Predictive Value of Autoantibody Markers in Children with Type 1 Diabetes Mellitus A Systematic Review and Meta -analysis

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Predictive Value of Autoantibody Markers in Children with Type 1 Diabetes Mellitus: A Systematic Review and Meta -analysis

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Abstract

Background: The association between autoantibodies and the risk of type 1 diabetes mellitus (T1DM) is well known. However, a quantitative overview of all associated autoantibodies and their effectiveness in diagnosing T1DM is still lacking.

Purpose: To perform a meta-analysis concerning the association between autoantibodies and the risk of T1DM

Methods: Published papers from PubMed, Embase, Cochrane, and Google Scholar were collected and analyzed using a fixed or random-effect model.

Results: Seven papers on 1266 T1DM patients and 982 controls relevant to our study were included in the analysis. Our pooled analysis found that autoantibody expression in children with T1DM was associated with age at diagnosis [mean diff: 4.35 (95% CI: 1.10-7.60) $p = 0.009$) and the number of autoantibodies detected [OR: 2.13 (95% CI: 1.65-2.76) $p < 0.00001$]. However, duration of disease [mean diff: 33.36 (95% CI: 8.78-75.50), $p = 0.12$] and HbA1c [mean diff: 21.63 (95% CI: 5.43-48.48), $p = 0.12$] did not differ significantly between the single and multiple autoantibody detection groups. We also found that the expression of anti-ZnT8, anti-glutamic acid decarboxylase (GAD), and IAA was associated with a higher risk of T1DM development in children [OR: 35.26 (23.28-53.41), $p < 0.00001$; OR: 25.59 (18.29-35.79), $p < 0.00001$; OR: 23.62 (15.79-35.36), $p < 0.0000$, respectively].

Conclusion: ZnT8 has a better predictive value than other single autoantibodies, but two or more autoantibodies give superior predictive power.

Keywords: autoantobody, ZnT8, GAD, IAA, T1DM

1. Introduction

Type 1 diabetes mellitus (T1DM) remains one of the world's major diseases, with an annual increase in incidence of about 2%-3% each year. The burden of T1DM is even more evident in children under 15 years old, particularly in those under 5 years old. Over 90% of T1DM patients are known to express

a measurable amount of islet autoantibodies, suggesting the need for a deeper understanding of the autoantibodies involved in the development of T1DM. The production of these autoantibodies results from the presentation of pancreatic β- cells to antigen-presenting cells, leading to innate and adaptive immune cascades. The resulting autoantibodies are capable of destroying pancreatic β- cells, resulting in endogenous insulin deficiency.[1]

To date, several autoantibodies involved in the pathogenesis of this disease have been identified, including islet cell autoantibodies (ICA), insulin autoantibodies (IAA), anti-glutamic acid decarboxylase (GAD), insulinoma-associated-2 autoantibodies (IA-2A), and zinc transporter-8 autoantibodies (anti-ZnT8). ICA is the first identified autoantibody and the most common autoantibody found in those with T1DM individuals. However, ICA has relatively low sensitivity in predicting T1DM. More recently autoantibodies, namely, IAA, anti-GAD, and IA-2A, have been shown to be highly predictive of T1DM, indicating their potential utility in the prediction and diagnosis of T1DM.[2] In terms of disease course, anti-GAD and IAA tend to appear first, followed by IA-2A[2], and thus these two autoantibodies are of particular interest in the current study. Anti-Zn8TA has also been shown to be highly expressed in T1DM patients, in both Caucasian and Asian populations.[3]

While the association between autoantibodies and the risk of T1DM is well established, little is known about the association between autoantibodies and the diagnosis and disease course of T1DM in children. Therefore, this meta-analysis was estabilised to investigate the predictive value of autoantibodies, especially anti-Zn8TA, anti-GAD, and IAA, in the development of T1DM in children and to explore the association between these autoantibodies and T1DM characteristics in pediatric populations.

