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SYSTEMATIC REVIEW AND META-ANALYSIS

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Type 1 Diabetic Populations Have an Increased Prevalence of Parietal Cell Antibody

A Systematic Review and Meta-Analysis

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Abstract: The presence of parietal cell antibody (PCA) in serum is a biomarker of autoimmune gastritis. PCA directly recognizes the H^+/K^+ ATPase expressed in parietal cells, which is responsible for the active transport of hydrogen ions in exchange for potassium ions to increase the acidity of gastric secretions. Type 1 diabetes mellitus (T1DM) mainly results from pancreatic β-cell destruction due to cell-type specific autoimmunity. Considering autoimmune factors may be the common characteristics of both PCA positivity and T1DM, it is likely that both disorders may coexist within the same patient. The main objective of this meta-analysis is to provide a reliable evaluation to clarify the association between PCA positivity and T1DM by combining the raw data from all of the relevant studies.

Literature databases, including the Medline, Embase, and Web of Science, were systematically queried for studies investigating the association between PCA positivity and T1DM and were published from January 1980 to December 2014. A total of 3,584 T1DM cases and 2,650 non-T1DM controls were included in this meta-analysis, which showed that PCA positivity was more prevalent in patients with T1DM than healthy controls. Publication bias testing found no significant biases and sensitivity analysis demonstrated that our statistics were relatively stable and credible.

Our findings suggested that T1DM was associated with an increased risk of PCA positivity compared to control populations.

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Abbreviations: PCA = parietal cell antibody, T1DM = type 1 diabetes mellitus.

INTRODUCTION

Parietal cell antibody (PCA) is a serum biomarker for autoimmune gastritis,[1] which is distinguished by chronic inflammation in the gastric corpus mucosa resulting from PCA-mediated autoimmune damage.[2] PCA directly recognizes H^+/K^+ ATPase, a hydrogen transporting enzyme mostly found in gastric parietal cell canaliculi that facilitates the transport of hydrogen ions by parietal cells into the gastric juice in exchange for potassium ions.[3] Although the underlying mechanisms of PCA production are still unknown, a complex interplay between genetic, endogenous, and environmental factors may be responsible to induce this form of autoimmunity.

Type 1 diabetes mellitus (T1DM) is characterized by a gradual reduction in insulin production, which leads to elevated blood sugar levels and defective protein and lipid metabolism.[4] T1DM likely results from various risk factors, but its exact pathogenesis is poorly understood. Importantly, the combined effect of genetic susceptibility and environmental factors may be necessary to initiate the autoimmune response against pancreatic β-cells.[5] Given that autoimmune factors have been shown to play a critical role in T1DM pathogenesis, an association may exist between T1DM and PCA positivity.

A number of studies have investigated the relationship between PCA positivity and T1DM by measuring PCA concentration in T1DM patient serum; however, the results of these analyses have been inconsistent. Furthermore, most of these reports examined a relatively small sample size that lacked the strength to demonstrate a significant association between PCA positivity and T1DM. To address this issue, we performed a meta-analysis by compiling the raw data from these relevant studies to provide a reliable evaluation of the association between PCA positivity and T1DM.

METHODS

Databases and Search Strategies

The Medline, Embase, and Web of Science databases were systematically searched for studies published in English from January 1980 to December 2014. Queries included the keywords ''gastric parietal cell antibody'' or ''parietal cell antibody,'' or ''PCA'' or ''GPCA,'' in combination with the terms ''type 1 diabetes mellitus,'' ''T1DM,'' ''insulin dependent diabetes mellitus,'' or ''IDDM.'' The search results were filtered, and only population-based studies were retained. The title, abstract, and main text of the retrieved reports were checked manually to ensure they fulfilled the inclusion criteria. The literature search was performed by 2 investigators independently, followed by a comparison of the selected studies and discussion of any inconsistencies.

The literature search yielded 589 reports of potential interest, which were then narrowed to 179 studies that might contain data of interest after reading the abstracts. These 179 publications were then read in full to determine whether they met the inclusion criteria for the meta-analysis. Ultimately, 18 reports were found suitable for further analysis.

