Association Between Autoimmune Diseases And Development Of Autoimmune Type 1 Diabetes (T1D): A Targeted Literature Review (TLR)

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POSTER HIGHLIGHT: Vitiligo and SLE increase the risk of developing T1D, while T1D patients show strong associations with CD, MS, and other autoimmune diseases, supporting early detection and intervention to delay progression.

INTRODUCTION

- Autoimmune Type I Diabetes (T1D) results from autoimmune β-cell destruction.
- It frequently coexists with other autoimmune diseases (AD), suggesting a shared genetic and immunopathogenic mechanism.[1]
- T1D patients are at an increased risk of developing AD, such as autoimmune thyroiditis, celiac disease, autoimmune gastritis, and autoimmune rheumatic diseases due to shared underlying immune system dysregulation.[2]
- Understanding these associations can aid in early identification, monitoring, and prevention strategies for high-risk individuals, particularly in genetically predisposed populations.

OBJECTIVE

To identify and characterize the association between ADs and the onset of T1D, as well as the development of ADs in individuals with pre-existing T1D.

METHODS

- A targeted literature review was conducted by searching Embase and MEDLINE® from database inception to April 11, 2024, following Cochrane Handbook guidelines. Eligible studies were observational studies reporting associations between ADs and T1D in adults (≥18 years).
- Conference abstracts (2022–2024) from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) were also reviewed.
- Two independent investigators screened abstracts, performed full-text review, and data extraction. Findings were summarized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[3]
- Study quality was assessed using the Joanna Briggs Institute (JBI) checklist.[4]

RESULTS

- A total of 7,882 abstracts were identified: 4,745 from Embase and 3,137 from MEDLINE®. After screening, 19 studies were included (Figure 1). Fifteen enrolled T1D patients, and four enrolled patients with other ADs (CD [n=2], vitiligo [n=1], and SLE [n=1]).
- Most studies were conducted in Europe (n=10), followed by the US (n=5), Middle Eastern countries (n=3), and China (n=1).

RESULTS

- Most reported studies were retrospective (n=9), followed by cross-sectional (n=6), Mendelian randomization analyses (n=2), prospective (n=1), and case-control designs (n=1).
- Sample sizes ranged from 107 to 158,865 patients (median: 1,212).

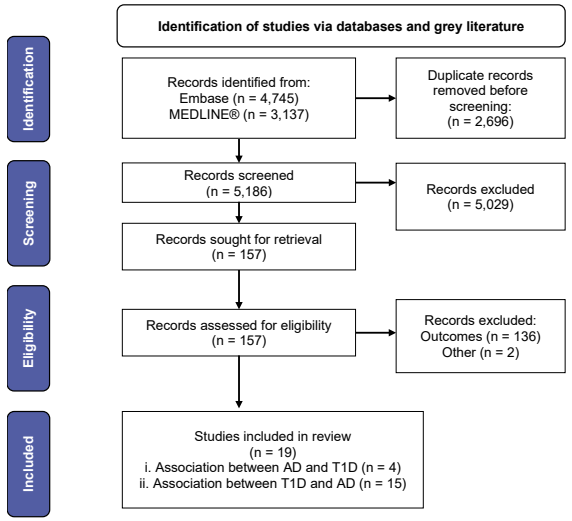
Among T1D studies:

- Mean age ranged from 12.5 to 51.4 years (median: 28.5, n=8).
- The proportion of males ranged from 37.0% to 54.8% (median: 51.3%, n=12).
- Diabetes duration varied from 2.9 to 35.5 years (median: 5.7, n=9).

For AD studies:

- One study reported on vitiligo: mean age of 52.3 years and 48.3% males.
- Another study reported on CD: median age of 8 years and 38.3% males.
- The third study enrolled 34.4% males with CD.

Figure 1: PRISMA Diagram



Association between ADs and the development of T1D

- Table 1 summarizes the findings across studies reporting association between ADs and the development of T1D.
- Rios-Duarte (2023) reported significant associations between vitiligo and T1D (OR 9.19, 95% CI 8.02 – 10.54, p<0.0001).
- Liu (2024) reported significant association between SLE and T1D (OR 1.108, 95% CI 1.074 – 1.144, p<0.001).
- No significant association was reported between CD and T1D.

