Lessons from Type 1 Diabetes for Understanding Natural History and Prevention of Autoimmune Disease

Kimber Simmons, MD, Aaron W. Michels, MD*

KEYWORDS

• Type 1 diabetes • Autoimmunity • Autoantibodies • Prevention • Immune therapies

KEY POINTS

- Type 1 diabetes is a chronic progressive autoimmune disorder with a preclinical phase of disease before clinical onset.
- Type 1 diabetes can be predicted based on the measurement of antibodies directed against islet antigens.
- Large prospective randomized double-blinded placebo-controlled secondary prevention trials for Type 1 diabetes have been completed.
- As rheumatoid arthritis and other rheumatic diseases have a defined preclinical stage of disease, the lessons learned from diabetes prevention efforts can be applied to rheumatic diseases.

INTRODUCTION

Type 1 diabetes mellitus (T1D), the immune-mediated form of diabetes requiring insulin treatment, is a prevalent chronic autoimmune disease affecting both children and adults.[1–3] The incidence of T1D is increasing dramatically, doubling in the past 20 years. The vast majority of T1D cases result from autoimmune-mediated, nonreversible destruction of insulin-producing beta cells within the pancreatic islets. Progressive beta cell destruction and decreased endogenous insulin production occur during a silent preclinical phase in which blood glucose levels remain normal. During

The authors have no conflicts of interest relevant to this article.
Department of Pediatrics, Barbara Davis Center for Childhood Diabetes, University of Colorado School of Medicine, 1775 Aurora Court, Aurora, CO 80045, USA
* Corresponding author. Barbara Davis Center for Childhood Diabetes, University of Colorado Denver, Mail Stop A140, 1775 Aurora Court, Aurora, CO 80045.
E-mail address: Aaron.michels@ucdenver.edu

Rheum Dis Clin N Am 40 (2014) 797–811
http://dx.doi.org/10.1016/j.rdc.2014.07.008 **rheumatic.theclinics.com**
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the preclinical phase of disease, autoantibodies directed toward beta cell–specific antigens can be measured in a patient's blood, and measurement of islet autoantibodies has made T1D a predictable disease. Inflammation and T-cell–mediated destruction of islet beta cells result in the development of clinically apparent disease marked by abnormal glucose homeostasis. With the ability to assess diabetes risk and predict disease onset, many large clinical trials aimed at disease prevention have been completed over the past decade. These studies have not completely prevented disease onset but hold promise for identifying an intervention to slow disease progression. This review focuses on the natural history of T1D, with brief sections on clinical diagnosis and treatment, prevention efforts in preclinical T1D, and a final section applying the lessons learned from diabetes prevention to rheumatic diseases.

EPIDEMIOLOGY

Great strides in understanding the natural history and pathogenesis of T1D have occurred in large part from longitudinal studies following children from birth for the development of islet autoantibodies and diabetes development (DAISY in the United States, EURODIAB in Germany, and the Type 1 Diabetes Prediction and Prevention Trial [DIPP] in Finland).[4–7] T1D incidence has also been well defined through these studies. The incidence of T1D varies greatly by geographic location, with an average annual incidence of 2.3% per year. The incidence among Caucasians in the United States is 17.8/100,000 patient years for children younger than 14 years. Unlike most other autoimmune diseases in which female individuals are affected more than male individuals, male and female individuals are equally affected with T1D. The age of diabetes onset has 2 peaks, 1 in children 5 to 7 years of age and again in adolescents 10 to 14 years old.[8] Adults also develop T1D, with approximately 25% of new T1D cases diagnosed in individuals older than 18 years of age.[3] With few exceptions, the incidence rate for T1D is rising in all age groups between 2.4% and 3.3% per year, with the largest increase among children who are younger than 5 years.[9]

T1D is still the predominant form of diabetes in youth, even though the incidence of type 2 diabetes (T2D) mellitus is increasing. More than 85% of people with T1D or T2D who are younger than 20 years old have T1D.[10] Although most individuals diagnosed with T1D have no family history of T1D, the development is strongly influenced by genetic factors.[11] In the general population, there is a 1 in 300 lifetime risk for developing T1D.[12] Individuals with a first-degree relative with T1D have a 1 in 7 to 1 in 30 lifetime risk of developing the disease depending on the affected relative. Children of mothers with T1D carry an approximately 3% lifetime risk of developing T1D, whereas the risk increases to approximately 5% for a father with diabetes.[11] A recent analysis of monozygotic twins who were initially discordant for T1D showed that by 60 years of age, persistent autoantibody positivity, T1D, or both had occurred in 78% of these individuals.[13]

RISK FACTORS

Genes

T1D is clearly a polygenic disorder, as evidenced by genome-wide association studies, which have identified more than 40 genetic polymorphisms that confer susceptibility to T1D development.[14,15] The HLA antigen class II region on chromosome 6 confers greater than 50% of the genetic susceptibility to T1D.[12] Specific major histocompatibility complex class II alleles can confer both risk and dominant protection. Individuals having a haplotype containing DR4 and DQ8, which are in close linkage disequilibrium, have the highest risk for disease development. Approximately 60% of all T1D patients have this haplotype, whereas 90% of patients have either or both

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