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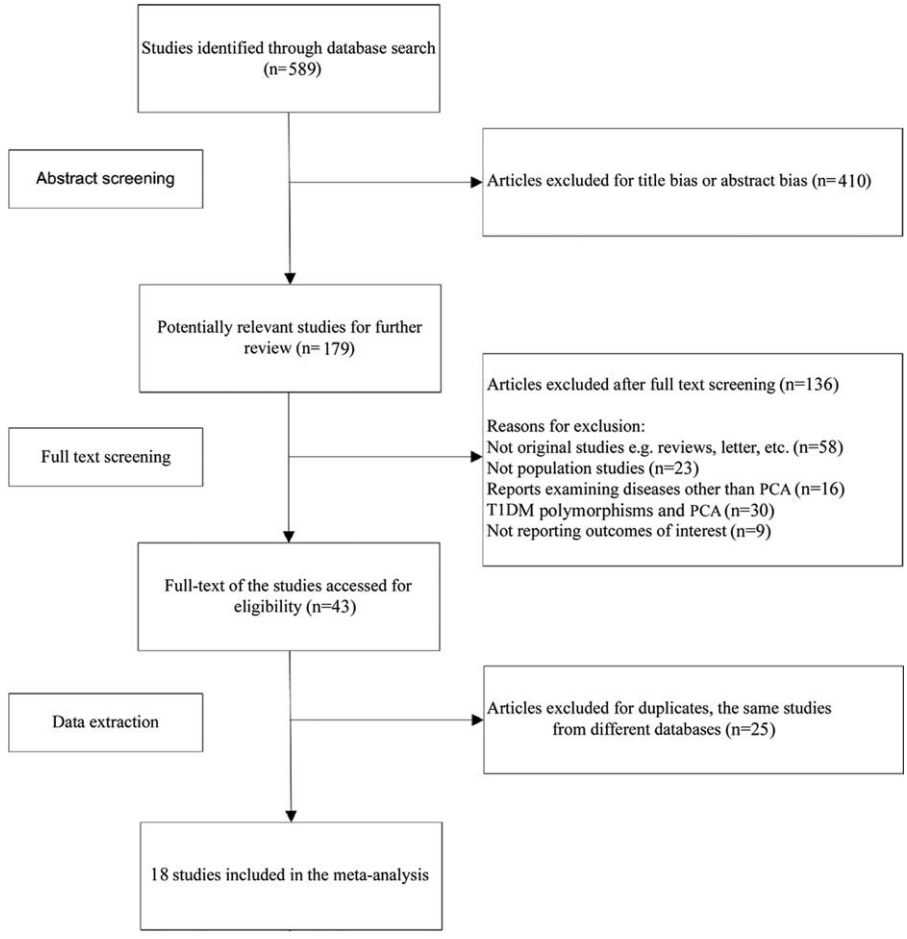

FIGURE 1. Flowchart of the selection process for the 18 studies included in the meta-analysis.

Inclusion Criteria

The studies included in the meta-analysis met all of the following conditions: analyzed the relationship between PCA positivity and T1DM; had a case–control design where the case and control groups were randomly and continuously included during a definite period; provided sufficient data on T1DM and non-T1DM control populations to allow for the calculation of an odds ratio (OR), 95% confidence interval (CI), and *P* value; controlled for population ethnicity and age; the case population consisted of patients with typical T1DM, other than latent autoimmune diabetes in adults; the control population consisted of nondiabetic subjects free from other diseases that might influence PCA prevalence; and excluded pregnant women from the analysis (to avoid any artifacts resulting from the immunosuppressive effects of parturiency).

Data Extraction

The following information was extracted from each included report: first author, year of publication, ethnicity of the study population, case and control population sizes, and PCA positivity rate among case and control populations.

Bias Risk Assessment of Included Studies

The quality of the selected studies was assessed by 2 investigators using the Newcastle–Ottawa Scale (NOS),[6] which has been recommended by the Cochrane Collaboration as a tool of bias risk assessment for observational studies.[7] Each of the included studies was assessed using a star rating system in the following 3 areas: selection of the study population, comparability between the case and control populations, and determination of exposure factors for the case and control populations. A star was allocated to the study when it met one of the criterions for each area. The compatibility rating was the only exception, for which a maximum of 2 stars could be allocated to each study. The NOS score ranged from 0 to 9 stars. Since the meta-analysis focused solely on the association between PCA and T1DM, the item ''no history of disease'' was set to ''no history of T1DM'' for the purposes of our study. Only studies deemed acceptable in terms of ''selection,'' ''comparability,'' and ''exposure'' by the NOS were included in the meta-analysis.