Table 1: Summary of associations between AD and the development of T1D

Author & Year	Starting disease (N)	Associations with T1D	
		Characteristics	Estimate value
Canova 2016[5]	CD (1,215)	Overall population	HR = 2.5 (95%CI: 0.94 – 6.66)
		Males	HR = 2.14 (95%CI: 0.55 – 8.29)
		Females	HR = 3 (95%CI: 0.72 – 12.55)
		Diagnosed before 18 years	HR = 2.27 (95% CI 1.00 – 7.37)
		CD diagnosis ≤5 years	HR = 1.67 (95% CI: 0.45 – 6.16)
		CD diagnosis ≥6 years	HR = 5 (95% CI: 1.01 – 24.78)
Khalaf 2020[6]	CD (107)	Overall population	(p = 0.265)#
		Age, 1-6 years vs 7-12 years	(p = 0.48)#
Liu 2024[7]	SLE (NR)	Overall population	OR = 1.108 (95% CI: 1.074 – 1.144, p <0.001)*
Rios-Duarte 2023[8]	Vitiligo (39,173)	Overall population	Adjusted OR = 9.38 (95% CI: 8.17 – 10.77, p = 0.027)
		Overall population	Crude OR = 9.19 (95% CI: 8.02 – 10.54, p <0.0001)*

*CD: Celiac disease; CI: Confidence interval; HR: Hazard ratio; OR: Odds ratio; SLE: Systemic lupus erythematosus; T1D: Type 1 diabetes.
Notes: *Significant associations as stated by authors; #only p values were reported by authors.

Association between T1D and associated ADs

- Fifteen studies examined T1D and autoimmune disease (AD): 12 reported direct associations, one focused on autoantibodies, and two addressed both AD and autoantibody associations.Hu (2023) reported a positive association between T1D and vitiligo.[9]
- Glowinska-Olszewska (2020) identified female sex, presence of anti-GAD IgG antibodies, and younger age at T1D onset as independent predictors for AITD in children.[10]
- Similarly, Barker (2005) found that elevated anti-thyroperoxidase, positive tissue transglutaminase antibodies, and 21-hydroxylase autoantibodies were significantly associated with AITD in pediatric and adult T1D patients.[11]
- Risk factors for CD in T1D patients included T1D diagnosis at ≤8 years and a positive family history of CD.[12]
- However, Kakleas (2021) found no significant association between T1D and CD in children/adolescents.[13]
- In contrast, Makimattila (2020) reported a significantly increased CD risk in T1D patients compared to non-diabetic controls (OR: 4.64).[14]
- Wagner (2011) linked CD development to female sex, first-degree family history of ADs, early T1D onset, longer disease duration, and absence of anti-tyrosine phosphatase antibodies.[15]
- Across studies, female sex and older age were consistently associated with a higher likelihood of coexisting ADs in T1D patients.[15-18]
- Gougourelas (2021) reported that LADA patients had a higher predisposition to ADs than those with T1D (OR: 2.64).[19]
- Milluzzo (2021) found that familial T1D cases had a higher risk of developing additional ADs than sporadic cases (OR: 1.9).[20]

DISCUSSION

- An association between T1D and the development of AD was reported in 15 studies. However, none of the studies investigated the association of T1D with the development of SLE separately. Thus, inference on the directionality of disease development cannot be made.
- Risk of bias was assessed for all included studies. No cross-sectional or observational studies were rated poor quality, though some studies reported unclear or lower scores due to methodological limitations.
- To our knowledge, this is the first review to examine the association between AD and development of T1D, as well as the link between T1D and onset of AD.
- A key limitation is that the analysis was qualitative. Future meta-analyses are warranted to provide quantitative estimates of these associations.

CONCLUSION

- Vitiligo and SLE significantly increased the likelihood of developing T1D. When investigating the association between development of AD in T1D patients, a significant link was found for CD, MS, and other ADs.
- Understanding the risk of developing T1D in patients with other autoimmune disorder could inform early diagnosis and intervention, potentially delaying disease progression.

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DISCLOSURES

Laura Wilson and Mariam Hanna are employees of Sanofi. Nishu Gaind, Divya Pushkarna and Boris Breznen are employees of Evidinno Outcomes Research Inc. which was contracted by Sanofi to conduct this research.