2.Method

Eligibility criteria

The following criteria were used to select papers for inclusion in our study: (1) papers assessing the association of ZnT8, anti-GAD, and IAA autoantibodies with the risk of T1DM; and (2) papers presenting data necessary for the calculation of mean difference and 95% CI. The exclusion criteria were as follows: (1) unrelated titles and abstracts, (2) reviews and commentaries, (3) incomplete data, and (4) low-quality article.

Outcome measures

The predictor covariate in the present study was the detection of autoantibodies in T1DM children with T1DM. The outcome measures were the duration of disease, age at diagnosis, HbA1c, and the number of autoantibodies detected, along with expression of the autoantibodies ZnT8, GAD, and IAA. They were determined after we performed initial screening for covariates to include in our meta-analysis calculation.

Assessment of methodological quality

The quality of each paper was assessed using the Newcastle-Ottawa scale (NOS) prior to inclusion in the meta-analysis. The NOS score ranges from 0 to 9, based onthree features: selection of patients (4 points), comparability of the groups (2 points), and ascertainment of exposure (3 points). Paper were interpreted as having low quality (for scores ≤ 4), moderate quality (for scores 5-6), or high quality

(for scores ≥ 7). Papers with low quality were excluded from our study. Two independent investigators (FF and YH) performed the NOS assessment; if there was a discrepancy between their assessments, consultation with a senior researcher (MF, NR) was conducted.

Statistical analysis

The correlations and effect estimates of autoantibody expression with the duration of disease, age at diagnosis, HbA1c, and the number of autoantibodies detected were assessed using a Z test. Prior to identification of the significant factors, data were evaluated for heterogeneity and potential publication bias. The heterogeneity among studies was assessed using the Q test. If heterogeneity existed ($p < 0.10$), a random-effect model was adopted; otherwise, a fixed-effect model was applied. Egger's test and funnel plot were used to identify reporting or publishing error ($p<0.05$ was considered indicate publication bias). The correlations and effect estimates were then presented using a forest plot. The data were analyzed using Review Manager version 5.3 (Revman Cochrane, London, UK). To avoid methodological errors, two independent authors (FF and YH) conducted the statistical analysis.

3. Results

Eligible studies

Our search identified 54 potentially relevant papers. Among them, 38 papers were excluded because of irrelevant titles and abstracts so 16 papers were included for a review of the full text. Of those, we excluded nine papers because they were reviews (n = 5), had incomplete data (n = 2), or were of low quality papers (n = 2). Thus, seven papers were finally included in our analysis. Figure 1 summarizes the paper selection pathway in our study. Table 1 outlines the baseline characteristics of the papers included in our meta-analysis.

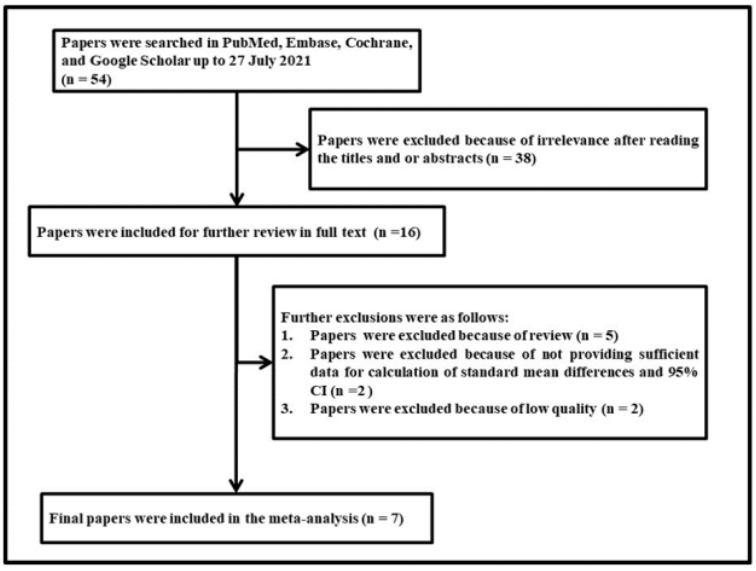
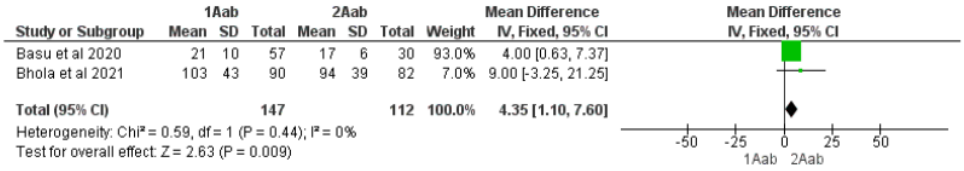


Figure. Paper selection pathway

A.



