

# World Journal of *Diabetes*

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AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJD* mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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## Evaluation of teplizumab's efficacy and safety in treatment of type 1 diabetes mellitus: A systematic review and meta-analysis

Xiao-Lan Ma, Dan Ge, Xue-Jian Hu

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### Abstract

#### BACKGROUND

Islets of Langerhans beta cells diminish in autoimmune type 1 diabetes mellitus (T1DM). Teplizumab, a humanized anti-CD3 monoclonal antibody, may help T1DM. Its long-term implications on clinical T1DM development, safety, and efficacy are unknown.

#### AIM

To assess the effectiveness and safety of teplizumab as a therapeutic intervention for individuals with T1DM.

#### METHODS

A systematic search was conducted using four electronic databases (PubMed, Embase, Scopus, and Cochrane Library) to select publications published in peer-reviewed journals written in English. The odds ratio (OR) and risk ratio (RR) were calculated, along with their 95%CI. We assessed heterogeneity using Cochrane Q and  $I^2$  statistics and the appropriate  $P$  value.

#### RESULTS

There were 8 randomized controlled trials (RCTs) in the current meta-analysis with a total of 1908 T1DM patients from diverse age cohorts, with 1361 patients receiving Teplizumab and 547 patients receiving a placebo. Teplizumab was found to have a substantial link with a decrease in insulin consumption, with an OR of 4.13 (95%CI: 1.72 to 9.90). Teplizumab is associated with an improved C-peptide response (OR 2.49; 95%CI: 1.62 to 3.81) and a significant change in Glycated haemoglobin A1c (HbA1c) levels in people with type 1 diabetes [OR 1.75 (95%CI: 1.03 to 2.98)], and it has a RR of 0.71 (95%CI: 0.53 to 0.95).

#### CONCLUSION

In type 1 diabetics, teplizumab decreased insulin consumption, improved C-peptide response, and significantly changed HbA1c levels with negligible side effects. Teplizumab appears to improve glycaemic control and diabetes management with

good safety and efficacy.

**Key Words:** Type-1 diabetes mellitus; Teplizumab; Anti-CD3 monoclonal antibody; Insulin; Glycated haemoglobin A1c; C-peptide

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**Core Tip:** Type 1 diabetes mellitus (T1DM) may benefit from teplizumab. However, there is limited data on its long-term effects on clinical T1DM development, safety, and efficacy. Given its perceived use, this research evaluated the effectiveness and safety of teplizumab for T1DM patients through a systematic review and meta-analysis of 8 randomized controlled trials, including 1908 patients from various age groups. It was found that teplizumab treatment results in reduced insulin use, improved C-peptide response, significant glycated haemoglobin A1c changes in T1DM patients with minimal side effects and improved glycaemic management.

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## INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a pathological condition of an autoimmune type wherein there is a progressive degeneration of beta cells located inside the islets of Langerhans[1]. Despite advancements in healthcare, the majority of individuals with type 1 diabetes struggle to reach the ideal glycaemic targets, resulting in a continued elevated risk of complications and mortality[2,3]. The development of immunotherapy targeting beta-cell destruction represents an unresolved requirement in the management of autoimmune type 1 diabetes, with potential future applicability in prediabetes[4]. The initiation of treatment during the clinical onset presents a favorable circumstance wherein individuals can be readily diagnosed and there is still a preserved functional beta-cell mass. The maintenance of residual beta-cell function, as indicated by elevated levels of C-peptide, contributes to improved glycaemic control, hence reducing the risk of retinopathy, nephropathy, hypoglycemia, and ketoacidosis. The use of immunotherapy at the time of diagnosis seeks to extend and enhance this impact by inhibiting additional B-cell mortality and potentially facilitating the restoration of functional capacity in surviving B-cells following the resolution of inflammation[5-7]. Various clinical trials evaluating different therapeutic drugs have demonstrated limited success in this context; nonetheless, treatment responses have frequently exhibited a decline within a span of two years[8,9]. Teplizumab is a monoclonal antibody that has been engineered to have a non-activating Fc region. It is believed to inhibit the activity of autoreactive T lymphocytes, which are responsible for inducing the death of beta-cells. It targets the CD3 protein specifically and is considered to be effective in this function.

The T cells undergo a transient depletion from the peripheral circulation throughout the course of immunotherapy, followed by their reconstitution within a few weeks upon discontinuation of the treatment[10,11]. Based on preclinical and clinical investigations, it has been observed that teplizumab medication has the potential to stimulate regulatory T-cell function, hence indicating an enhancement in immunological tolerance[12-14]. According to recent research, the administration of teplizumab has been found to effectively mitigate beta-cell apoptosis after one year of treatment, modulate CD8+ T lymphocytes as well as enhance C-peptide reactions in clinical trials involving individuals with type 1 diabetes[15,16]. However, additional study is necessary to examine the long-term effects on b-cell activity and survival, as well as to ascertain the safety and efficacy of teplizumab therapy in modifying the progression towards clinical type 1 diabetes. Therefore, in this systematic review and meta-analysis, we assessed the effectiveness and safety of teplizumab as a therapeutic intervention for T1DM *via* analysis of 8 randomized controlled trials (RCTs)[17-24] selected as per the predetermined inclusion and exclusion criteria.

This meta-analysis and systematic review was conducted with the purpose of determining whether or not teplizumab is an effective and safe treatment intervention for people who have T1DM.

## MATERIALS AND METHODS

### Search strategy

The present meta-analysis was conducted following a comprehensive search across various databases, including PubMed, Embase, Scopus, and Cochrane library. The search covered from the year 2000 to 2023 and utilized specific keywords such as "Type-1 Diabetes mellitus", "T1DM", "Teplizumab", "anti-CD3 monoclonal antibody", "Insulin", "Glycated haemoglobin A1c", "HbA1C", "C-peptide", "Adverse events", "Randomized controlled trials", "RCT",

"Systematic review" and "meta-analysis". Based on the PICO framework[25], the keywords were identified and found to be consistent in both the Medline and Embase databases, as indicated in Table 1. In the context of searching Scopus, the Title (ti)-Abstract (abs)-keyword (key) field was utilized with the aforementioned keywords. The key phrase "Teplizumab" and "Type-1 diabetes mellitus" was utilized in the Cochrane database. The PICO format was utilized to construct precise selection criteria. In this context, "P" denoted T1DM patients, "I" referred to Teplizumab drug, "C" denoted control drug, and "O" encompassed clinical outcomes, reduction in insulin use, change in C-peptide response, change in glycated haemoglobin A1c (HbA1C) level and adverse events. The design methodology employed in this study was confined to the utilization of RCTs. The inclusion criteria specified that only papers published in the English language were considered. The inclusion of articles was conducted in accordance with the principles outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[26]. Two researchers, identified as Xiao-Lan Ma and Dan Ge, independently conducted a comprehensive review of the pertinent literature to identify relevant studies.

