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Lessons from type 1 diabetes for understanding natural history and prevention of autoimmune disease

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Abstract

Type 1 diabetes (T1D) is a chronic autoimmune disorder resulting from immune mediated destruction of insulin producing beta cells within the pancreatic islets. The natural history of T1D is well defined with distinct stages in disease development. Genetics and environmental factors contribute to disease susceptibility, followed by autoimmune targeting of proteins within beta cells. Preclinical T1D is marked by the presence of islet autoantibodies and normal blood glucose levels. Prediction of T1D is now possible as having two or more islet autoantibodies confers a 100% risk of diabetes development; however the time to disease onset varies amongst individuals. Once enough insulin producing beta cells are destroyed, hyperglycemia results, and treatment with insulin is necessary. With the ability to assess risk and predict disease development, large clinical trials to prevent diabetes onset have been completed and are currently underway. This review focuses on the natural history, prediction, and prevention trials in T1D. We will review the lessons learned from these attempts at preventing a chronic autoimmune disease and apply the paradigm from T1D prevention to other autoimmune disorders including rheumatoid arthritis.

Keywords

Type 1 Diabetes; Autoimmunity; Autoantibodies; Prevention; Immune therapies

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 last 20 years. The vast majority of T1D cases result from autoimmune mediated, non-reversible destruction of insulin producing beta cells within the pancreatic islets. Progressive beta cell destruction and

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decreased endogenous insulin production occur during a silent preclinical phase in which blood glucose levels remain normal. During 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 last 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, 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 DIPP in Finland).⁴⁻⁷ T1D incidence has also been well defined through these studies. The incidence of T1D varies greatly by geographical 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 less than 14 years of age. Unlike most other autoimmune diseases in which females are affected more than males, males and females are equally affected with T1D. The age of diabetes onset has two peaks, one in children 5–7 years of age and again in adolescents 10–14 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 2.4–3.3% per year, with the largest increase among children who are less than 5 years old.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 diabetes who are less than 20 years of age have T1D.¹⁰ Although the majority of 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 1/7 to 1/30 lifetime risk of developing the disease depending on the affected relative. Children of mothers with T1D carry a ~3% lifetime risk of developing T1D, while the risk increases to ~5% for a father with diabetes.¹¹ A recent analysis of monozygotic twins that 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 (GWAS), which has identified more than 40 genetic polymorphisms that confer

susceptibility to T1D development.^{14,15} The human leukocyte antigen (HLA) class II region on chromosome 6 confers >50% of the genetic susceptibility to T1D.¹² Specific MHC 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, while 90% of patients have either or both the DR4/DQ8 and DR3/DQ2 haplotypes. Those individuals with a DQ6 allele (DQB1*06:02) are protected from diabetes development with a striking odds ratio of 0.03 for disease development.¹⁶

Besides the HLA class II genes, non-HLA genes also confer genetic risk for T1D. Of the non-HLA genes, the insulin gene (INS), protein tyrosine phosphatase non-receptor type 22 (PTPN22), CTLA4, and IL2RA have the greatest association with T1D development.¹⁷ Similar to the class II genes, the insulin gene polymorphisms confer both risk and protection for T1D. Variable number of tandem repeats (VNTR) 5' of the insulin gene allow for more or less insulin message to be expressed in the thymus. More insulin expressed in the thymus results in central tolerance and increased protection of T1D. On the other hand, less insulin message in the thymus correlates with a lack of negative selection for autoreactive CD4 T cells and risk for T1D development.¹⁸ Many non-HLA genes appear to be markers of generalized autoimmunity as a number are present in other autoimmune disorders. For example, PTPN22 is associated with rheumatoid arthritis (RA), Crohn's Disease, Grave's Disease, and systemic lupus erythematosus.¹⁹ PTPN22 is expressed in lymphocytes and is involved in T cell activation.

