factors such as time of onset and non-immunological mechanisms might also be involved and proper consideration of such factors might be the key to making sense of these results.

### **Sources that support a positive association between type 1 diabetes and atopy**

As mentioned, the many studies investigating the interaction between atopy and autoimmune diseases like T1DM have had contrasting results. In the previous section several examples of studies implying an inverse association between T1DM and various atopic disorders were discussed. Examples were also given of results that showed no statistically significant relation between diabetes and atopy. However, there are also sources that show a positive association in these cases. Large population studies have found no evidence for inverse relationship between atopy existence of and autoimmune diseases (19,20), moreover they have found a direct association between these pathologic entities. (21). Sheikh and colleagues also found no correlation between sensitization, tested through skin prick tests, and T1DM. However, this same study found a significant positive association between type one diabetes and a history of allergic episodes. (20)

From the start, it is important to make a distinction between disease associations at an individual and at a population level. It is a well established fact that the incidence of both atopic and autoimmune diseases has been on the rise for decades. A 2012 study lead by Fsadni and colleagues attempted to study the incidence of diabetes correlated to the prevalence of atopic diseases in Europe. They used the data gathered in 2 large studies, ISAAC for atopy and DiaMond for diabetes, which they sorted by country and analyzed. They proved a significant association between diabetes and atopic dermatitis and wheezing at a population level. This might imply that T1DM and some atopic diseases have common risk factors, be they environmental or genetic. These findings might support the hygiene hypothesis. It states that with the rise of hygiene level in developed countries children come

into contact with fewer antigens and this might lead to atypical immune responses like the ones seen in autoimmune diseases and allergies. It is interesting to note that data on allergic rhinitis was also available but no significant association with diabetes could be determined, authors concluding that environmental factors predispose to hay would be different from those that predispose T1DM, wheezing and atopic dermatitis. (22,1)

Such population level results do not necessarily have relevance at an individual level nor do they negate the Th1/Th2 paradigm. It is possible that both T1DM and certain atopic conditions have common risk factors and thus rising incidence but at the same time inhibit each other in individual patients. For this reason examples of studies which investigate the topic at individual level must be examined.

In order to highlight the atopic condition, clinical studies consisting of measurements of total IgE, specific IgE antibodies or skin prick tests have been performed. Clinical studies have not found any an association between IgE values in patients with DM and the control group. (20,23,24).

Several studies have shown no correlation between T1DM and atopic disorders. An example is the 2009 Italian study lead by Tosca and colleagues. They used skin prick tests for inhalatory antigens and examined the subjects history of rhinitis or asthma. No significant correlation between the sensitization to inhalatory antigens and diabetes was found (18).

Other studies proved that some atopic disorders have a higher prevalence among diabetic patients compared to the general population. The 2011 American study ran by Black and colleagues investigated the effects of asthma in the treatment of diabetic patients. In their study group of T1DM patients approximately 10% had asthma, which is a higher prevalence than the 8,7% found in the general American population at that time. (25) Villanova and colleagues investigated clinical signs of atopy in Brazilian diabetes patients and performed prick tests for a wide range of antigens to determine the sensitization level of these patients. They found that the prevalence of allergic rhinitis was higher in the diabetes study group (52%) than the known prevalence of rhinitis in the general population of similar age in Brazil (27-28%). Such results contradict the Th1/Th2 paradigm as well as the conclusions of other articles such as the ones discussed in the previous section. (26)

Seiskari and colleagues also investigated the interaction between T1DM and atopy. However they also compared this interaction in populations with a high standard of living with its state in populations with a lower standard of living. The study investigated subjects from both Finland and neighboring Russian Karelia. The two regions have very different quality of life but, as the study proved, similar genetic pools of HLA variants that could predispose to T1DM. In this way, the genetic risk factors for diabetes in the two regions were considered to be similar, leaving the environmental ones as the main reason for variation between them. A wide range of tests were performed including determining specific IgEs for several antigens and acquiring the subject's history of atopic conditions. In Russian Karelia serologic determination of HAV was also performed. As a fecal-oral transmitted disease, hepatitis A was considered an approximate measure for the hygiene level and for the risk of infections in general. The Finland study group had a higher prevalence of both T1DM and atopic diseases compared with the Karelia group. However, within the Finland group no correlation between diabetes and atopy could be determined. The results in the Karelia group were different. That group showed a significant positive association between T1DM and atopy especially among subjects that tested negative for HAV. (9)

The results of this last study open up several possibilities. Most of the other studies on this topic have been held in countries with a high standard of living, in other words in populations where the hygiene hypothesis would best apply. It is possible that autoimmune and atopic conditions interact differently in such populations than in regions where hygiene is low and the rate of infections high. The group of researchers led by Bach proposed the extending the „hygiene hypothesis“ for autoimmune diseases, such as T1DM, based on the idea that certain infectious agents may be protective against the development of autoimmune diseases. (27,28)

As seen, there are many studies that contradict the Th1/Th2 paradigm as well as the articles that support it. There might be other factors involved in the interaction of T1DM and atopic conditions that could explain this variety of results. Regional variations and the hygiene hypothesis might be the key to understanding why these diseases seem to interact differently in different studies.

## CONCLUSIONS

It is difficult to draw a clear conclusion on this complex and poorly understood topic. As seen, the evidence gathered so far is contradictory and inconstant. Still, the attempts of the past can determine how this subject should be approached in the future.

It is established that the incidence of both autoimmune and atopic diseases is on the rise in developed countries and has been for decades. This makes both categories a prime subject for study and experimentation. It is important that the attempts to elucidate the mechanisms and interactions of these diseases continue and evolve by learning from the cumulative knowledge gathered from past studies.

Many of the above mentioned articles admitted to encountering difficulties and weaknesses which could have led to biased results and should be considered carefully by future studies. Determining a subject's history of allergic episodes, for example, has been proven problematic in many cases. Memory bias is a clear danger. Hospital records have their limitations as well, since subjects might not visit a doctor for mild episodes. A further possible cause for error is the fact that diabetic children receive more medical attention than healthy ones and their atopic episodes are more likely to be observed. Moreover, parents of diabetic or atopic children have been proven to be more willing to answer mails demanding data for study. All these methodological difficulties must be solved in order to obtain trustworthy results. Some studies have partially did this by employing objective tests such as prick tests or determining serum IgE levels and it is perhaps in this way that future tests will obtain solid results.

The object of the described studies was similar but there were differences that could be the reasons for the great variety of results encountered. Some of these differences were mentioned and discussed above. In order for results to be comparable, the studies providing them should have the same parameters. The time of onset of one disease in relation to the other might be a factor. The interaction between T1DM and atopy could be reciprocal or unidirectional. There are non-immunological mechanisms that can affect the association between diabetes and certain atopic conditions, such as the drop in airway hypersensitivity in the absence of insulin. The difference in the prevalence of infections between regions could influence the way these diseases develop and then interact. These and more should be clearly considered in future studies so as to deliver comparable results.

Moreover, the progress of our understanding of the cellular and molecular mechanisms that govern these diseases could direct future attempts. The study of newly discovered lymphocyte classes like Th17 and their involvement in autoimmunity and allergy could modify the classical Th1/Th2 paradigm. A better understanding of how infections can modulate the function of Treg cells in children can prove or disprove the hygiene hypothesis.

In conclusion, although up to now studies on this subject present seemingly discordant results, each attempt raises new questions and sheds light on new factors involved in the interaction of these diseases. They present much needed stepping stones for future studies to learn from and adapt.

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