REVIEW ARTICLES

Established and emerging biomarkers for the prediction of type 1 diabetes: a systematic review

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Type 1 diabetes (T1D) is an autoimmune disease with a prolonged and variable latent period that culminates in the destruction of pancreatic β-cells and the development of hyperglycemia. There is a need for diagnostic biomarkers to detect more accurately individuals with prediabetes to expedite targeting for prevention and intervention strategies. To assess the current ability to predict the insidious development of T1D, we conducted a comprehensive systematic review for established and prospective predictive markers of T1D using the Medline, OVID, and EMBASE databases. Resulting citations were screened for relevance to subject. Our research generated five major categories of markers that are either currently used or forthcoming: genetic, autoantibody, risk score quantification, cellular immunity, and β-cell function. The current standard used to assess T1D onset or predisposition focuses on autoimmune pathology and disease-associated autoantibodies. Research studies in general go beyond autoantibody screening and assess genetic predisposition, and quantitate risk of developing disease based on additional factors. However, there are few currently used techniques that assess the root of T1D: β-cell destruction. Thus, novel techniques are discussed with the potential to gauge degrees of β-cell stress and failure via protein, RNA, and DNA analyses. (Translational Research 2014;164:110–121)

Abbreviations: Ab = antibody; BMI = body mass index; CXCL1 = chemokine ligand 1; DPT-1 = Diabetes Prevention Trial 1; DPTRS = DPT-1 risk score; ER = endoplasmic reticulum; GAD = glutamic acid decarboxylase; HLA = human leukocyte antigen; IA2 = insulinoma antigen 2; IAA = insulin autoantibody; ICA = islet cell autoantibody; Ig = immunoglobulin; miRNA = microRNA; NOD = nonobese diabetic; PI:C = proinsulin-to-C-peptide ratio; SNP = single nucleotide polymorphism; T1D = type 1 diabetes; T2D = type 2 diabetes; ZnT8 = zinc transporter 8

The discovery and subsequent development of recombinant human insulin, designer insulin analogs, sophisticated insulin pumps, and sensors as therapies for type 1 diabetes (T1D) represent collectively a remarkable therapeutic achievement. However, insulin is not a cure, and T1D remains an irreversible and progressive disease with life-threatening complications. In light of this, there

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remains a tremendous need for continued research into primary and secondary prevention strategies as well as improvements in treatment modalities.

One major hindrance in the design of effective prevention studies is the lack of precise biological measures to detect individuals early during their course of β-cell decompensation. The latent period in the progression to T1D can be defined as the period during which indolent β-cell immune destruction has started, yet adequate residual insulin-secreting β-cells remain to prevent overt hyperglycemia. This period is clinically silent and characterized by β-cell stress, β-cell destruction, insulitis, and autoimmunity.[1,2] During the preclinical stage of progression to T1D, there is an associated decrease in β-cell function as measured by β-cell glucose sensitivity during oral glucose tolerance testing.[3] The length of this "prediabetic" period is unpredictable, sometimes lasting for just a few months and sometimes spanning many years.[4]

Before the implementation of prevention modalities, especially those that have significant risks, biomarkers and diagnostic tests that can indicate accurately the impending development and progression of T1D need to be established. These tests may also shed light on novel mechanisms leading to the development of T1D. Risk scores have been developed to determine which antibody (Ab)-positive relatives of persons with T1D are most likely to develop T1D during the subsequent 5 years, yet the positive predictive power of these scores before the development of dysglycemia remains insufficient to provide a precise prognosis for a given individual.[5] Yet, it is during this time that immunomodulatory therapies targeted to prevent irreversible loss of β-cells may be most efficacious. Clinical intervention trials have been most successful in individuals with greater residual insulin production and those with the least time since disease onset.[6-8]

This systematic review aims to highlight established and emerging biomarkers in the detection of incipient T1D. Using a systematic literature review, we identified an array of available or emerging biomarkers to detect β-cell autoimmunity or loss of β-cell mass. These include genetic markers, autoantibodies, cellular immunity markers, risk score quantification techniques, and β-cell stress markers (Fig 1, A).

REVIEW METHODS

We searched Medline, OVID, and EMBASE for English-language articles published between January 2003 and March 2013. We used the following phrases: predictive type 1 diabetes markers, detection of β-cell death, biomarkers in type 1 diabetes, and immune autoantibody markers type 1 diabetes. Two reviewers conducted these searches and results were combined. Titles and abstracts of articles were screened initially to identify those most relevant to the topic area of biomarkers predictive of T1D. Articles were retrieved and then screened secondarily based on topic, information relevance, and redundancy of material with other identified resources.

This review conforms with relevant ethical guidelines pertaining to the use of humans and animals in research.

REVIEW RESULTS

Our initial search yielded 317 citations. Of these, 72 citations were identified that referred to markers in T1D. Nineteen articles were identified as relevant for the purposes of this review. Five additional articles were identified for this review using the references of articles found in the secondary screen (Fig 1, B). Table I provides a list of the articles covered in this review and the category of biomarkers the article covered.

DISCUSSION

Genetic markers in the prediction of T1D. T1D usually arises in individuals who have both a genetic susceptibility and subsequent exposure to elusive environmental factors. Although only 10% of individuals with T1D have a positive family history, this genetic predisposition puts first-degree relatives at a 20-fold increased risk of disease.[9-11] Therefore, further refinement of genetic markers that predict susceptibility to or protection against disease may assist in identifying those individuals with the greatest lifetime risk, and may allow therapies to be targeted to those already in the latent period of T1D development.

Human leukocyte antigen (HLA) genes and non-HLA genes play roles in the genesis of T1D. HLA corresponds to the major histocompatibility complex genes in humans. HLA genes are responsible for cellular immune responses and play a key role in autoimmunity.[12] Certain HLA-DR and HLA-DQ genetic polymorphisms (in particular, HLA-DR3 and DR4 at the DRB1 locus) are well known to be associated with increased T1D risk.[13] Three specific HLA polymorphisms confer the greatest risk for developing T1D (Table II[14]). The greatest predisposition occurs with commonly abbreviated short serology notation DR3/DR4. Children heterozygous for the high-risk DR3/DR4 genotype have a 1 in 20 chance of developing T1D by the age of 15 years.[14] Conversely, HLA-DR2 is associated with protection from T1D development and is linked to the most common DR-DQ haplotype in Caucasians.

More than 40 non-HLA genes are also known to contribute to the risk of T1D, although with much