Environment

Despite significant research efforts aimed at identifying an environmental trigger that leads to a loss of tolerance and T1D development in genetically susceptible individuals, no clear risk factor has been causally linked to islet autoimmunity (detected by the measurement of serum autoantibodies) or T1D onset. T1D natural history studies indicate that islet autoantibodies can be detected become between 9 months and 2 years of age in genetically high-risk newborns, suggesting that the initiating environmental trigger may occur in utero or early in post-natal life. Many viruses have been proposed to break tolerance, initiate the preclinical phase of T1D, and accelerate the onset of clinical T1D. These include cocksackie virus, cytomegalovirus, and enterovirus with the most recent research focusing on enteroviruses. In the Diabetes Autoimmunity Study in the Young (DAISY) cohort, there was a strong correlation between children who developed autoantibodies and enterovirus in their serum.²⁰

Other hypothesized environmental triggers include the hygiene hypothesis in which a lack of exposure to bacterial pathogens during childhood leads to altered protective immunity and increased risk of autoimmune diseases. The north-south gradient hypothesis postulates that a lack of vitamin A and D early in life triggers the onset of autoimmune disorders such as T1D and multiple sclerosis. Vitamin D is implicated to have immune modulatory and antiinflammatory effects, thereby protecting from disease development. Studies suggest that supplementation with Vitamin D may have a protective effect on T1D development.^{21,22} Another well studied environmental factor is the introduction of cow's milk or gluten early

in life may trigger islet autoimmunity. Two recent studies found that exposing an infant to gluten prior to 3 months of age or after 7 months of age is associated with the development of islet autoantibodies.^{23,24} There is limited evidence suggesting that other environmental factors, including vaccinations, confer any risk for islet autoimmunity or progression to diabetes. Potential environmental triggers that are under further evaluation include delivery via C-section, mothers with pre-eclampsia or advanced maternal age, exposure to nitrosamine compounds, increased body weight, and exposure to rubella virus.

Pathophysiology and Islet Autoantibody Development

Three decades ago, it was hypothesized that T1D is a chronic autoimmune disorder that develops in stages. The model combined genetic, immunologic, and metabolic markers for disease development and still remains relevant today.⁶ The adapted model in figure 1 proposes that in genetically susceptible individuals there is a precipitating event that leads to the development of preclinical disease where there are overt immunologic abnormalities leading to progressive loss of beta cell mass, reduced insulin release, and intermittent dysglycemia. Serum autoantibodies in the preclinical stage of disease development are present years prior to metabolic decompensation. The four islet autoantibodies are directed against insulin (IAA), glutamic decarboxylase (GAD), tyrosine phosphatase-like insulinoma antigen (IA-2), and zinc transporter 8 (ZnT8).²⁵ These autoantibodies are markers of disease while T cell mediated destruction results in beta cell loss. As the disease progresses and there is approximately 10–20% of beta cell mass remaining, a patient will become symptomatic and satisfy clinical criteria for T1D diagnosis. At this time there will be minimal endogenous insulin release and abnormal blood glucose levels.

Multiple antibodies tend to develop simultaneously in an individual, indicating that epitope spreading occurs rapidly. If a single antibody is detected in children, it is most often to insulin. Insulin autoantibody levels directly correlate to T1D progression.²⁶ In adults who develop T1D, GAD and IA-2 tend to be the most common detected antibodies. The risk of developing T1D is strongly correlated with the number of positive antibodies, and individuals with two or more go onto develop T1D with almost 100% certainty.²⁷ Autoantibodies are most useful in predicting disease when they are present at a young age, in high levels, or in individuals with high-risk HLA genotypes. In general islet autoantibodies persist until diagnosis and up to several decades thereafter. It is estimated that 5–10% of all T1D patients are islet autoantibody negative, indicating that other islet autoantigens may exist.²⁸

There are many hypotheses as to how beta cell autoimmunity is initiated following a precipitating event, none of which are proven. One hypothesis is that the inciting event is an environmental determinant that shares amino acid sequence homology with beta cell proteins and through molecular mimicry induces autoimmune destruction of beta cells. Another hypothesis proposes genetic susceptibility may lead to abnormal central tolerance (i.e. specific HLA alleles do not allow for negative selection of islet antigens) followed by an inciting event that causes acute immune activation and targeting of beta cells when there are higher levels of antigen to be presented to T cells. One final proposal is that beta cells become more sensitive to free radical or cytokine-activated inflammation that is present

following a triggering event.²⁹ Recent efforts to study pancreata of T1D organ donors, the network for pancreatic organ donors (nPOD), have shed light on the islets infiltrates of T1D patients.³⁰ In those cases that have mononuclear cell infiltration within the islets (insulinitis), there is a reduction of insulin producing beta cells and an infiltrate consisting of CD8 T cells most frequently along with CD4 T cells, B-lymphocytes and macrophages.³¹