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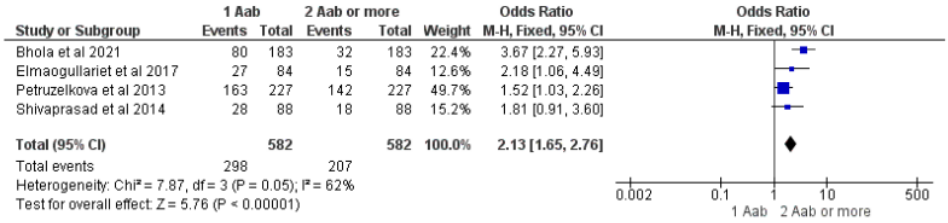
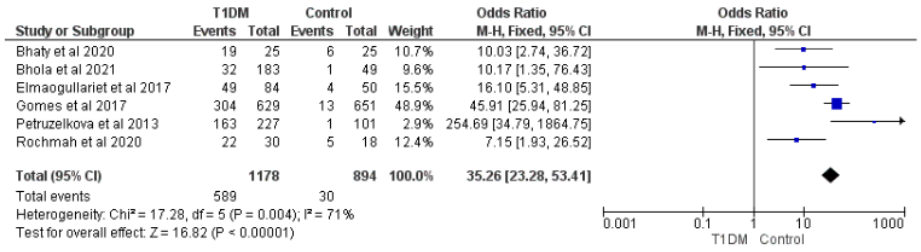


Figure 2, Forest Plot of the association between autoantibodies expression and outcome parameters in children with T1DM. A). Age at diagnosis, B). the number of autoantibodies detected



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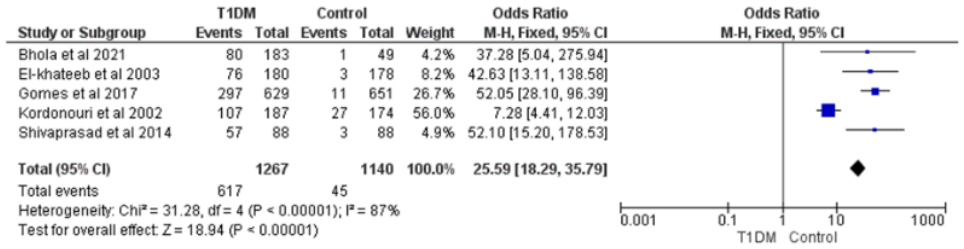

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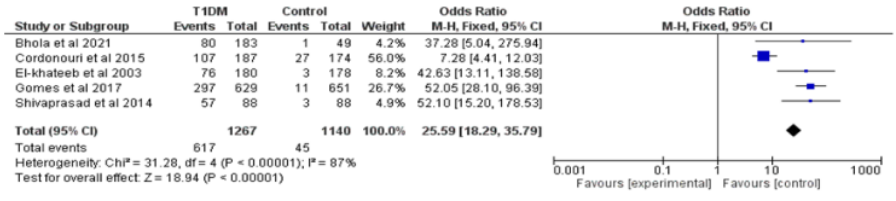

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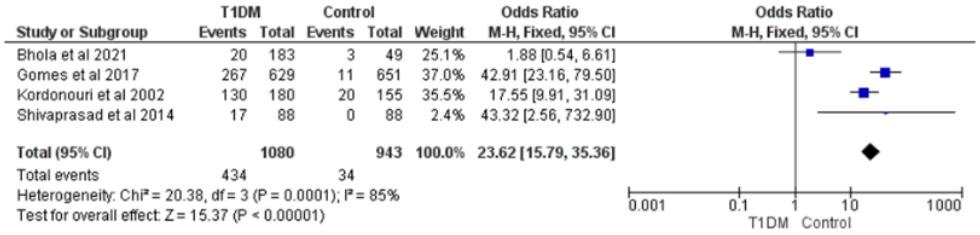

Figure 3. Forest Plot of the association between autoantibodies expression and the risk of T1DM development, A). ZnT8, B). GAD, C). IAA.