### Criteria for inclusion and exclusion

The current analysis comprised studies that showed data on the efficacy and safety of Teplizumab for the treatment of T1DM. Those studies that satisfied the subsequent inclusion criteria were incorporated: (1) Including patients with T1DM; (2) Adolescents and adult patients ranging in age from 7 to 40 years; (3) Evaluating the comparative efficacy and safety of teplizumab for the treatment of T1DM; and (4) Implementation of RCT as the chosen study design. From the year 2000 all the way up until the year 2023, the selection of studies covered the entire time span. We chose papers that were available in full text and offered sufficient information for a table that was two by two. Several clinical outcomes were used as primary measures in this meta-analysis. These outcomes included a decrease in insulin utilization, a change in response to C-peptide, a change in the level of HbA1C, and adverse events that occurred in participants who were treated with teplizumab and those who were in the control group. Additionally, the comparative glycemic control experienced by the teplizumab group in comparison to the control group was also assessed. We did not include references that were either out of date, anecdotal, or based on the opinions of experts. Additionally, we did not include studies that were not cross-sectional, studies that contained experimental data from animal studies or trials, and studies for which we were unable to receive primary data and key information from the authors. Studies that included patients with diabetes in addition to those with HIV, cancer, and other systemic problems were also removed from consideration. Additionally, articles that were not research papers, qualitative studies, and papers published in languages other than English were also removed. Separately, the researchers (Xiao-Lan Ma and Dan Ge) acquired demographic profiles of the patients as well as event data with important components from the studies that were included.

### Risk of bias evaluation of studies incorporated

The potential for bias in the papers that were examined was evaluated using a pre-established and standardized questionnaire. For the purpose of determining the potential for bias, a tool developed by the Cochrane Collaboration[27] and included in the Cochrane Handbook (version 5.3) was utilized. The instrument consisted of five components: Bias resulting from the randomization process, bias resulting from deviations from the interventions that were intended, bias resulting from the absence of outcome data, bias resulting from the assessment of the outcome, and bias resulting from the selection of the outcomes that were presented. Two different reviewers, Xiao-Lan Ma and Dan Ge, each carried out their own research in order to determine the potential for bias. An additional reviewer, who will be referred to as Xue-Jian Hu, acted as an arbitrator to settle any disagreements that were still outstanding. At the end of the day, the potential bias was evaluated and classified as either "high risk," "low risk," or "unclear risk." Through the utilization of a funnel plot [28], the presence of publication bias was evaluated, and Begg's test[29] was carried out with the assistance of the MedCalc program[30] in order to ascertain the statistical significance of the findings.

### Statistical analysis

For the purpose of evaluating and analyzing the influence of a number of dichotomous and continuous outcomes, the software package Review Manager (RevMan) 5.3[31] was applied. Through the employment of reference management software, the categorization, extraction, and elimination of duplicate references were made easier. The development of forest plots[32] was attempted with the purpose of evaluating the influence of outcome determinants across all of the investigations. A  $2 \times 2$  table[33] that was generated with event data was utilized in order to compute the odds ratio (OR). This was done by employing the DerSimonian Lair method. The examination of dichotomous outcomes included the utilization of OR[34] and risk ratios (RR)[35] in addition to a CI covering 95% of the possible outcomes. The assessment of heterogeneity was examined through the utilization of statistical techniques, such as the  $\chi^2$  test with a matching  $P$  value and the  $I^2$  test[36]. A random-effects model was utilized in the event that there was heterogeneity between the studies, which was demonstrated by an  $I^2$  value that was greater than fifty percent or a  $P$  value that was less than five percent. A fixed-effect model was utilized for the pooled analysis[37], which was otherwise not the case. It was determined that a  $P$  value that was lower than 0.05 to be statistically significant[38]. In addition to this, a box and whisker plot[39] was also created in order to assess the glycaemic control[40] in the Teplizumab administration group with the control group.

## RESULTS

### Literature search results

A thorough search of a number of databases was carried out with the use of electronic scanning tools, which led to the

**Table 1 Database search strategy**

Database	Search strategy
Scopus	<sup>1</sup> "Type-1 Diabetes mellitus" OR "T1DM" OR "Teplizumab" OR "anti-CD3 monoclonal antibody" <sup>2</sup> "Insulin" OR "Glycated hemoglobin A1c" OR "HbA1C" OR "C-peptide" OR "Adverse events" OR "Randomized controlled trials" OR "RCT" OR "Systematic review" OR "meta-analysis" <sup>3</sup> <sup>1</sup> AND <sup>2</sup>
PubMed	<sup>1</sup> "Type-1 Diabetes mellitus" OR "T1DM" (MeSH Terms) <sup>1</sup> OR "Teplizumab" (all fields) OR "anti-CD3 monoclonal antibody" (all fields) <sup>2</sup> "Insulin" (MeSH Terms) OR "Glycated hemoglobin A1c" (all fields) OR "HbA1C" (all fields) OR "C-peptide" (all fields) OR "Adverse events" OR "Randomized controlled trials" (all fields) OR "RCT" (all fields) OR "systematic review" OR "meta-analysis" <sup>3</sup> <sup>1</sup> AND <sup>2</sup>
Embase	"Type-1 Diabetes mellitus" / exp <sup>2</sup> OR "T1DM" / exp OR "Teplizumab" / exp OR "anti-CD3 monoclonal antibody" / exp <sup>2</sup> "Insulin" / exp OR "Glycated hemoglobin A1c" / exp OR "HbA1C" / exp OR "C-peptide" / exp OR "Adverse events" / exp OR "Randomized controlled trials" / exp OR "RCT" / exp OR "systematic review" / exp OR "meta-analysis" <sup>3</sup> <sup>1</sup> AND <sup>2</sup>
Cochrane library	<sup>1</sup> (Type-1 Diabetes mellitus): Ti, ab, kw <sup>3</sup> OR (T1DM): Ti, ab, kw OR (Teplizumab): Ti, ab, kw OR (anti-CD3 monoclonal antibody): Ti, ab, kw OR (Cortisol): Ti, ab, kw (Word variations have been searched) <sup>2</sup> (Insulin): Ti, ab, kw OR (Glycated hemoglobin A1c): Ti, ab, kw OR (HbA1C): Ti, ab, kw or (C-peptide): Ti, ab, kw or (Adverse events): Ti, ab, kw or (Randomized controlled trials): Ti, ab, kw or (systematic review): Ti, ab, kw or (meta-analysis): Ti, ab, kw (Word variations have been searched) <sup>3</sup> <sup>1</sup> AND <sup>2</sup>

<sup>1</sup>MeSH terms: Medical subject headings.<sup>2</sup>exp: Explosion in emtree- searching of selected subject terms and related subjects.<sup>3</sup>ti, ab, kw: Either title or abstract or keyword fields.

discovery of a total of 356 studies that fulfilled the inclusion criteria that were stated by the PICOS framework. We were able to exclude a total of 245 papers after conducting an exhaustive review of their titles and identifying instances of duplication. This left us with 111 records that were taken through additional screening. After applying the inclusion-exclusion criteria, however, a total of 103 studies were determined to be ineligible and were consequently removed from consideration. The absence of inclusion criteria, which included a comparison of the safety and effectiveness of teplizumab with a control drug in patients with T1DM, insufficient data to construct  $2 \times 2$  tables, and the absence of necessary outcome measures, were the primary factors that contributed to the cancellation of studies. As can be seen in **Figure 1**, this meta-analysis made use of a total of eight RCT that satisfied the inclusion criteria that were stated and that covered the years 2000 to 2023. A total of 1908 type 1 diabetes patients from a variety of age groups were included in the papers that were analyzed for this particular research. The selection of patients for this trial was carried out through the use of a random sampling technique. The group that received Teplizumab consisted of 1361 individuals, whereas the group that served as the control consisted of exactly 547 people. The demographic features of the studies that were utilized in this meta-analysis are presented in **Table 2**. It is stated in the text that the author identification number, the year of publication, the journal of publication, the country of publication, the study setting, the study design, the total number of participants, the diagnosis, the age of participants, the number of participants in the teplizumab group and the control group, the duration of the study, the gender (male/female ratio), and the primary outcomes that were measured are all included. After that, the data from the events that were described earlier were utilized for the purpose of carrying out the meta-analysis later on.