Clinical Features

The classic clinical presentation of T1D consists of a triad of symptoms: polyuria, polydipsia, and weight loss. From the American Diabetes Association (ADA), an individual meets diagnostic criteria for diabetes if they have one of the following: 1) a fasting (8 hours) plasma glucose ≥ 126 mg/dl; 2) a random plasma glucose ≥ 200 mg/d with symptoms of hyperglycemia; 3) a 2 hour plasma glucose after a standard oral glucose tolerance test ≥ 200 mg/dl; 4) a hemoglobin A1C $\geq 6.5\%$. In distinguishing which type of diabetes an individual has, the ADA defines T1D as a disease caused by cellular-mediated autoimmune destruction of pancreatic beta cells; autoantibodies against beta cell antigens (insulin, GAD, IA-2, and ZnT8) are markers of this destruction.³² Measurement of autoantibodies remains the best way to distinguish T1D from other forms of diabetes at this time.

Studies screening genetically at risk individuals for islet autoantibodies, have identified patients early in the disease course (i.e. more remaining beta cell mass). Hemoglobin A1c values rise 1–1.5 years prior to clinically apparent disease indicating that hyperglycemia occurs before acute disease onset.^{33,34} Without an effective treatment to prevent beta cells destruction, all individuals eventually develop hyperglycemia and T1D. After diagnosis, many patients enter a “honeymoon” period in which there is endogenous insulin production, and they require small amounts of exogenous insulin in order to maintain good glycemic control. Unfortunately, the destruction of beta cells continues and all individuals eventually become reliant on exogenous insulin to maintain euglycemia. Although intensive insulin therapy decreases the risk for complications in T1D, macrovascular and microvascular complications are still prevalent. Over time sustained hyperglycemia damages small vessels and leads to nephropathy, retinopathy, and neuropathy. Large vessels also are damaged and cardiovascular events occurring 10 times more often in people with T1D than in age-matched controls.³⁵

Management

The mainstay of treatment for T1D is the subcutaneous administration of insulin. Currently, there are no Food and Drug Administration approved therapies that effectively preserve residual beta cell mass. In large diabetes centers, patients are almost exclusively started on multiple daily injection therapy (MDI) with a long acting insulin analogue to counteract basal glucose release from the liver and a short acting insulin analogue to cover the carbohydrate content of meals and correct for hyperglycemia (i.e., basal-bolus therapy). Many patients go on to use insulin pump therapy that provides continuous subcutaneous insulin infusion (CSII).³⁶ Studies show that CSII has a clear effect on lowering the rate of hypoglycemic events by up to $\sim 70\%$.^{37–39} In order to dose insulin and keep blood glucoses in target range, T1D patients perform self monitoring of their blood glucose with a glucometer

on average 4–6 times daily. Recent advances in technology now provide patients the option of a continuous glucose monitoring system (CGM). With CGM, a subcutaneous sensor is inserted and interstitial blood glucose is continuously measured. A significant amount of research is focused on creating a closed loop system, combining CGM data with algorithms to automatically deliver insulin from an insulin pump, which would function autonomously as an artificial pancreas.⁴⁰

Prevention Trials

With the incidence and disease burden of T1D increasing, international efforts at delaying or preventing diabetes onset have occurred over the last 15 years. Large clinical trial networks have helped define the natural history of T1D, identify those individuals with preclinical disease, and provide infrastructure for coordinating prevention trials. Both primary and secondary prevention efforts in T1D are reviewed below.

