Autoimmunity & Type 1 diabetes patients: Review Article

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Abstract

Background: Increased blood glucose levels (hyperglycemia) are a hallmark of type 1 diabetes mellitus (T1DM), a chronic autoimmune illness marked by insulin insufficiency as a result of the destruction of the pancreatic islet cells. T1DM is a widespread metabolic disorder in children. The loss of cells is due to autoimmunity in most individuals (70-90%) with T1DM(concomitant with the formation of T1DM-associated autoantibodies). Autoantibodies are often detected months or even years before the start of symptoms in people with T1DM. These autoantibodies are indicators of the onset of autoimmunity rather than pathogens. Many autoimmune diseases have symptoms of T1DM.–Such factors may profoundly impact clinical care of the illness, particularly in children. The four most common autoimmune disorders are vitiligo, Addison's disease, celiac disease, and autoimmune thyroid disease.

Objectives: To outline the association of T1DM as an autoimmune disease with other comorbid autoimmune illnesses

Conclusion: Several endocrine and non-endocrine autoimmune diseases are strongly linked to type 1 diabetes mellitus.

Keywords: Autoimmune disease; Type 1 diabetes mellitus; Celiac disease; Autoimmune thyroid disease; Addison's disease; Vitiligo.

Introduction

T1DM is an endocrine disorder characterized by the disappearance of insulin-secreting pancreatic beta cells, and T lymphocytes play a critical role in its progression **(Boldison and Wong, 2016)**. Additional autoimmune illnesses, such as thyroid and celiac problems, are more common in patients with T1DM **(Kylokas et al., 2016)**.

Comparatively, children with T1DM have a higher risk of developing other autoimmune disorders than children without diabetes **(Hughes et al., 2016)**. Patients with T1DM with a coexisting autoimmune illness might have a wide range of clinical symptoms, from modest complaints to potentially life-threatening conditions in the case of adrenal insufficiency **(Khoury et al., 2014)**.

Therefore, reliable risk assessments for autoimmune illness, followed by the creation of effective screening and treatment plans, are crucial for people with T1DM, since they help improve glucose management and quality of life. **(Bakker et al., 2013).** Although there are several anecdotal accounts of an increased frequency of concomitant auto-immune disorders in patients with T1DM, a thorough investigation is lacking.

Prevalence of T1DM and associated auto-immune diseases

Over the last 40 years, the number of adults diagnosed with (T1D) has almost doubled globally. Roughly 400 million people throughout the globe have been diagnosed with diabetes mellitus, with T1D accounting for 5-10% of these cases **(Kahaly et al., 2016)**. T1D occurs in 15 out of every 100,000 persons, and its prevalence is 9.5% among those who are at risk. The rate of new cases per 10000 persons is 3.5% in Africa, 12.2% in the US, and 6.9% in both Asia and Europe. **(Mobasseri et al., 2020)**.

While (T1D) may develop on its own as a monoglandular autoimmune condition, it is also very common to co-occur with a broad variety of other autoimmune disorders (AID). Researchers have found both glandular and non-glandular AID in people with T1DM . In addition to autoimmune thyroid disease (AITD), type A gastritis (15% prevalence), celiac disease (3%_ 12% prevalence), vitiligo (1%), rheumatoid arthritis (1.2%), systemic lupus erythematosus (1.15% prevalence), Addison's disease (0.5%), and psoriasis (5% prevalence) are also linked autoimmune disorders. Auto-Ab against particular antigens causes inflammation and, ultimately, tissue damage in all AID **(Frommer and Kahaly, 2020)**.

Antibodies associated with this condition are often detected in these individuals, and they are typically present with latent or latently manifested illness. Autoimmunity of the stomach, vitiligo, and adrenal gland insufficiency has also been linked to type 1 diabetes. Pathogenesis of these disorders was revealed to include similar genetic variables and immunologic mechanisms that are crucial to disease etiology (**Nederstigt et al., 2019**).

Pathogenesis of T1DM and associated auto-immune diseases

Insulin-producing cells are targeted for autoimmune destruction, which is one step in the multistep pathophysiology of T1D. Beta cell autoimmunity in T1DM .may be measured by testing for antibodies against enzymes such as protein tyrosine phosphatase and glutamic acid decarboxylase, islet cell autoantibody (ICA), and insulin autoantibody (IAA). **(Table.1) (Walther et al., 2016).** Ab is a risk factor for T1DM , and its presence in childhood increases that risk. Ab may first show up months or even years before any noticeable symptoms develop. The IAA Ab is the first to show in children, often appearing before the age of five.To get an accurate titer, insulin treatment must have not yet begun. For most children, IAA is already present at the time of diagnosis, making it the initial indicator of T1DM risk **(Anaya, 2014).** For this reason, there is a robust negative relationship between

the age of diabetes beginning and the incidence of IAA. Sixty percent of those with T1D also have IA-2A, and between 69 and 90 percent of people with T1D also have ICA. GAD-Ab positivity in T1D patients continues for years, but ICA and IAA titers diminish following diagnosis.