Statistical Analysis

The association between PCA positivity and T1DM was evaluated by calculating the OR and 95% CI. Statistical significance of the calculated OR was examined by Z test, and *P* values less than 0.05 were considered statistically significant. Furthermore, Q tests were performed to examine heterogeneity between the included studies and used to determine whether a random-effects model or fixed-effects model was selected to

TABLE 1. General Characteristics of the Studies Included in This Meta-Analysis

Study	Country	Continent	T1DM Cases (n/N)	Non-T1DM Controls (n/N)	Quality Score
Neufeld et al, 1980[8]	USA	American	44/504	2/147	★★★★★
Delespesse et al, 1980[9]	Belgium	European	21/56	6/134	★★★★★
Srikanta et al, 1981[10]	India	Asian	14/110	12/123	★★★★★★
Bright et al, 1982[11]	USA	American	14/198	2/117	★★★★★
Riley et al, 1982[12]	USA	American	62/771	13/600	★★★★★
Menser et al, 1983[13]	Australia	Oceanian	20/227	0/200	★★★★★★
Betterle et al, 1984[14]	Italy	European	12/239	4/250	★★★★★★
Hägglöf et al, 1986[15]	Sweden	European	2/30	0/30	★★★★★★★
Lorini et al, 1986[16]	Italy	European	19/55	10/75	★★★★★★
Odugbesan et al, 1988[17]	UK	European	3/36	2/41	★★★★★★★
Landin-Olsson et al, 1989[18]	Sweden	European	12/389	1/321	★★★★★★★
Abdullah et al, 1990[19]	Saudi Arabia	Asian	8/86	2/45	★★★★★★
Magzoub et al, 1994[20]	UK	European	6/96	0/86	★★★★★★
De Block et al, 2001[21]	Belgium	European	48/272	5/100	★★★★★★
Jaeger et al, 2001[22]	Germany	European	11/197	5/150	★★★★★
Erten et al, 2007[23]	Turkey	Asian	6/73	2/55	★★★★★★★
Fröhlich-Reiterer et al, 2011[24]	Austria	European	9/170	2/101	★★★★★★
Pinto et al, 2013[25]	Brazil	American	10/75	0/75	★★★★★★

n = number of people with positive antibodies, N = total number of people with T1DM disease or Non-T1DM controls, T1DM = type 1 diabetes mellitus.

calculate the OR. In Q tests, $P < 0.1$ or $I^2 > 50\%$ indicated a great interstudy heterogeneity and subsequent use of a random-effects model in the OR calculation. Studies with Q test scores of $P > 0.1$ or $I^2 < 50\%$ were assessed using the fixed-effects model. In addition, Begg test was used to assess publication bias of the selected studies. All of the statistical analyses were performed using Stata Version 12.0 software (Stata Corporation, College Station, TX).

RESULTS

Characteristics of Included Studies

Eighteen case–control studies met the inclusion criteria and were included in the meta-analysis, all of which assessed the association between PCA positivity and T1DM by measuring the positive rate of PCA in T1DM and control populations. The process of study selection is illustrated in Figure 1. The