Primary Prevention

Primary prevention trials have been conducted in high-risk individuals who have no islet autoantibodies or metabolic abnormalities. These individuals are generally first-degree relatives of T1D patients and have the presence of high-risk HLA genes. These trials involve infants and young children, necessitating minimal risk, and therefore they have been mostly limited to early in life dietary interventions. A clinical trial completed in Finland enrolled 230 high-risk infants, based upon HLA and a first-degree relative with T1D, to receive either a casein hydrosylate formula or a conventional cow's milk formula at the time when breastfeeding was decreased or no longer available within the first 6–8 months of life. Casein hydrosylate contains more processed proteins than cow's milk or traditional infant formula. Islet autoantibodies were measured periodically over 10 years, and the study showed that individuals who received the casein hydrosylate formula had a decreased incidence of developing positive autoantibodies.⁴¹ Based on this data, the Trial to Reduce Incidence of Diabetes in Genetically at Risk (TRIGR) study was initiated. Enrollment at 77 centers in 15 countries was completed in 2006. In this trial, infants with HLA susceptibility and a first degree relative with T1D were randomized to casein hydrosylate or conventional formula at birth and are allowed to breastfeed as often as desired. The main outcomes from this trial include islet autoantibody positivity and clinical development of T1D. Although this trial is still ongoing, an interim analysis suggests that hydrolyzed infant formula may lessen the risk of developing a single islet autoantibody and a trend towards developing two islet autoantibodies ($p=0.07$).⁴² Further follow up is needed to determine if clinical diabetes onset is delayed with this dietary intervention. Another pilot study took place in a similar genetically at risk population, the Finnish Dietary Intervention Trial for the Prevention of Type 1 Diabetes (FINDIA). The study examined the removal of bovine insulin from whey-based hydrolyzed formula and randomized children to one of three intervention groups (1) cow's milk formula, (2) whey-based hydrolyzed formula which contains bovine insulin, or (3) whey-based hydrolyzed formula without bovine insulin. Islet autoantibodies were followed for 3 years and the infants assigned to the whey-based formula without bovine insulin had a lower risk of developing islet autoantibodies.⁴³

A final primary prevention trial underway is the TrialNet Nutritional Intervention to Prevent (NIP) Type 1 Diabetes Pilot Trial which aims to assess the effect of omega-3 fatty acid supplementation on prevention of T1D autoimmunity. Dietary omega-3 fatty acid intake has been shown to reduce the risk of islet autoimmunity in genetically at risk infants when analyzed retrospectively and is believed to have anti-inflammatory properties.⁴⁴ At risk infants were recruited into the NIP study and received docosahexaenoic acid (DHA) or placebo for 6 months. Enrollment is now complete and the study is currently in the follow up phase assessing for islet autoantibody development.

Secondary Prevention

T1D develops in stages and the preclinical period is readily defined by the presence of two or more islet autoantibodies. Many secondary prevention trials that are aimed at delaying or preventing the progression to T1D in individuals with islet autoantibodies have been completed (Table 1). To conduct these large randomized double-blinded placebo-controlled trials, infrastructure in the form of financial support and a clinical trials network has been necessary. The first T1D clinical trials network emerged in the early 1990s as the National Institutes of Health sponsored Diabetes Prevention Trial-Type 1 (DPT-1). DPT-1 became known as TrialNet, and conducts clinical intervention trials focused on delaying/preventing T1D onset and identifying therapies to preserve residual beta cell mass in newly diagnosed T1D patients. TrialNet is an international consortium with 18 clinical centers and an additional 150-affiliated sites.⁴⁵ TrialNet has already completed many studies and provides ongoing support for clinical trials with several prevention trials currently enrolling participants.

Most secondary prevention trials have focused on antigen specific therapies, mainly utilizing preparations of insulin. Antigen specific therapies are believed to enhance the function of regulatory T cells, which traffic to the tissue specific site of the antigen, and potentially protect beta cell mass from immune mediated destruction.⁴⁶ The first clinical trial sponsored through DPT-1 was a randomized, placebo-controlled study aimed at evaluating the effects of insulin in relatives of patients with T1D. At risk individuals identified by HLA susceptibility and the presence of one or more islet autoantibodies, were treated with subcutaneous or oral insulin. To enroll both of these insulin prevention trials, 84,228 individuals were screened for islet cell antibodies and 3,152 (3.7%) were positive when the screening was conducted between the years of 1994 to 2000.⁴⁷ Participants aged 3 to 45 years who already had signs of abnormal glucose metabolism (n=339) were given 0.25 units/kg/day of Ultralente insulin twice daily. They also received a continuous intravenous insulin infusion for four days at the beginning of the study and then annually. The study showed no effect of low-dose insulin on delaying the progression to T1D diagnosis.⁴⁷ Participants in the DPT-1 trial who did not yet have signs of abnormal glucose tolerance were given 7.5 mg/kg of oral insulin daily (n=372). The primary endpoint was diagnosis of diabetes, and an oral glucose tolerance test was completed every 6 months during a 6-year follow up. The study did not show any delay in progression to T1D in the oral insulin group. However, interestingly, a post-hoc analysis showed that in participants with persistently high levels of insulin autoantibody (IAA) (> 80 U/ml), there seemed to be a delay in T1D onset.⁴⁸ Furthermore, after stopping oral insulin, the rate of progression to T1D onset was faster.⁴⁹