### Assessment of risk of bias

**Table 3** presents the results of the risk of bias assessment for the studies that were included, which were derived from the questionnaire that was designed beforehand. As can be seen from the graph depicting the risk of bias (**Figure 2A**) and the summary depicting the risk of bias (**Figure 2B**), the current meta-analysis appears to have a low probability of being biased. Out of the eight studies that were considered for inclusion in the analysis, six of them had a low risk of bias, while one of them had a substantial risk of bias. It was determined that the bias that occurred as a result of the randomization technique was caused by the moderate risk. In spite of this, there was a specific study that displayed a substantial high risk because of the bias in the selection of the data that were published. The symmetrical form of the funnel plot that is represented in **Figure 3** and the statistically insignificant *P* value of Begg's test (0.249) that is higher than the preset significance level of 0.05 both indicate that there is a minimal risk of publishing bias. In addition, the symmetrical form of the funnel plot is used to illustrate the little risk of publication bias.

### Statistical analysis findings

The current meta-analysis was comprised of a sample of eight RCTs, which included a total of seventeen thousand eight

Table 2 Brief summary of the included studies

Ref.	Year of publication	Journal of publication	Country of study	Study setting	Study design	Total number of participants (n)	Diagnosis	Age of patients	Teplizumab group (n)	Control group (n)	Duration of study	Sex (M/F)	Primary outcomes
Herold <i>et al</i> [17]	2002	<i>The New England Journal of Medicine</i>	United States	HIC	RCT	24	Type-1 diabetes	7-30 years	12	12	1 year	18/6	Positive outcomes: Lower insulin uses and decrease in value of HbA1c, Adverse events
Hagopian <i>et al</i> [18]	2013	<i>Diabetes</i>	Sweden	HIC	RCT	410	Type-1 diabetes	8-35 years	311	99	2 years	295/115	Positive outcomes: Change in area under the curve for C-peptide, lower insulin uses and decrease in value of HbA1c, Adverse events
Herold <i>et al</i> [19]	2013	<i>Diabetologia</i>	United States	HIC	RCT	58	Type-1 diabetes	12-15 years	31	27	1 year	30/28	Positive outcomes: Change in area under the curve for C-peptide, and decrease in value of HbA1c, Adverse events
Herold <i>et al</i> [20]	2019	<i>New England Journal of medicine</i>	United States	HIC	RCT	76	Type-1 diabetes	12-22 years	44	32	2 years	36/40	Positive outcomes: Decrease in value of HbA1c, Adverse events
Herold <i>et al</i> [21]	2023	<i>Diabetes care</i>	United States	HIC	RCT	609	Type-1 diabetes	8-35 years	375	234	1 year	370/239	Positive outcomes: Change in area under the curve for C-peptide, and decrease in value of HbA1c, Adverse events
Perdigoto <i>et al</i> [22]	2019	<i>Diabetologia</i>	United States	HIC	RCT	43	Type-1 diabetes	8-30 years	31	12	2 years	26/17	Positive outcomes: Change in area under the curve for C-peptide, and decrease in value of HbA1c, Adverse events
Sherry <i>et al</i> [23]	2011	<i>Lancet</i>	United States	HIC	RCT	763	Type-1 diabetes	8-35 years	513	99	2 years	325/438	Positive outcomes: Lower insulin uses and decrease in value of HbA1c, Adverse events
Sims <i>et al</i> [24]	2021	<i>Science Translation medicine</i>	United States	HIC	RCT	76	Type-1 diabetes	8-39 years	44	32	2 years	40/36	Positive outcomes: Change in area under the curve for C-peptide and decrease in value of HbA1c, Adverse events

HbA1c: Glycated haemoglobin A1c; RCT: Randomized controlled trial; M: Male; F: Female; HIC: High income countries.

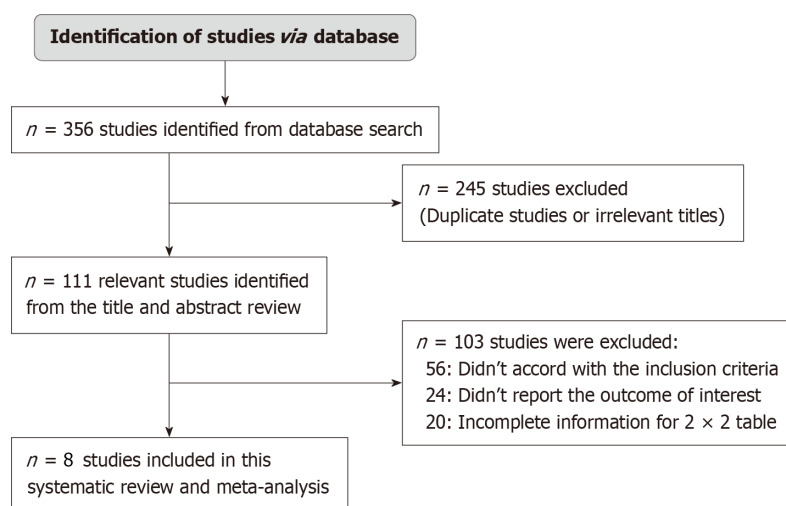
hundred eight individuals with T1DM. Among the whole population, Teplizumab was delivered to 1361 patients, while 547 patients were given a control medication for the treatment of type 1 diabetes. On the basis of the statistical analysis that was carried out on the most important results of the study, the following conclusions were reached:

**Reduction of insulin use in teplizumab *vs* control group:** To investigate the reduction in insulin-use in patients treated with either Teplizumab or a control drug, an OR was calculated using the event data extracted from the included studies, as depicted in Figure 4A. From the calculated results, it was found that the patients in the teplizumab group have a higher likelihood of reduction in insulin use, with an OR of 4.13 (95%CI: 1.72 to 9.90) and a tau<sup>2</sup> value of 0.41,  $\chi^2 = 9.64$ , degree of freedom(df) = 2, Z = 3.18, P = 79% and P = 0.001.