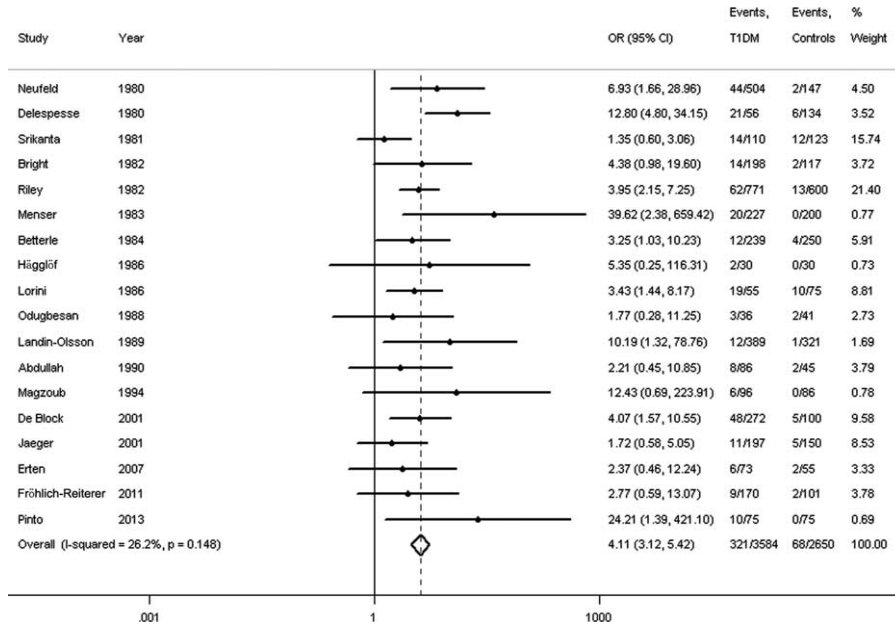

FIGURE 2. Forest plots comparing PCA-positive rates between T1DM and non-T1DM control populations. The rhombus represents the OR and 95% CI obtained for the combined calculation.

TABLE 2. Meta-analysis of the association between T1DM and prevalence of parietal cell antibody (PCA)

Continent	Eligible Studies	OR (95% CI)	*P*-Value	Heterogeneity Test	Effect Model
Asian	3	1.64 (0.85–3.16)	0.140	P-H = 0.761, I^2 = 0.0%	Fixed
American	4	4.90 (2.94–8.18)	0.000	P-H = 0.586, I^2 = 0.0%	Fixed
European	10	4.22 (2.84–6.27)	0.000	P-H = 0.318, I^2 = 13.5%	Fixed
Oceanian	1	39.62 (2.38–659.42)	0.010	—	Fixed
Total	18	4.11 (3.12–5.42)	0.000	P-H = 0.148, I^2 = 26.2%	Fixed

CI = confidence interval, OR = odds ratio, PCA = parietal cell antibody, T1DM = type 1 diabetes mellitus.

resulting meta-analysis included a total of 3,584 T1DM patients and 2,650 non-T1DM controls. The associated characteristics of the 18 studies are summarized in Table 1.

Results of the Meta-Analysis

Results regarding the association between PCA positivity and T1DM were obtained by a combined analysis of the raw data from the 18 included studies. A comparison of the PCA positivity rates between T1DM and control populations showed an increased prevalence in T1DM populations than in control populations (OR = 4.11, 95% CI = 3.12–5.42). Forest plots comparing PCA-positive rates between the T1DM and control populations are shown in Figure 2.

Subgroup analyses for Asian, American, European, and Oceanian populations revealed that the PCA-positive rate among T1DM populations was higher than that of control populations in the American, European, and Oceanian subgroups (OR = 4.90, 95% CI = 2.94–8.18; OR = 4.22, 95% CI = 2.84–6.27; OR = 39.62, 95% CI = 2.38–659.42, respectively), whereas no such trend was found in the Asian subgroup (OR = 1.64, 95% CI = 0.85–3.16). The results are presented in Table 2.

Sensitivity Analysis

To assess whether any individual study had a disproportionate influence on the results of the overall meta-analysis, ORs were calculated after the successive exclusion of each study. All ORs from this analysis fell within the 95% CI of the overall meta-analysis, indicating that no individual study imparted a strong influence on the results of the overall meta-analysis (Fig. 3). This finding suggested that our statistical results were relatively stable and reliable.

Publication Bias

To investigate whether a potential publication bias existed in the included studies, Begg testing was performed on a generated funnel plot. The relative symmetry of the point distribution in funnel plot indicated that no significant publication bias was present (Fig. 4). Similarly, the results of Begg test provided no evidence for any publication bias in the meta-analysis ($Pr > |z| = 0.363$).

DISCUSSION

PCA is a biomarker of autoimmune gastritis[26] and requires a serum titer greater than the upper limit of the normal reference range for diagnosis. T1DM primarily occurs as a result of autoimmune-mediated pancreatic β-cell destruction.[27] Individuals suffering from an autoimmune disease are generally thought to be at higher risk for other forms of chronic immunity.[28] Moreover, since autoimmune factors are a common feature of both PCA positivity and T1DM, these 2 clinical findings are likely to co-occur in some patients. The potential association between PCA positivity and T1DM deserves special attention because it may help to develop prophylactic and therapeutic strategies.