Based on these findings, TrialNet is currently recruiting individuals for a larger oral insulin trial to determine if oral insulin can delay the progression to T1D in participants with high IAA levels (NCT00419562).

The Belgian T1D Registry also studied parenteral insulin administration. Participants who were positive for insulin autoantibodies and did not have a diabetes protective HLA haplotype (presence of a DQB1*06:02 allele) were enrolled in a prospective non-randomized study and given two injections of insulin for 36 months (n=50). There was no difference in the development of T1D between the participants who were treated with insulin and those who refused treatment or agreed to observation.⁵⁰

Insulin has also been administered nasally, as opposed to parental and oral administration, in an attempt to delay or prevent diabetes onset. Mucosal administration of antigens can induce a protective immune response with regulatory T cells and it was hypothesized that this may lead to disease prevention.⁵¹ The Intranasal Insulin Trial (INIT-I) was a randomized, double-blinded, crossover pilot study was done in Australia in people who were high risk by HLA and had one or more islet autoantibodies present (n=38). The results indicated that intranasal insulin decreases T cell responsiveness, arguing for a protective effect on the development of T1D.⁵² A larger study, the Intranasal Insulin Trial (INIT-II), is now enrolling individuals to determine if intranasal insulin can delay or prevent the progression to T1D (NCT 00336674). The Type 1 Diabetes Prediction and Prevention Trial (DIPP) in Finland screened infants and siblings of children with T1D for high risk HLA. Participants who were high risk were then followed for autoantibody development. Upon developing two or more autoantibodies, participants (n=264) were eligible for randomization and if randomized to the intranasal insulin arm (n=137), they received 1 units/kg/day of insulin. The trial was stopped early because interim analyses showed no benefit of intranasal insulin in delaying the onset of T1D.⁵³

Nicotinamide (vitamin B6) is a water-soluble vitamin that increases nicotinamide adenine dinucleotide (NAD) which is believed to consequently reduce beta cell inflammation, and has inhibited the development of T1D in animal models of autoimmune diabetes.^{54–56} Initial pilot trials in first-degree relatives of people with T1D and who were positive for 1 or more islet cell antibodies have had conflicting results.^{57–59} In New Zealand school age children were screened for autoantibodies and then treated with nicotinamide in a randomized, non-placebo controlled trial. Children who received nicotinamide supplementation developed T1D at a much lower rate than eligible children who did not participate in the trial.⁶⁰ However, follow up larger clinical trials failed to validate these findings. The European Nicotinamide Diabetes Intervention Trial (ENDIT) was a randomized, placebo-controlled, double-blinded study that enrolled people aged 5–40 years from 15 different countries who had a first degree relative with T1D and one or more islet cell antibodies (n=552). The participants randomized to receive nicotinamide received 1.2 mg/m² for 5 years. There was no difference between the two groups in the development of T1D.⁶¹ The German (Deutsch) Nicotinamide Diabetes Intervention Study (DENIS) was a randomized, placebo-controlled, double-blinded study that enrolled siblings of children with T1D who were aged 3–12 years and had high titers of islet cell autoantibodies. There was no significant difference in the rate of diabetes onset between the two groups.⁶² There have been several pilot studies completed

using other non-autoantigen specific therapies. These therapies include Ketotifen (histamine antagonist), oral Cyclosporine, and Bacille Calmette-Guerin (BCG) injections. Although oral cyclosporine showed a slight delay in the development of T1D, none of these studies showed prevention of development of T1D.^{63–66}