Abbrevation: T1DM, type 1 diabetes mellitus; ZnT8, zinc transporter-8; GAD, glutamic acid decarboxylase antibody; IAA, insulin autoantibody

Table 1. Baseline characteristics of articles included in our study

Author & year	Sample size		Case setting	Age at diagnosis (month) (mean ± SD)	Ethnicity	NOS	Main findings
	Control	T1DM					
Bhaty et al 2020	25	25	T1DM	160.8 ± 60,6	Asian	6	ZnT8 autoantibodies was associated with T1DM patients.
Bhola et al 2021	49	183	T1DM	180 ± 60	Caucasian	7	The prevalence of positive ZnT8, GAD65 and IA2 autoantibodies with T1DM in black south africans lower than in Eropean and African American population
Kordonouri et al 2002	155	180	T1DM	110.4 ± 10,8	Caucasian	6	GAD and IA2 autoantibodies titer significantly increased in

							T1DM children and didn't depend on age
Elmaogullariet et al 2017	50	84	T1DM	113.4 ± 48	Caucasian	7	ZnT8 autoantibodies testing should be more widely used to identified new onset of T1DM because it's found positive while other antibodies (GADA, IA-2A and IA) negative
Gomes et al 2017	651	629	T1DM	132 ± 72	Caucasian	7	ZnT8 antibodies can be used as autoimmunity marker to diagnosed T1DM especially in mixed populations. Unlike GAD65 A, which were greater in females, the levels of ZnT8 and IA-2A were unrelated to gender and ethnicity
Petruzelkova et al 2013	101	227	T1DM	96 ± 12	Caucasian	7	GAD, IA-2, insulin and ZnT8 autoantibodies in combination have a sensivity 96% for

							identifying T1DM
Rochmah et al 2020	18	30	T1DM	85.11 ± 44.8	Asian	7	ZnT8 could be potentially used to diagnose T1DM because this marker can detected earlier than IAA, IA-2A, and GADA

Notes:

Abbreviations: NOS, Newcastle-Ottawa scale; ZnT8, zinc transporter-8; T1DM, type 1 diabetes mellitus; GAD, glutamic acid decarboxylase antibody; IAA, insulin autoantibody; IA-2A, insulinoma associated-2 autoantibody; HbA1c, Hemoglobin A1C

Data synthesis

In the data synthesis, we included two papers assessing the association between autoantibodies and duration of disease, two papers assessing the correlation between autoantibodies and age at diagnosis, seven papers assessing the association between autoantibodies and HbA1c, and four papers assessing the relationship between autoantibody marker detection (expression) and autoantibody positivity (the number of autoantibodies detected). Our pooled analysis found that the detection of two or more autoantibody markers, compared with the detection of single one, was associated with earlier age at diagnosis [mean diff: 4.35 (95% CI: 1.10-7.60) $p = 0.009$] and autoantibody positivity [OR: 2.13 (95% CI: 1.65-2.76), $p < 0.00001$)]. However, multiple autoantibodies were not associated with the duration of disease [mean diff: 33.36 (95% CI: 8.78-75.50), $p = 0.12$] and HbA1c [mean diff: 21.63 (95% CI: 5.43-48.48), $p = 0.12$].