Although the existence of an association between PCA positivity and T1DM has been evaluated in previous studies, inconsistent conclusions were drawn. In addition, the relatively small sample sizes used in these reports limits their strength and reliability. The meta-analysis performed in the present study using 18 independent case–control studies showed that rate of PCA positivity was significantly higher in T1DM populations when compared with that of control populations. Geographical subgroup analysis also revealed that this finding was consistent among American, European, and Oceanian subgroups, while this trend was not found in Asian populations. Despite the heterogeneity between the included studies, sensitivity analysis indicated that none of the individual studies had a disproportionate influence on the OR value of the overall meta-analysis. Additionally, the stratified analysis according to different geographical factors showed no significant differences. Together, these statistical results further demonstrated the stability and reliability of the conclusions drawn from this meta-analysis.

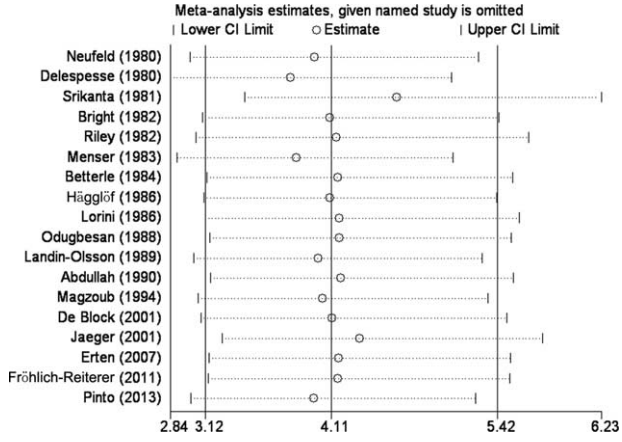

FIGURE 3. Sensitivity analysis of the studies included in the meta-analysis. The figure shows the OR obtained by combined analysis of the remaining studies after the successive exclusion of each study individually. The excluded study is listed on the left, and the corresponding horizontal lines indicate the OR and CI obtained by re-calculation after its exclusion. The CI for the overall meta-analysis of the studies is indicated by two vertical lines.

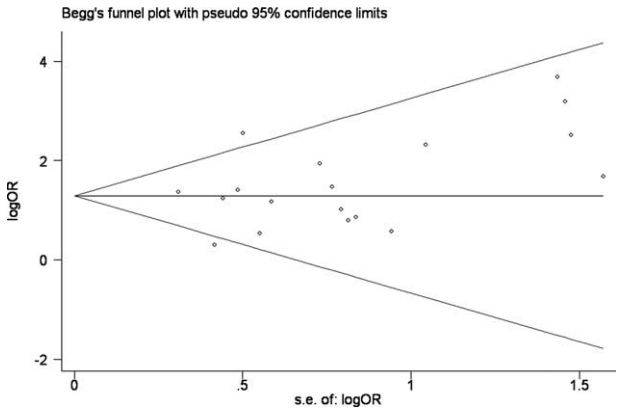

FIGURE 4. Begg's funnel plot for publication bias analysis. Each point represents a separate study.

Although this study is statistically sound, a few limitations need to be noted. First, a number of relevant studies were not included in the meta-analysis owing to the incompleteness of their original data or publication restrictions. Second, the meta-analysis only focuses the association between T1DM and PCA due to a lack of consistent criteria for gastric function evaluation between different countries. Third, in the subgroup analysis, the number of studies examining Oceanian population was relatively small; thus, there was not enough statistical power to evaluate the level of association in this group to the desired accuracy. Additionally, no data were available from African populations. Fourth, given that the included studies differed in their authors, geographical location, and time, the variability of the assays used in each study may have some influence on the overall conclusion. Lastly, the results of the meta-analysis were derived from uncorrected raw data, and a more accurate analysis should be performed if permitted by the data. For example, the meta-analysis could be repeated and control for any influence attributed to population age, environmental factors, and/or lifestyle. Given these limitations, the conclusions of this study should be interpreted with caution.

In conclusion, this meta-analysis indicates that PCA positivity is more prevalent in T1DM populations than non-T1DM control counterparts, which supports that T1DM may increase the risk of PCA positivity.

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