Several trials aimed at modifying the immune system in high-risk individuals are currently underway. CTLA4-Ig (Abatacept) for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At-Risk is a multicenter, randomized, controlled, double-blinded trial currently enrolling first degree relatives of people with T1D aged 6 to 45 years who have developed autoantibodies (NCT 01773707). Participants will receive fourteen infusions of either abatacept or normal saline over one year. Participants will have an oral glucose tolerance test every 6 months and will be monitored for the development of abnormal glucose tolerance. Anti-CD3 mAb (Teplizumab) for Prevention Of Diabetes In Relatives At Risk For Type 1 Diabetes Mellitus is the other TrialNet study, which is enrolling high risk, autoantibody positive relatives of people with T1D who are aged 8 to 45 years. Participants will be monitored for the development of T1D. DIAPREV-IT is an ongoing study in children 4 years of age and older who are positive for GAD and one or more additional autoantibodies (NCT 01122446). Participants will receive a GAD/alum vaccine at enrollment and at 30 days; then follow up for the development of T1D over the ensuing five years.

Although none of the secondary prevention studies have yet been able to delay the progression to T1D diagnosis, these trials have confirmed repeatedly that large scale controlled clinical prevention trials are feasible. Another added benefit of these trials is that close follow-up permits earlier diagnosis of T1D in many individuals. This in turn leads to the decreased incidence of diabetic ketoacidosis at diagnosis and the initiation of insulin therapy while there is still beta cell mass present. Other lessons from these trials are listed in Table 2.

Application to Rheumatic Diseases

T1D has many similarities to other rheumatic diseases, especially rheumatoid arthritis and lupus that have been demonstrated to have preclinical periods marked by autoantibodies in absence of clinically apparent disease (Table 3).^{67,68} Using T1D as an example, large randomized double-blinded placebo-controlled trials for prevention can be undertaken in these rheumatic diseases. For prevention of a chronic autoimmune disorder several key features are necessary:

1. ability to assess preclinical disease risk
2. adequate prevalence of disease
3. infrastructure for clinical trial support
4. clinically well-established and easily administered therapies

For both T1D and in particular RA, both autoimmune diseases are marked by a preclinical phase prior to clinical manifestations of disease. These preclinical stages are characterized by immunologic markers of underlying autoimmunity, islet autoantibodies in T1D and anti-

citrullinated protein antibodies ACPA in RA.^{69,70} Titers of ACPA antibodies can predict risk of the development of clinical RA within three years' time.⁷¹ With biomarkers of preclinical disease and prediction measurements, subjects can now be readily identified for clinical intervention trials for RA prevention. Second, the prevalence of RA in first-degree relatives is similar to that of T1D. The overall prevalence in the general population is estimated to be 1/300 for T1D and 1/100 for RA.⁷² However, when taking into account a first degree relative the prevalence for both diseases is approximately 1/30. These high rates of disease development make for effective screening efforts.

In T1D, the initial Diabetes Prevention Trial (DPT-1) provided infrastructure and a framework for identifying at risk relatives and conducting prevention trials for T1D. The DPT investigators reorganized into Type 1 Diabetes TrialNet, which is funded by the National Institutes of Health, and focuses on screening at risk relatives for islet autoantibodies (TrialNet Natural History Study) and then placing these individuals into clinical intervention trials. At the current time, approximately 25,000 at risk relatives are screened each year for islet autoantibodies through the TrialNet Natural History Study. In RA, there are several established investigational networks similar to TrialNet including Studies on the Etiology of Rheumatoid Arthritis (SERA) and the Rheumatoid Arthritis Investigational Network (RAIN).⁷³ SERA investigators are identifying at risk subjects in the preclinical stage of RA, assessing biomarkers, and laying the foundation for RA prevention trials. Furthermore, there is a growing population of FDR being identified in the preclinical stage of RA development in clinics worldwide. RAIN investigators have focused on investigator-initiated trials to define better treatments for RA and have pioneered the use of medication combinations for treatment.⁷⁴

