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Review article

Risk of beta-cell autoimmunity presence for progression to type 1 diabetes: A systematic review and meta-analysis

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Background: Islet autoantibodies have been applied for diagnosis of type 1 diabetes mellitus (T1DM) at an asymptomatic stage in individuals with high-risk genotypes. Evidence is insufficient to support a broad application of islet autoantibody screening for T1DM in clinical practice. The aim of this study was to assess the evidence of an association between islet autoantibodies and the development of T1DM in a pooled population of both genetically at-risk individuals and general people without definite genetic background.

Methods: A comprehensive literature search was performed of Pubmed, Web of knowledge and Cochrane library. Prospective cohort studies evaluating the role of islet autoantibodies in prediction of T1DM progression were included. Risk ratios (RRs) were calculated and pooled to arrive at summary estimate. χ^2 and I^2-values were calculated as measures of heterogeneity and subgroup analyses were performed to explore sources of heterogeneity.

Results: Twenty-one studies matched the inclusion criteria. A total of 71,482 nondiabetic participants who were genetically at-risk individuals or from the general population were included, and 926 cases of T1DM were reported during a median follow-up of 7 years. Compared with people free of islet autoantibody, those positive for any type or number of islet autoantibody showed a significantly increased risk of developing T1DM (RR 150.42 [95% CI 87.34, 259.04]). Moreover, the risk for people with multiple islet autoantibodies was 8.59-fold higher than the risk for those with single islet autoantibody, although a moderate heterogeneity existed between studies. The subgroup analysis further revealed that RRs of multiple islet autoantibodies in at-risk population and general population were 7.17 and 13.72, respectively.

Conclusion: This study established the association between the seroconversion of islet autoantibodies and T1DM progression in nondiabetic people with or without definite genetic susceptibility, providing further evidence for an extensive application in routine clinical practice to identify individuals at risk of T1DM.

Contents

1. Introduction 00
2. Methods 00
   2.1. Literature search 00
   2.2. Study selection 00

Abbreviations: T1DM, Type 1 diabetes mellitus; IFA, Immunofluorescence assay; RBA, Radiobinding assay; ICA, Islet cell autoantibody; IAA, Insulin autoantibody; GADA, Glutamic acid decarboxylase autoantibody; IA-2A, Insulinoma-associated protein 2 autoantibodies; RR, Risk ratio; CI, Confidence intervals.

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2.3. Data extraction and quality assessment 00
2.4. Statistical analysis 00
3. Results 00
3.1. Search results 00
3.2. Study characteristics 00
3.3. Islet autoantibody seroconversion and risk of T1DM development 00
3.4. Multiple islet autoantibodies and risk of T1DM development 00
3.5. Different types of single islet autoantibody and risk of T1DM development 00
3.6. Sensitivity analysis 00
3.7. Publication bias 00
4. Discussion 00
4.1. Main findings 00
4.2. Strengths and limitations 00
4.3. Implications for practice and research 00
Contribution statement 00
Funding 00
Duality of interest 00
Supplementary data 00
References 00

1. Introduction

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease that results from T cell mediated destruction of pancreatic beta-cells [1,2]. The incidence of T1DM is increasing globally, with an annual increase of 3% among children [3]. Patients with T1DM are susceptible to present diabetic ketoacidosis (DKA) as the first manifestation of the disease, which is still an important cause of mortality in T1DM [4–6]. Also, clinical signs of T1DM are concomitant with up to 60%–90% loss of functional beta-cells mass [7]. Therefore, diagnosis of patients at a stage as early as possible may be beneficial for preventing acute complications, preserving beta-cell function, and thus improving prognosis.

Islet beta-cell autoimmunity represents an initiation of the disease continuum characterized by the presence of autoantibodies against islet antigens. Islet cell autoantibody (ICA) was the first antibody identified for T1DM more than 40 years ago [8]. Subsequently, antibodies to insulin, glutamic acid decarboxylase (GAD), protein tyrosine phosphatase (IA2 or ICA512), and zinc transporter 8 have been identified [9–12]. Currently, islet autoantibodies are widely used in patients with symptomatic dysglycemia to confirm the diagnosis of T1DM [13]. The number and type of autoantibodies at the onset of T1DM are correlated to the progression of beta-cell destruction [14–16].

Seroconversion to the positive status of islet autoantibodies can be detected years before the development of clinical T1DM [17,18]. Several cohort studies have performed screening of islet autoantibodies in nondiabetic individuals who were first-degree relatives of T1DM probands or carriers of high-risk human leukocyte antigen (HLA) genotypes. The prospective observation was then continued to examine the development of islet autoantibodies and subsequently T1DM [19,20]. These studies demonstrated that the appearance of islet autoantibodies was a sign of beta-cell autoimmunity with an increased risk for further progression to clinical diabetes. Thus, islet autoantibodies were increasingly recommended as biomarkers to diagnose T1DM at an asymptomatic stage for at-risk population [21]. Nevertheless, the screening of first-degree relatives or those with susceptible genotypes may still leave a gap in identifying individuals at risk. Because T1DM tends to be a sporadic disease with few cases have a definite family history. Besides, genetic screening is not applicable in all clinics. Despite there are a few studies carried out in the general population showing an increased risk of T1DM associated with islet autoantibodies [22,23], the evidence is still insufficient to support a broad application of autoantibody screening for T1DM in clinical practice.

The aim of this systematic review and meta-analysis was to assess the evidence of an association between islet autoantibodies and the development of T1DM in a pooled population including both genetically at-risk individuals and general people without definite genetic background.

2. Methods

This study was reported according to the Meta-analysis of Observational Studies in Epidemiology guidelines [24].

2.1. Literature search

PubMed, Web of Knowledge, and Cochrane Library were searched for articles published before December 2016 by using the following terms: (type 1 diabetes) OR (T1D) OR (insulin-dependent diabetes mellitus) OR (IDDM) AND (autoantibodies OR autoantibody) AND prediction. Reference lists of retrieved studies and review articles were also reviewed. The searches were limited to studies on humans, but without language or country restrictions. When necessary, authors of original studies were contacted for additional data.

2.2. Study selection

Two reviewers (QL and JL) working independently reviewed titles and abstracts resulting from the search and then the full text of those that seemed potentially eligible. Studies were included based on the following criteria: (1) they were prospective cohort studies; (2) they were designed to analyze the role of islet autoantibodies including ICA, GADA, IAA, and IA-2A in predicting clinical onset of T1DM; (3) they were conducted on nondiabetic people; (4) at least two of these islet autoantibodies were tested and assessed for the predictive role; (5) studies used T1DM as the outcome; (6) the number of people positive for each of the four islet autoantibodies at entry or during follow-up was reported; and (7) the number of people progressing to T1DM was reported. If the same population was studied in more than one study, the one with the longest duration of follow-up was selected. Studies were excluded if: (1) studies were designed for evaluating assays for the

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