The prevalence of GAD-Ab at first presentation is between 70% and 80%. Therefore, GAD is the optimal method of assessment for persons with type 2 diabetes **(Frommer and Kahaly, 2020).**

Patients with T1DM who simultaneously have another autoimmune disorder have additional challenges in managing their condition and may experience a wide range of clinical symptoms, from relatively modest complaints to potentially life-threatening conditions in the case of adrenal insufficiency **(Nederstigt et al., 2019)**. Therefore, it is crucial for people with T1DM to have accurate risk assessments for autoimmune diseases, followed by the creation of effective screening and treatment plans **(Khoury et al., 2014)**. Next we will discuss the most common autoimmune disorders Such as vitiligo, Addison's disease, celiac disease, and autoimmune thyroid disease.

Autoimmune Thyroid Disease (AITD)

In certain cases, individuals will be diagnosed with both (AITD) and (T1DM), two of the most common autoimmune diseases **(Li et al., 2020).** Graves' disease (GD), Hashimoto's thyroiditis (HT), and atrophic thyroiditis (ATI) are only a few examples of the many organ-specific autoimmune illnesses that fall under the umbrella of autoimmune thyroid disease (ITD) **(Ruggeri et al., 2018).** It's usually linked to other autoimmune diseases, both glandular and otherwise **(Kahaly et al., 2018).**

Table 1. Relevant autoantibodies in type 1 diabetes (Frommer and Kahaly, 2020).

Autoantibody against	Antigen	Sensitivity (%)	Specificity (%)	Normal Range	Occurrence
Glutamic acid decarboxylase	Glutamic acid decarboxylase (65 kd)	65-75	99	< 10 IE/mL	70% more common after adolescence
Islet cell	Islet cells	70	99	Negative	80% at diagnosis
Protein tyrosine phosphatase	Tyrosine phosphatase-related islet antigen 2	50-90	99	< 10 IE/mL	60% at diagnosis
Insulin	Pro-/insulin	74	99	< 0.4 U/mL	50% at diagnosis. First Ab detected in children. Less common after adolescence
Zinc transporter 8	C terminal domain of the zinc transporter 8	65-75	99	< 15 U/mL	Up to 80% at diagnosis

Common ancestry is a major factor in the tight link between these two illnesses. Many people have a genetic tendency for having the HLA antigens DQ2 (DQA1*0501-DQB1*0201) and DQ8 (DQA1*0301-DQB1*0302), which are in turn closely connected with DR3 and DR4. Furthermore, functional single nucleotide polymorphisms (or rare variants) of various genes involved in immune regulation have been identified to confer susceptibility to both T1D and AITD.

These genes include cytotoxic T-lymphocyte-associated antigen (CTLA4), protein tyrosine phosphatase non-receptor type 22 (PTPN22), interleukin-2 receptor (IL2Ra), vitamin D receptor (VDR), and tumor necrosis factor alpha - (TNF) **(Frommer and Kahaly, 2021).**

Anti-thyroid autoantibodies are found in roughly 20% of children with T1DM at the time of diagnosis; they are more frequent in females. It has also been noted that anti-thyroid antibodies are increasingly common as people become older and that having them at the time of a diagnosis of T1DM is a good predictor of whether or not the patient would go on to develop thyroid illness **(Kota et al., 2012)**. Anti-glutamic acid decarboxylase (GAD), anti-thyroid peroxidase (TPO), and anti-thyroglobulin (TG) were more often found in T1DM patients (56.8%, 36.4%, and 19.7%, respectively) compared to controls (5.6%, 9.7%, and 4.2%) in a study of 132 Saudi children **(Hassan et al., 2017)**. In the meanwhile, a Brazilian cross-sectional investigation found that 21% of children and adolescents with T1DM also had AITD, as indicated by positive TPOAb and TGAb **(Riquetto et al., 2015).**

Antithyroid antibodies are associated with an 18-fold increased risk of thyroid illness in individuals. Glastras et al. advised measuring anti-thyroid antibodies and TSH at T1DM start and annually beyond the age of 12 years for early diagnosis of AITD in children with T1D **(Glastras et al., 2005)**. Screening for thyroid function by analyzing circulating TSH is also recommended by the International Society for Pediatric and Adolescent Diabetes (ISPAD) Consensus Clinical Guidelines, first at the time of diabetes diagnosis and then every 2 years in asymptomatic individuals without goiter and more frequently if the goiter is present **(Kawasaki et al., 2014).**

Celiac disease (CD)

Since T1D patients are now routinely screened for CD, the link between the two diseases has been more well acknowledged. When both illnesses are present in the same patient, T1D often develops before CD (this happens in around 5% of people with T1D). Traditional theories suggest that the presence of shared high-risk human lymphocyte antigen (HLA) genotypes accounts for the correlation between these diseases (DR-DQ) **(Kaur et al., 2018)**.

France has a 1.6% prevalence rate for both CD and T1D, Finland 2.4%, Sweden 9.7%, and North India 11.1%. As a result, professional clinical practice recommendations advise repeat screening for all pediatric and adolescent T1D patients 2 and 5 years following diagnosis if the first test is negative **(Goodwin et al., 2019)**.