Other than that, we included seven papers assessing the association between ZnT8 detection in T1DM and controls, five papers assessing the association between GAD detection in T1DM and controls, and four papers assessing the association between IAA detection in T1DM and controls. Our pooled analysis found that ZnT8, GAD, and IAA were associated with the risk of T1DM in children [OR: 35.26 (23.28-53.41), $p < 0.00001$;OR: 25.59 (18.29-35.79), $p < 0.00001$; OR: 23.62 (15.79-35.36), $p < 0.00001$, respectively]. Summaries of the association of autoantibodies with T1DM characteristics and the risk of developing T1DM are presented in Tables 2 and 3, respectively. [3-9]

Source of heterogeneity

Heterogeneity among studies

Our analysis found evidence for heterogeneity in the following covariates: duration of disease, age at diagnosis, and HbA1c. Therefore, a random-effect model was used to assess the association of autoantibody expression with the duration of disease, age at diagnosis, and HbA1c. Conversely, we found no evidence of heterogeneity in autoantibody-positivity markers, ZnT8, GAD, and IAA

covariates. Therefore, a fixed-effect model was used to evaluate the correlation between autoantibody markers and autoantibody-positivity markers, ZnT8, GAD, and IAA covariates. The evidence of heterogeneity among studies in the present meta-analysis is presented in Tables 2 and 3.

Potential publication bias

We used Egger's test to determine the potential publication bias among the studies. Overall, there was no publication bias in our studies. Summaries of thepublication bias are presented in Tables 2 and 3.

Table 2. Summary of the association between Duration of Disease, Age at Diagnosis, HbA1c and the risk of T1DM

Parameters	Outcome measure		Mean Difference	95% CI	pE	pHet	P
	1 Aab	2 or more Aab					
Duration of Disease (months)	49 ± 28.6	26.8 ± 12	33.36	8.78-75.50	0.848	0.000	0.12
Age at Diagnosis (months)	62.3 ± 50.2	55.5 ± 22.5	4.35	1.10-7.60	0.000	0.400	0.009
HbA1c	9.75 ± 1.86	9.3 ± 1.9	21.63	5.43-48.48	2.081	0.000	0.12
Autoantibodies expression	51%	36%	2.13	1.65-2.76	0.353	0.049	<0.00001

Notes: data were presented in mean ± SD

Abbreviations: CI, confidence interval; pE, p Egger; pHet, p Heterogeneity.

Table 3 Summary of the association between ZnT8, antiGAD, and IAA autoantibodies and the risk of T1DM

Parameters	Outcome measure		Mean Difference / Odds Ratio in number of events	95%CI	pE	pHet	P
	Control	T1DM					
ZnT8	3.2%	48.73%	35.26	23.28-53.41	0.801	0.012	<0.00001
GAD	3.9%	48.69%	25.59	18.29-35.79	1.104	0.000	<0.00001
IAA	4.6%	40.2%	23.62	15.79-35.36	1.069	0.000	<0.00001

Notes: data were presented in mean ± SD

Abbreviations: CI, confidence interval; pE, p Egger; pHet, p Heterogeneity.

4.Discussion

A total of seven studies were analyzed to assess the association between autoantibodies and T1DM. We found that AA, anti-GAD, and anti-ZnT8 were highly predictive of the development of T1DM, with anti-ZnT8 being the most predictive biomarker, followed by anti-GAD and IAA. These findings confirmed the results of Bo et al., who found that the 5-year cumulative risk of developing T1DM was the highest among patients expressing ZnT8 autoantibodies.[10] Our findings also supported the recommendation by Bo et al. to screen all first-degree relatives of T1DM patients for anti-ZnT8 and IA-2A, especially considering their high predictive value.[10] Our findings also indicated that the number of autoantibodies present was also positively associated with an increased risk of T1DM development, which is in line with the findings of Ling et al.[11]