**Table 3 Risk of bias assessment of included studies**

	Herold <i>et al</i> [17]	Hagopian <i>et al</i> [18]	Herold <i>et al</i> [19]	Herold <i>et al</i> [20]	Herold <i>et al</i> [21]	Perdigoto <i>et al</i> [22]	Sherry <i>et al</i> [23]	Sims <i>et al</i> [24]
Did the study avoid inappropriate exclusions	Y	Y	Y	Y	Y	Y	Y	Y
Did all patients receive the same reference standard	Y	Y	Y	Y	Y	Y	Y	Y
Were all patients included in the analysis	N	N	N	N	N	N	N	N
Was the sample frame appropriate to address the target population	Y	Y	Y	Y	Y	Y	Y	Y
Were study participants sampled in an appropriate way	Y	Y	Y	Y	Y	Y	Y	Y
Were the study subjects and the setting described in detail	Y	Y	Y	Y	Y	Y	Y	Y
Were valid methods used for the identification of the condition	Y	Y	Y	Y	Y	Y	Y	Y
Was the condition measured in a standard, reliable way for all participants	Y	Y	Y	Y	Y	Y	Y	Y

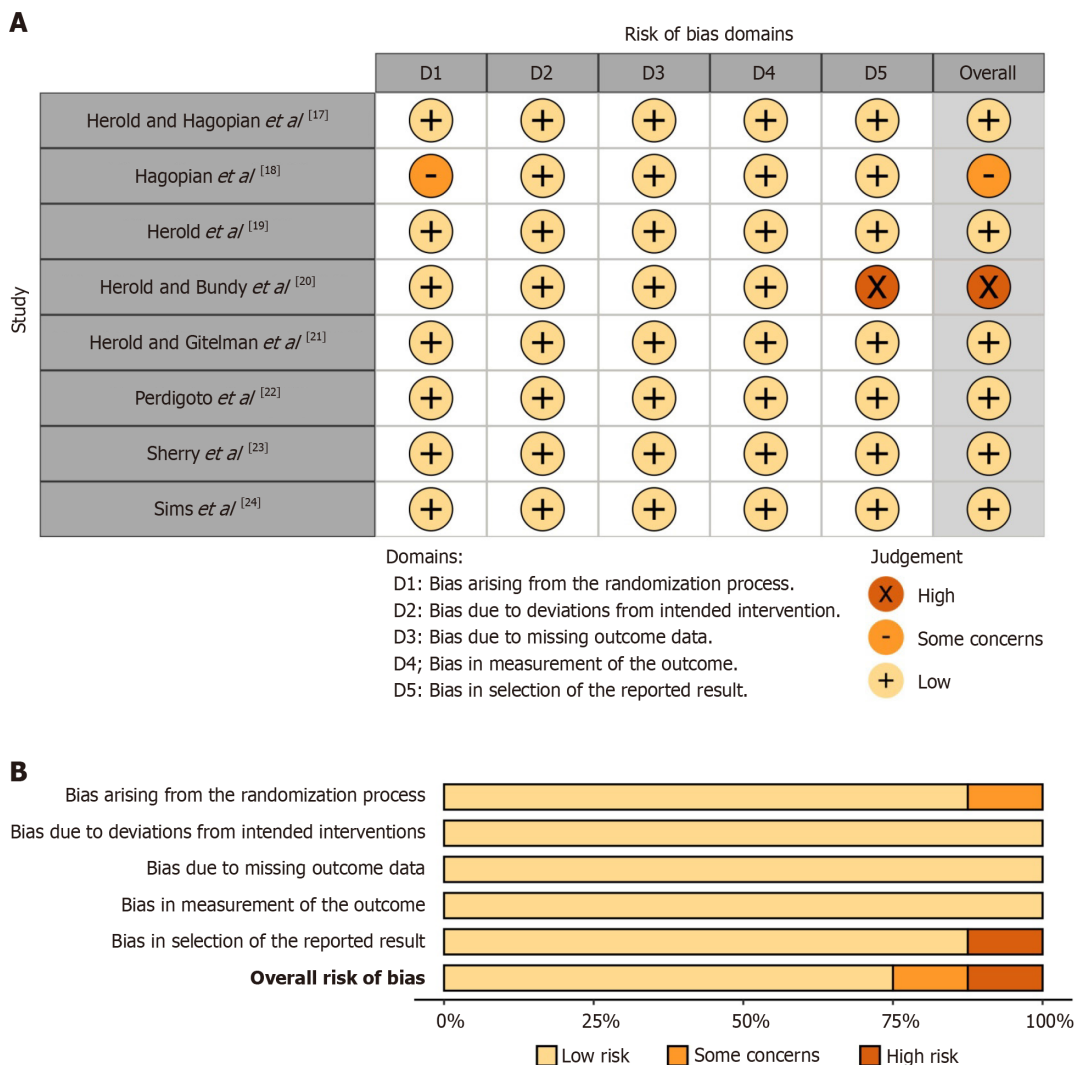
Y: Yes; N: No.

**Figure 1** Flow of selection of studies.

**Change in C-peptide response in teplizumab *vs* control group:** To examine the change in C-peptide response in patients treated with either Teplizumab or a control drug, an OR was calculated using the event data extracted from the included studies. From the calculated results shown in [Figure 4B](#), it was found that the patients in the teplizumab group have a higher likelihood of change in C-peptide response, with an OR of 2.49 (95%CI: 1.62 to 3.81) and a  $\tau^2$  value of 0.08,  $\chi^2 = 6.12$ ,  $df = 4$ ,  $Z = 4.19$ ,  $I^2 = 75\%$  and  $P < 0.0001$ .

**Change in HbA1C level in teplizumab *vs* control group:** To assess the change in HbA1C level in Teplizumab *vs* control group, a comparative analysis of glycated haemoglobin value in the patients treated with either teplizumab or control drug was carried out, as depicted in [Figure 4C](#). From the calculations, it was found that the patients in the teplizumab group have a higher likelihood of change in HbA1C level, with an OR of 1.75 (95%CI: 1.03 to 2.98) and a  $\tau^2$  value of 0.32,  $\chi^2 = 23.06$ ,  $df = 7$ ,  $Z = 2.05$ ,  $I^2 = 70\%$  and  $P = 0.04$ .

**Comparison of adverse events in patients of teplizumab *vs* control group:** In order to assess the comparative risk of adverse events between the Teplizumab and control groups, a RR analysis was conducted. This analysis specifically examined the occurrence of adverse events, such as systemic inflammations and allergic responses, in patients who received either teplizumab or the control medicine. The results of this analysis are presented in [Figure 5](#). Based on the



**Figure 2 Assessment of risk of bias.** A: Traffic light plot for assessment of risk of bias of included studies; B: Summary plot for assessment of risk of bias of included studies.

computed data, it was determined that the individuals in the control group exhibit a greater susceptibility to experiencing unfavorable outcomes, as shown by a RR of 0.71 (95%CI: 0.53 to 0.95). Additionally, the  $\tau^2$  value turned out to be 0.14, the  $\chi^2$  value was 44.64 with df 7, the Z score was 2.26, the  $I^2$  value was 84%, and the  $P$  value was 0.02.

**Comparison of glycaemic control in patients of teplizumab vs control group:** Box and whisker plot was generated using the event data obtained from the studies included in the analysis to evaluate the relative effectiveness of teplizumab vs the control medication in managing glycaemic control in patients. This figure is depicted in Figure 6. The plot exhibited a symmetrical distribution of data points with a median positioned at the centre of the box, and the whiskers extending to almost equal ranges on both sides of the box. The group receiving teplizumab has favorable glycaemic control, characterized by optimal serum glucose concentrations, in comparison to the control group. This effect contributes to the prevention of diabetes complications.