Checking levels of anti-tissue transglutaminase antibodies (anti-tTG) and serum IgA is used as a screening test for CD. The anti-tTG test combines high sensitivity and specificity, yielding a positive predictive value of 72%. Due to the possibility of a false positive anti-tTG serology, specialists recommend that anti-endomyseal antibodies be sent to validate an abnormally elevated anti-tTG in the T1D population. Further, when aberrant anti-tTG titers are modest, to begin with, a raised anti-tTG antibody level might return to normal on its own **(Snyder et al., 2018).** Even if a person with T1D has been screened regularly for CD in the past, they should still be checked if they display signs of CD, such as unexplained weight loss (or inadequate weight gain), stomach pain, bloating, or loose stools. In addition to gastrointestinal issues, the clinician should be aware of non-gastrointestinal symptoms of CD, such as delayed puberty, poor growth, osteopenia, anemia, dental enamel abnormalities, and depression. CD might sometimes reveal itself in the form of hypoglycemia that has no obvious cause.

Although CD in adults with T1D is widely established, most cases of CD in juvenile T1D patients occur during the first 5 years following diagnosis **(Hagopian et al., 2017).**

More than one in twenty people with T1DM also have coeliac disease, according to a meta-analysis; long-term coeliac disease may affect the risk of retinopathy and chronic renal disease in—T1DM, possibly because of an increased prevalence of microvascular complications in these people (**Elfstrom et al., 2014**).

Gastric autoimmunity

Corpus and fundal atrophy, as well as autoantibodies against parietal cells (PCA) and their secretory product, intrinsic factor, are hallmarks of autoimmune gastritis (AIF). Up to 20% of those with autoimmune gastritis have iron deficiency anemia, while between 15% and 25% have pernicious anemia (**De Block et al., 2008**).

The incidence of parietal cell antibodies was around two times greater than in the general population in a recent meta-analysis, while anemia due to vitamin B12 insufficiency was twenty times higher. Nonetheless, it further supports the need to routinely check for anemia and vitamin B12 insufficiency (**Nederstigt et al., 2019**).

Vitiligo

Due to a loss of cutaneous melanocytes, vitiligo is an acquired depigmentation condition. Genetic and epidemiological research has linked vitiligo not just to self-consciousness over skin color but also some other systemic disorders. (**Spritz and Andersen, 2017**). A meta-analysis encompassing 9 research and 15,657 vitiligo patients, found a strong correlation between the skin condition and T1DM (**Chang et al., 2019**). Vitiligo and T1DM may have the same etiology of autoreactive cytotoxic T-cell mediated damage (**van den Boorn et al., 2009**).

Autoimmune hepatitis

The autoimmune liver disease hepatitis (AIH) has been documented inT1DM . The prevalence of T1D-related autoantibodies in children with AIH was studied; results showed that islet cell antibodies and insulin autoantibodies were present in 60.7% and 18.5% of kids with AIH, respectively (**Al-Hussaini et al., 2014**).

Adrenal gland insufficiency

People with T1DM likely have a rising trend in both the incidence and prevalence of Addison's disease (AD). One in 12 people with Alzheimer's disease also has T1DM (**Bensing et al., 2016**). The loss of adrenal function and reduced cortisol production that characterizes Addison's disease (autoimmune adrenal gland insufficiency) is a devastating condition. Adrenal insufficiency manifests most severely and perhaps fatally as a shock during a crisis, but it also makes it harder to control diabetes by increasing the likelihood of hypoglycemia and tampering with potassium balance (**Nederstigt et al., 2019**).

Autoimmune polyglandular syndromes(PAS)

A variety of autoimmune illnesses, affecting both endocrine and non-endocrine organs, may develop in patients with (PAS), making PAS a complicated, heterogeneous condition. Having autoimmunity harm at least two organs is required to diagnose PAS (**Frommer and Kahaly, 2019**).

Organ involvement allows further categorization of PAS into four types. Addison's disease (AD), mucocutaneous candidiasis, and hypoparathyroidism are all hallmarks of PAS I or early-onset PAS, which is caused by a mutation in the autoimmune regulator (AIRE) gene (**Bain et al., 2014**). When Alzheimer's disease (AD) is present, together with autoimmune thyroid disorders (AITDs) and/orT1DM , a person is said to have polygenic adaptive syndrome II (PA T1DM). AITD in PAS III may arise in conjunction with any autoimmune condition other than AD. PAS IV patients are those who don't fit into the other three categories (**Cutolo, 2014**).

Typical features of PAS include lymphocytic infiltration of endocrine and non-endocrine organs, the production of autoantibodies against the affected organs, and abnormalities in cellular and humoral immune responses (**Kahaly and Frommer, 2018**).

The HLA, CTLA-4, and PTPN-22 genes are particularly vulnerable in PAS types 2 and 3. Although certain autoimmune illnesses must be present to make the diagnosis, both PAS II and PAS III have been linked to a broad range of other autoimmune conditions. **(Frommer and Kahaly, 2019).**

Conclusion

Several endocrines and non-endocrine autoimmune illnesses are strongly linked to (T1D).

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