Further analysis revealed that the expression of multiple autoantibodies was associated with an earlier age of diagnosis. This is in accordance with previous findings by Mrena et al., who stated that the number of autoantibodies present, in addition to the patient's age, the patient's sibling's age of diagnosis, human leukocyte antigen (HLA) susceptibilities, and autoantibody concentrations, was associated with an earlier diagnosis.[12] A potential explanation for this is that these autoantibodies synergistically compromised the pancreatic β-cells.[13] IAA directly binds to insulin and prevents it from initiating glucose metabolism, while ICA and IA-2A destroy pancreatic islet cytostructures through the lymphocytic process.[2] Furthermore, anti-GAD breaks down the immunological tolerance of β-cells by preventing the synthesis of γ-aminobutyric acid (GABA)[14], which wouldotherwise exert protective effects on pancreatic β-cells by stimulating α- to β-cell fate switch[15]. Antibodies to ZnT8 also degranulate membrane proteins, thus impeding the synthesis of insulin.[3] The resulting synergistic effect of these autoantibodies accelerates disease progression.[13] Nonetheless, it should be noted that only Basu et al.[16] stated that the expression of autoantibodies was associated with earlier age at diagnosis, while Bhola et al.[5] stated otherwise. This indicates that further studies are required to confirm these findings, especially considering that a previous report by Steck et al.[17] stated that only IAA might predict the age of diagnosis of T1DM.

Among the included studies, most were conducted on Caucasian populations, while only two studies investigated the role of autoantibodies in diabetic Asians. Although this may suggest that heterogeneity of autoantibody positivity between ethnicities is related to the epidemiological disparities, previous reports stated that the prevalence rates of islet autoantibodies namely ICA, anti-GAD, and IA-2A, among Korean T1DM populations were comparable to those in Caucasians[18,19], where one report showed that about 70%-90% of children with T1DM were seropositive for at least one autoantibody[19]. The incidence of T1DM in Asia is generally lower than in Western countries.[18] This may be explained by the fact that the contribution of HLA-DR3/DR4, the expression of which confers a predisposition to T1DM, to the pathogenesis of T1DM among Asian populations is lower than in Caucasians. In Asians, moderate-risk haplotypes are more commonly expressed than high-risk ones such as HLA-DR3/DR4, explaining the relatively low incidence observed in Asian populations.[18,19]

Altogether, this systematic review supports the routine investigation of islet autoantibodies in identifying children at risk of developing T1DM. While a previous meta-analysis by Ling et al. also recommended a similar strategy[7], the present study adds to the supporting body of evidence by investigating the association of autoantibodies and T1DM characteristics (i.e., disease course and age

at diagnosis), thus providing a better understanding of the role of autoimmunity in the development of T1DM in the pediatric population. The investigation of islet autoantibodies in routine clinical practice is important considering that a considerable proportion of children with T1DM diagnosed at a later stage of the disease, thus predisposing these children to morbidity and mortality.[1,15] The identification of children with T1DM at early stages may facilitate prompt intervention to reduce the risk of diabetic ketoacidosis[1,6] and other T1DM-related complications, for example, other autoimmune diseases, as a previous systematic review by Nederstigt et al.[16] stated that T1DM patients were at a higher risk of developing comorbid autoimmunity. Furthermore, these strategies may also improve glycemic control.[1,7] Recently, teplizumab, an anti-CD3 monoclonal antibody, has been shown to be effective in delaying the development and progression of T1DM and is currently awaiting approval from the U.S. Food and Drug Administration. [17,18] The approval of this first-in-class agent will further emphasize the urgent need to identify populations with T1DM autoantibodies, thus allowing alleviation of the disease burden of T1DM among children and the general population.

This systematic review has some limitations. First, the high heterogeneity observed in this study, which may have been caused by the difference of sample sizes among the included studies, means that our findings should be interpreted with caution. In addition, owing to the paucity of studies, we were unable to pool the adjusted estimates of the covariates. To the best of our knowledge, this is the first systematic review and meta-analysis investigating the association between islet autoantibodies and T1DM in children. Nevertheless, given the current limitations, we recommend that further studies with larger sample sizes and an appropriate set of adjustment factors be conducted to confirm our findings.

5.Conclusion

The current study identified that ZnT8 has a better predictive value than other single autoantibodies, but that two or more autoantibodies provide superior predictive power. However, the duration of disease and HbA1c level did not differ significantly between the groups with a single autoantibody marker and two or more autoantibody markers. Our study potentially clarifies the correlation between autoantibodies to aid the diagnosis of children with T1DM and the identification of other factors that may influence it.

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Disclosure

The authors report no conflicts of interest in this work.

Author Contributions

All authors made significant contributions to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11