## DISCUSSION

T1DM is an autoimmune disorder resulting from the destruction of pancreatic  $\beta$ -cells responsible for insulin production, either with or without any remaining functional tissue[41]. Type 1 diabetes can be attributed to various factors, such as viral infections, drug-induced effects, and autoimmune mechanisms. These variables contribute to the death of  $\beta$ -cells and result in a complete absence of insulin in the bloodstream, leading to elevated levels of blood glucose[42,43]. Individuals diagnosed with T1DM necessitate the continuous administration of insulin throughout their whole lifespan. The majority of individuals necessitate a minimum of two injections of insulin each day, wherein the dosage is modified in accordance with self-monitoring of blood glucose levels[44]. Teplizumab, also known as teplizumab-mzwv, is a monoclonal antibody of the IgG1 kappa class that has been humanized. It is primarily utilized for the purpose of delaying the onset of type 1 diabetes and as a therapy option for those with T1DM[45]. In November 2022, teplizumab was granted approval as the

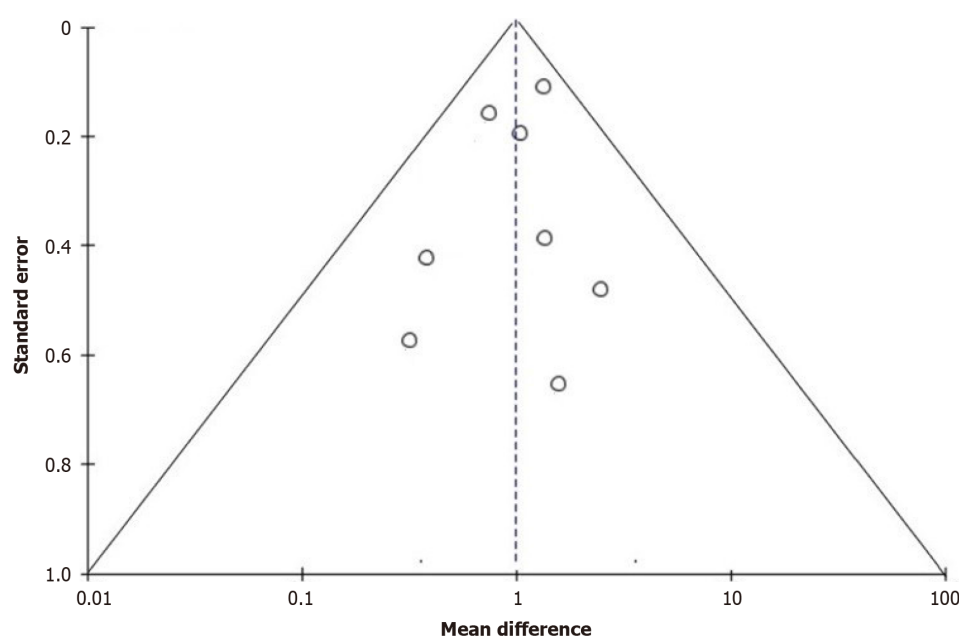


Figure 3 Funnel plot for assessment of publication bias of included studies.

inaugural medication for the purpose of postponing the initiation of stage 3 type 1 diabetes in individuals aged eight years and older, encompassing both adults and children[46].

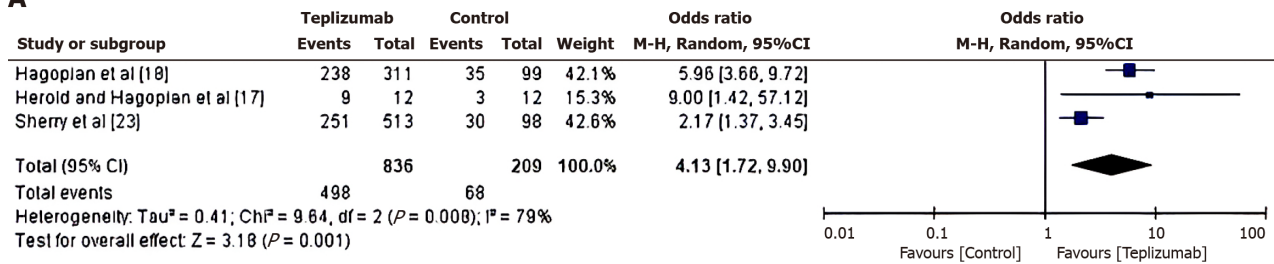
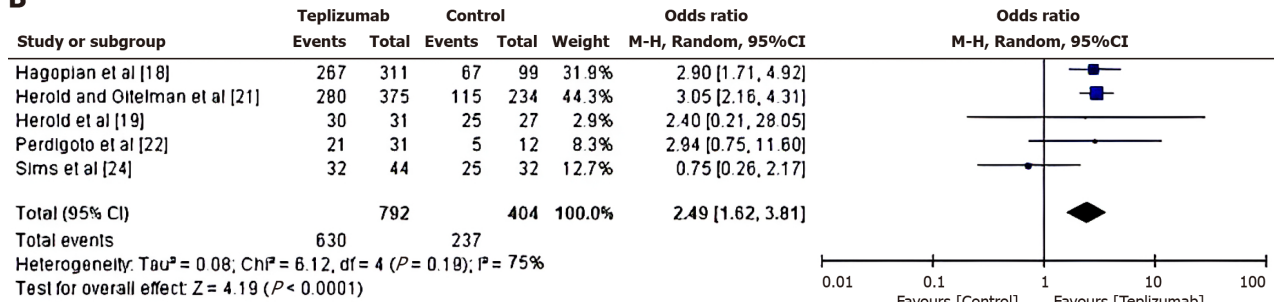
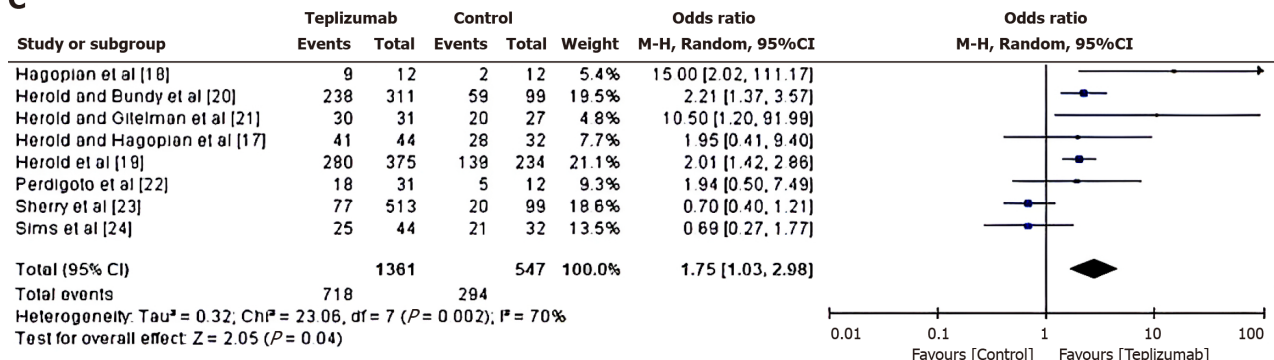
Multiple investigations have revealed that Teplizumab demonstrates disease-modifying characteristics through the preservation of  $\beta$ -cell functioning. In a recent systematic review and meta-analysis conducted by Nourelden *et al*[47], the authors examined the effects of teplizumab on insulin use, C-peptide response, and adverse effects in patients with type 1 diabetes. The study included eight randomized clinical trials with a total of 866 participants. The findings of the analysis revealed that Teplizumab was associated with a significant reduction in insulin use [mean difference (MD) = -0.17, 95%CI (-0.24, -0.09)]. Additionally, the administration of Teplizumab resulted in a higher C-peptide response [MD = 0.08, 95%CI (0.01, 0.15)] and a lower incidence of adverse effects. In a systematic review and meta-analysis conducted by Ashraf *et al* [48] in 2023, the authors examined 11 RCTs with a total of 1397 participants. Their findings indicated that treatment with teplizumab resulted in a significant increase in the C-peptide response, as evidenced by a MD of 0.114 (95%CI: 0.069 to 0.159). Additionally, teplizumab treatment was found to significantly reduce patients' insulin intake across all timeframes, with a MD of -0.123 (95%CI: -0.151 to -0.094). Similarly, Liu *et al*[49] and Evans-Molina and Oram[50] have documented in their respective research investigations that Teplizumab, an anti-CD3 monoclonal antibody, exhibits promise as a therapeutic intervention for enhancing the area under the curve of C-peptide and insulin utilization in individuals with type 1 diabetes.