In addition to assessing disease risk in a prevalent condition and having the appropriate infrastructure in place, a potential therapy that could delay the onset or prevent progression to clinically apparent disease should be available for testing. In T1D, until very recently, most therapies were limited to various formulations of insulin. Insulin is the mainstay of treatment of all patients with T1D and was a natural choice for a preventative agent with hopes that early administration could lead to immune tolerance to anti-insulin autoimmunity. Currently there are no Food and Drug Administration approved immune therapies for the treatment of T1D to preserve residual beta cell function after clinical diagnosis. In RA, there are numerous clinically well-established treatments with immunologic targets that could be considered for use in prevention of disease.⁷⁵ A prevention therapy needs to be safe, easily administered, and affordable as all participants will not have any clinical symptoms of disease. Hydroxychloroquine (plaquenil) fulfills these requirements as it has been in clinical use for decades, orally administered, limited adverse effects, and is not cost prohibitive for treating large numbers of subjects. However, it is our belief that eventually therapies for T1D or RA prevention will need to be tailored to cohorts of individuals based upon genetic and immunologic assessments.

T1D and RA are both prevalent chronic autoimmune disorders with readily identifiable preclinical stages of disease. Prediction of disease onset is possible in both diseases and prevention is now a goal. The lessons learned from T1D prevention efforts can be applied to RA and reduce the disease burden by making RA a preventable disease.

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Key Points

- Type 1 diabetes is a chronic progressive autoimmune disorder with a preclinical phase of disease prior to clinical onset.
- Type 1 diabetes can be predicted based upon 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 defined preclinical stage of disease, the lessons learned from diabetes prevention efforts can be applied to rheumatic diseases.

Figure 1.

Hypothetical stages and loss of beta cells in the development of type 1 diabetes. Genetics and the environment play a central role in initiating the loss of beta cell mass, followed by preclinical disease marked by the presence of islet autoantibodies (insulin, GAD, IA-2, and ZnT8) but normal glucose homeostasis, and finally the development of overt type 1 diabetes marked by the loss of insulin release and hyperglycemia. The model allows for prevention strategies early in the disease course (primary prevention) and during preclinical disease (secondary prevention). Islet autoantibodies are used to define preclinical disease, as the presence of two or more of these antibodies always lead to the development of clinically diagnosed type 1 diabetes.

Table 1

Selected Phase II/III Secondary Prevention trials in T1D

Study	Agent	Number Randomized	Age (years)	Comments
DIAPREV-IT	GAD/Alum	50	4–18	Trial in follow-up phase
* Abatacept	CTLA-4 Ig	currently enrolling	6–45	TrialNet Sponsored
* Teplizumab	Anti-CD3 mAb	currently enrolling	8–45	TrialNet Sponsored
* INIT-II ⁵²	Intranasal Insulin	currently enrolling	4–20	Less frequent dosing than prior studies
* Oral Insulin	Oral Insulin	currently enrolling	3–45	TrialNet Sponsored
Diabetes Prevention Trial – Type 1 Study Group (DPT-1) ^{48,49}	Oral Insulin	372	3–45	Post-hoc analysis shows delay to T1D diagnosis in subset of patients
ENDIT ⁶¹	Nicotinamide	552	3–40	No effect on prevention
Diabetes Prediction & Prevention Trial (DIPP) ⁵³	Intranasal Insulin	224	1–5	No effect on prevention
Diabetes Prevention Trial – Type 1 Study Group (DPT-1) ⁴⁷	Parenteral Insulin	339	4–45	No effect on prevention

* indicates trials currently enrolling at the time of publication

Table 2

Lessons learned from T1D prevention trials.

• It is possible to do large-scale prevention trials as randomized double-blinded placebo-controlled trials.
• The trials have allowed for better understanding of disease natural history, heterogeneity, and biomarker identification.
• The trials validated the prediction and risk assessments in preclinical disease for diabetes development.
• Once the infrastructure for prevention trials is in place, more trials with specific therapies will follow. This is evidenced by the abatacept, teplizumab, intranasal and oral insulin trials that are currently enrolling.

Table 3

Similarities between T1D and RA for disease prevention.

	Type 1 Diabetes	Rheumatoid Arthritis
Prevalence (General Population)	~1/300	~1/100
Infrastructure	TrialNet	SERA RAIN FDRs in clinic
Risk	Islet autoantibodies, HLA	CCP, RF, CRP, others
Therapies	Insulin	hydroxychloroquine methotrexate sulfasalazine leflunomide azathioprine biologics others