Our findings align with the aforementioned results, indicating positive correlation between teplizumab and a decrease in insulin usage, with an OR of 4.13 (95%CI: 1.72 to 9.90). Additionally, teplizumab is associated with an improved C-peptide response (OR 2.49; 95%CI: 1.62 to 3.81) and a significant change in HbA1c levels among individuals diagnosed with type 1 diabetes [OR 1.75 (95%CI: 1.03 to 2.98)], while exhibiting minimal adverse effects, as indicated by a RR of 0.71 (95%CI: 0.53 to 0.95). In addition, teplizumab has been shown to offer improved glycaemic management. Nevertheless, our analysis solely encompasses studies conducted exclusively in high-income nations. This highlights the need of conducting such studies in low- and middle-income countries (LMICs), where the prevalence of T1DM is higher among adults and adolescents.

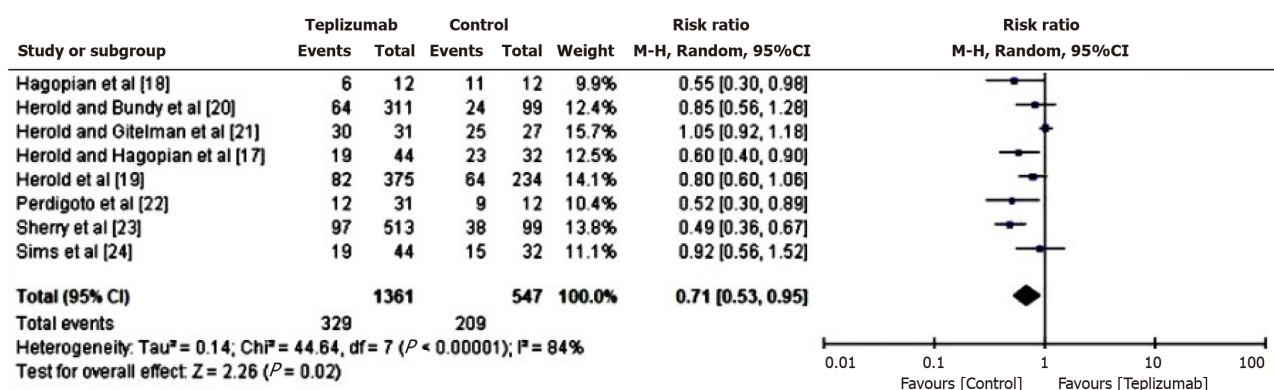
### Limitations

One of the most important aspects of this research is the utilization of all-encompassing search phrases that encompass the investigation of "type-1 diabetes mellitus" and "teplizumab" across a number of different databases.

However, it is necessary to illustrate certain limitations. Firstly, studies done in languages other than English were not included in this analysis. Given that a sizable number of the publications included in our meta-analysis were eliminated, it is also imperative to recognize the possibility of selection bias in our research. Furthermore, it was not possible to determine a correlation between the results and factors like gender, age, or ethnicity, and it is unclear whether these conclusions will apply to people who do not appear to be at risk for type 1 diabetes but do not have first-degree relatives who have the disease. Thirdly, the limited sample size used in the current meta-analysis – just eight studies – showed notable variability and heterogeneity. It is impossible to determine whether repeated doses will prolong therapeutic effects or offer additional advantages in comparison to the drug administered for a single course. Finally, one more limitation of our analysis is that it only includes studies from high-income nations. This emphasizes the importance of doing this kind of research in LMICs, where T1DM is more common in adults and adolescents.

**A****B****C**

**Figure 4 Forest plot for positive outcomes.** A: Reduction in insulin use; B: Change in C-peptide response; C: Change in glycated haemoglobin A1c level in Teplizumab versus control group. HbA1c: Glycated haemoglobin A1c; df: Degree of freedom; M-H: Mantel-Haenszel.



**Figure 5 Forest plot for risk of adverse events in teplizumab vs control group.** df: Degree of freedom; M-H: Mantel-Haenszel.

## CONCLUSION

Based on the results of the present meta-analysis, it can be concluded that the utilization of teplizumab is linked to a reduction in insulin use, an enhanced C-peptide response, and a significant alteration in HbA1c levels among individuals diagnosed with type 1 diabetes, while exhibiting minimal adverse effects. The findings indicate that teplizumab exhibits favorable safety and efficacy profiles in promoting improved glycaemic control and managing diabetes mellitus. However, additional study is necessary to investigate the potential synergistic effects of combining immune and

metabolic therapy. This research is crucial in order to maintain the immunological responses that are related with the preservation of C-peptide responses and the attainment of good outcomes that have a significant therapeutic impact.

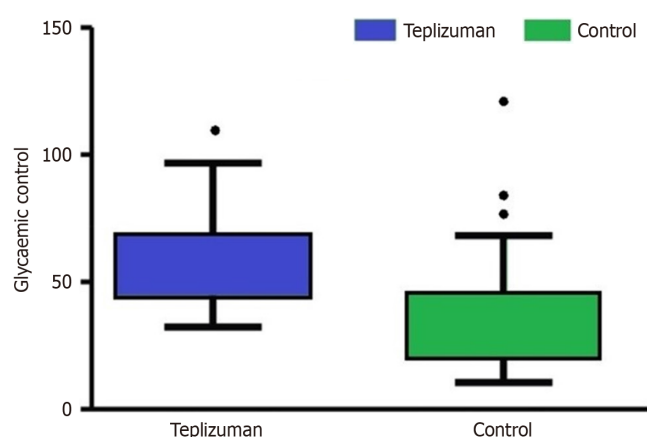


Figure 6 Box and Whisker plot for comparative Glycaemic control in Teplizumab vs control group.

## FOOTNOTES

**Author contributions:** Ma XL contributed to concept and designed the study; Ge D contributed to analyzed data and drafting of the manuscript; Hu XJ contributed to collect the data and helped in data analysis.

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## REFERENCES

- Katsarou A, Gudbjörnsdóttir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, Jacobsen LM, Schatz DA, Lernmark Å. Type 1 diabetes mellitus. *Nat Rev Dis Primers* 2017; **3**: 17016 [PMID: 28358037 DOI: 10.1038/nrdp.2017.16]
- Rodrigues Oliveira SM, Rebocho A, Ahmadpour E, Nissapatorn V, de Lourdes Pereira M. Type 1 Diabetes Mellitus: A Review on Advances and Challenges in Creating Insulin Producing Devices. *Micromachines (Basel)* 2023; **14** [PMID: 36677212 DOI: 10.3390/mi14010151]
- Galderisi A, Sherr JL. A Technological Revolution: The Integration of New Treatments to Manage Type 1 Diabetes. *Pediatr Ann* 2019; **48**: e311-e318 [PMID: 31426099 DOI: 10.3928/19382359-20190725-03]
- Burrack AL, Martinov T, Fife BT. T Cell-Mediated Beta Cell Destruction: Autoimmunity and Alloimmunity in the Context of Type 1 Diabetes. *Front Endocrinol (Lausanne)* 2017; **8**: 343 [PMID: 29259578 DOI: 10.3389/fendo.2017.00343]
- Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis GA, Vogiatzi G, Papaioannou S, Deftereos S, Tousoulis D. The Role of Inflammation in Diabetes: Current Concepts and Future Perspectives. *Eur Cardiol* 2019; **14**: 50-59 [PMID: 31131037 DOI: 10.15420/eur.2018.33.1]
- Warshawer JT, Bluestone JA, Anderson MS. New Frontiers in the Treatment of Type 1 Diabetes. *Cell Metab* 2020; **31**: 46-61 [PMID: 31839487 DOI: 10.1016/j.cmet.2019.11.017]
- Smith MJ, Simmons KM, Cambier JC. B cells in type 1 diabetes mellitus and diabetic kidney disease. *Nat Rev Nephrol* 2017; **13**: 712-720 [PMID: 29038537 DOI: 10.1038/nrneph.2017.138]
- Padhi S, Nayak AK, Behera A. Type II diabetes mellitus: a review on recent drug based therapeutics. *Biomed Pharmacother* 2020; **131**: 110708 [PMID: 32927252 DOI: 10.1016/j.biopha.2020.110708]
- Song P, Hwang JS, Park HC, Kim KK, Son HJ, Kim YJ, Lee KM. Therapeutic Applications of Type 2 Diabetes Mellitus Drug Metformin in

- Patients with Osteoarthritis. *Pharmaceuticals (Basel)* 2021; **14** [PMID: 33668426 DOI: 10.3390/ph14020152]
- 10 **Misra S, Shukla AK.** Teplizumab: type 1 diabetes mellitus preventable? *Eur J Clin Pharmacol* 2023; **79**: 609-616 [PMID: 37004543 DOI: 10.1007/s00228-023-03474-8]
  - 11 **Novograd J, Frishman WH.** Teplizumab Therapy to Delay the Onset of Type 1 Diabetes. *Cardiol Rev* 2023 [PMID: 37158990 DOI: 10.1097/CRD.0000000000000563]
  - 12 **Ben-Skowronek I, Sieniawska J, Pach E, Wrobel W, Skowronek A, Tomczyk Z, Rosolowska I.** Potential Therapeutic Application of Regulatory T Cells in Diabetes Mellitus Type 1. *Int J Mol Sci* 2021; **23** [PMID: 35008819 DOI: 10.3390/ijms23010390]
  - 13 **Waldron-Lynch F, Henegariu O, Deng S, Preston-Hurlburt P, Tooley J, Flavell R, Herold KC.** Teplizumab induces human gut-tropic regulatory cells in humanized mice and patients. *Sci Transl Med* 2012; **4**: 118ra12 [PMID: 22277969 DOI: 10.1126/scitranslmed.3003401]
  - 14 **Linsley PS, Greenbaum CJ, Nepom GT.** Uncovering Pathways to Personalized Therapies in Type 1 Diabetes. *Diabetes* 2021; **70**: 831-841 [PMID: 33741606 DOI: 10.2337/db20-1185]
  - 15 **Nagy G, Szekely TE, Somogyi A, Herold M, Herold Z.** New therapeutic approaches for type 1 diabetes: Disease-modifying therapies. *World J Diabetes* 2022; **13**: 835-850 [PMID: 36312000 DOI: 10.4239/wjcd.v13.i10.835]
  - 16 **Felton JL, Griffin KJ, Oram RA, Speake C, Long SA, Onengut-Gumuscu S, Rich SS, Monaco GSF, Evans-Molina C, DiMeglio LA, Ismail HM, Steck AK, Dabelea D, Johnson RK, Urazbayeva M, Gitelman S, Wentworth JM, Redondo MJ, Sims EK; ADA/EASD PMDI.** Disease-modifying therapies and features linked to treatment response in type 1 diabetes prevention: a systematic review. *Commun Med (Lond)* 2023; **3**: 130 [PMID: 37794169 DOI: 10.1038/s43856-023-00357-y]
  - 17 **Herold KC, Hagopian W, Auger JA, Poumian-Ruiz E, Taylor L, Donaldson D, Gitelman SE, Harlan DM, Xu D, Zivin RA, Bluestone JA.** Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. *N Engl J Med* 2002; **346**: 1692-1698 [PMID: 12037148 DOI: 10.1056/NEJMoa012864]
  - 18 **Hagopian W, Ferry RJ Jr, Sherry N, Carlin D, Bonvini E, Johnson S, Stein KE, Koenig S, Daifotis AG, Herold KC, Ludvigsson J; Protégé Trial Investigators.** Teplizumab preserves C-peptide in recent-onset type 1 diabetes: two-year results from the randomized, placebo-controlled Protégé trial. *Diabetes* 2013; **62**: 3901-3908 [PMID: 23801579 DOI: 10.2337/db13-0236]
  - 19 **Herold KC, Gitelman SE, Willi SM, Gottlieb PA, Waldron-Lynch F, Devine L, Sherr J, Rosenthal SM, Adi S, Jalaludin MY, Michels AW, Dziura J, Bluestone JA.** Teplizumab treatment may improve C-peptide responses in participants with type 1 diabetes after the new-onset period: a randomised controlled trial. *Diabetologia* 2013; **56**: 391-400 [PMID: 23086558 DOI: 10.1007/s00125-012-2753-4]
  - 20 **Herold KC, Bundy BN, Long SA, Bluestone JA, DiMeglio LA, Dufort MJ, Gitelman SE, Gottlieb PA, Krischer JP, Linsley PS, Marks JB, Moore W, Moran A, Rodriguez H, Russell WE, Schatz D, Skyler JS, Tsalikian E, Werrett DK, Ziegler AG, Greenbaum CJ; Type 1 Diabetes TrialNet Study Group.** An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. *N Engl J Med* 2019; **381**: 603-613 [PMID: 31180194 DOI: 10.1056/NEJMoa1902226]
  - 21 **Herold KC, Gitelman SE, Gottlieb PA, Knecht LA, Raymond R, Ramos EL.** Teplizumab: A Disease-Modifying Therapy for Type 1 Diabetes That Preserves  $\beta$ -Cell Function. *Diabetes Care* 2023; **46**: 1848-1856 [PMID: 37607392 DOI: 10.2337/dc23-0675]
  - 22 **Perdigoto AL, Preston-Hurlburt P, Clark P, Long SA, Linsley PS, Harris KM, Gitelman SE, Greenbaum CJ, Gottlieb PA, Hagopian W, Woodwyk A, Dziura J, Herold KC; Immune Tolerance Network.** Treatment of type 1 diabetes with teplizumab: clinical and immunological follow-up after 7 years from diagnosis. *Diabetologia* 2019; **62**: 655-664 [PMID: 30569273 DOI: 10.1007/s00125-018-4786-9]
  - 23 **Sherry N, Hagopian W, Ludvigsson J, Jain SM, Wahlen J, Ferry RJ Jr, Bode B, Aronoff S, Holland C, Carlin D, King KL, Wilder RL, Pillemer S, Bonvini E, Johnson S, Stein KE, Koenig S, Herold KC, Daifotis AG; Protégé Trial Investigators.** Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trial. *Lancet* 2011; **378**: 487-497 [PMID: 21719095 DOI: 10.1016/S0140-6736(11)60931-8]
  - 24 **Sims EK, Bundy BN, Stier K, Serti E, Lim N, Long SA, Geyer SM, Moran A, Greenbaum CJ, Evans-Molina C, Herold KC; Type 1 Diabetes TrialNet Study Group.** Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Sci Transl Med* 2021; **13** [PMID: 33658358 DOI: 10.1126/scitranslmed.abc8980]
  - 25 **Brown D.** A Review of the PubMed PICO Tool: Using Evidence-Based Practice in Health Education. *Health Promot Pract* 2020; **21**: 496-498 [PMID: 31874567 DOI: 10.1177/1524839919893361]
  - 26 **Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D.** The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700 [PMID: 19622552 DOI: 10.1136/bmj.b2700]
  - 27 **Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group.** The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928 [PMID: 22008217 DOI: 10.1136/bmj.d5928]
  - 28 **Sterne JA, Egger M.** Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001; **54**: 1046-1055 [PMID: 11576817 DOI: 10.1016/S0895-4356(01)00377-8]
  - 29 **Begg CB, Mazumdar M.** Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**: 1088-1101 [PMID: 7786990 DOI: 10.2307/2533446]
  - 30 **Elovic A, Pourmand A.** MDCalc Medical Calculator App Review. *J Digit Imaging* 2019; **32**: 682-684 [PMID: 31025219 DOI: 10.1007/s10278-019-00218-y]
  - 31 **Schmidt L, Shokraneh F, Steinhilber K, Adams CE.** Introducing RAPTOR: RevMan Parsing Tool for Reviewers. *Syst Rev* 2019; **8**: 151 [PMID: 31242929 DOI: 10.1186/s13643-019-1070-0]
  - 32 **Dettori JR, Norvell DC, Chapman JR.** Seeing the Forest by Looking at the Trees: How to Interpret a Meta-Analysis Forest Plot. *Global Spine J* 2021; **11**: 614-616 [PMID: 33939533 DOI: 10.1177/21925682211003889]
  - 33 **George BJ, Aban IB.** An application of meta-analysis based on DerSimonian and Laird method. *J Nucl Cardiol* 2016; **23**: 690-692 [PMID: 26245193 DOI: 10.1007/s12350-015-0249-6]
  - 34 **Szumilas M.** Explaining odds ratios. *J Can Acad Child Adolesc Psychiatry* 2010; **19**: 227-229 [PMID: 20842279]
  - 35 **Viera AJ.** Odds ratios and risk ratios: what's the difference and why does it matter? *South Med J* 2008; **101**: 730-734 [PMID: 18580722 DOI: 10.1097/SMJ.0b013e31817a7ee4]
  - 36 **Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J.** Assessing heterogeneity in meta-analysis: Q statistic or I<sup>2</sup> index? *Psychol Methods* 2006; **11**: 193-206 [PMID: 16784338 DOI: 10.1037/1082-989X.11.2.193]
  - 37 **Barili F, Parolari A, Kappetein PA, Freemantle N.** Statistical Primer: heterogeneity, random- or fixed-effects model analyses? *Interact Cardiovasc Thorac Surg* 2018; **27**: 317-321 [PMID: 29868857 DOI: 10.1093/icvts/ivy163]

- 38 **Andrade C.** The P Value and Statistical Significance: Misunderstandings, Explanations, Challenges, and Alternatives. *Indian J Psychol Med* 2019; **41**: 210-215 [PMID: [31142921](#) DOI: [10.4103/IJPSYM.IJPSYM\\_193\\_19](#)]
- 39 **Ndako JA**, Olisa JA, Ifeanyichukwu IC, Ojo SKS, Okolie CE. Evaluation of diagnostic assay of patients with enteric fever by the box-plot distribution method. *New Microbes New Infect* 2020; **38**: 100795 [PMID: [33299564](#) DOI: [10.1016/j.nmni.2020.100795](#)]
- 40 **Bin Rakhis SA Sr**, AlDuwayhis NM, Aleid N, AlBarrak AN, Aloraini AA. Glycemic Control for Type 2 Diabetes Mellitus Patients: A Systematic Review. *Cureus* 2022; **14**: e26180 [PMID: [35891859](#) DOI: [10.7759/cureus.26180](#)]
- 41 **DiMeglio LA**, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet* 2018; **391**: 2449-2462 [PMID: [29916386](#) DOI: [10.1016/S0140-6736\(18\)31320-5](#)]
- 42 **Giwa AM**, Ahmed R, Omidian Z, Majety N, Karakus KE, Omer SM, Donner T, Hamad ARA. Current understandings of the pathogenesis of type 1 diabetes: Genetics to environment. *World J Diabetes* 2020; **11**: 13-25 [PMID: [31938470](#) DOI: [10.4239/wjd.v11.i1.13](#)]
- 43 **van Belle TL**, Coppieters KT, von Herrath MG. Type 1 diabetes: etiology, immunology, and therapeutic strategies. *Physiol Rev* 2011; **91**: 79-118 [PMID: [21248163](#) DOI: [10.1152/physrev.00003.2010](#)]
- 44 **Janež A**, Guja C, Mitrakou A, Lalic N, Tankova T, Czupryniak L, Tabák AG, Prazny M, Martinka E, Smircic-Duvnjak L. Insulin Therapy in Adults with Type 1 Diabetes Mellitus: a Narrative Review. *Diabetes Ther* 2020; **11**: 387-409 [PMID: [31902063](#) DOI: [10.1007/s13300-019-00743-7](#)]
- 45 **Masharani UB**, Becker J. Teplizumab therapy for type 1 diabetes. *Expert Opin Biol Ther* 2010; **10**: 459-465 [PMID: [20095914](#) DOI: [10.1517/14712591003598843](#)]
- 46 **Keam SJ.** Teplizumab: First Approval. *Drugs* 2023; **83**: 439-445 [PMID: [36877454](#) DOI: [10.1007/s40265-023-01847-y](#)]
- 47 **Nourelden AZ**, Elshanbary AA, El-Sherif L, Benmelouka AY, Rohim HI, Helmy SK, Sayed MK, Ismail A, Ali AS, Ragab KM, Zaazouee MS. Safety and Efficacy of Teplizumab for Treatment of Type One Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Endocr Metab Immune Disord Drug Targets* 2021; **21**: 1895-1904 [PMID: [33302842](#) DOI: [10.2174/1871530320999201209222921](#)]
- 48 **Ashraf MT**, Ahmed Rizvi SH, Kashif MAB, Shakeel Khan MK, Ahmed SH, Asghar MS. Efficacy of anti-CD3 monoclonal antibodies in delaying the progression of recent-onset type 1 diabetes mellitus: A systematic review, meta-analyses and meta-regression. *Diabetes Obes Metab* 2023; **25**: 3377-3389 [PMID: [37580969](#) DOI: [10.1111/dom.15237](#)]
- 49 **Liu Y**, Li W, Chen Y, Wang X. Anti-CD3 monoclonal antibodies in treatment of type 1 diabetes: a systematic review and meta-analysis. *Endocrine* 2024; **83**: 322-329 [PMID: [37658243](#) DOI: [10.1007/s12020-023-03499-0](#)]
- 50 **Evans-Molina C**, Oram RA. Teplizumab approval for type 1 diabetes in the USA. *Lancet Diabetes Endocrinol* 2023; **11**: 76-77 [PMID: [36623518](#) DOI: [10.1016/S2213-8587\(22\)00390-4](#)]



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