Can J Diabetes 38 (2014) 279–284

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Review

Trials in the Prevention of Type 1 Diabetes: Current and Future

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ARTICLE INFO

Article history:
Received 5 March 2014
Received in revised form
4 May 2014
Accepted 5 May 2014

Keywords:
autoimmunity
clinical trials
genetics
immunology
prevention
type 1 diabetes

ABSTRACT

A major thrust in type 1 diabetes research is stopping the destruction of beta cells that leads to type 1 diabetes. Research over the past 30 years has defined genetic factors and evidence of autoimmunity that have led to the development of robust prediction models in those at high risk for type 1 diabetes. The ability to identify those at risk and the development of new agents and of collaborative research networks has led to multiple trials aimed at preventing beta cell loss. Trials at all stages of beta cell loss have been conducted: primary prevention (prior to the development of autoimmunity); secondary prevention (after autoantibodies are found) and tertiary prevention (intervening after diagnosis to maintain remaining beta cells). Studies have shown mixed results; evidence of maintained insulin secretion after the time of diagnosis has been described in a number of studies, and primary and secondary prevention is proving to be elusive. Much has been learned from the increasing number of studies in the field in terms of network creation, study design and choice of intervention that will facilitate new avenues of investigation

Mots clés :
auto-immunité
essais cliniques
génétique
immunologie
prévention
diabète de type 1

RÉSUMÉ

Un des grands axes de la recherche sur le diabète de type 1 est d'empêcher la destruction des cellules bêta qui est responsable du diabète de type 1. Au cours des 30 dernières années, la recherche a déterminé les facteurs génétiques et les données scientifiques sur l'auto-immunité qui ont mené à l'élaboration de modèles de prédiction fiables du diabète de type 1 chez les personnes exposées à un risque élevé de cette maladie. La capacité à déterminer les personnes exposées à ce risque, et le développement de nouveaux agents et de réseaux de recherche en collaboration ont mené à de multiples essais visant la prévention de la perte des cellules bêta. Des essais à toute étape de la perte des cellules bêta ont été réalisés : la prévention primaire (avant le développement de l'auto-immunité); la prévention secondaire (après que les autoanticorps aient été retrouvés); la prévention tertiaire (l'intervention après le diagnostic pour maintenir les cellules bêta restantes). Les études ont montré des résultats partagés; les données sur le maintien de l'insulinosécrétion après le diagnostic ont été décrites dans de nombreuses études, et la prévention primaire ou secondaire s'avère être inconcevable. Le nombre croissant d'études a apporté de nombreuses connaissances en matière de création de réseaux, de plan d'étude et de choix d'intervention qui déboucheront sur de nouvelles avenues de recherche.

Introduction

The number of studies aimed at prevention of beta cell loss prior to or soon after the development of type 1 diabetes has accelerated in recent years. Evidence developed over the past 30 years shows that type 1 diabetes is the result of a chronic autoimmune process that leads to beta cell destruction and insulin dependence. Eisenbarth initially described the main features and stages in the pathogenesis of type 1 diabetes in 1986, and he and colleagues updated this model in 2014 (Figure 1) (1,2).

1. Genetic susceptibility is a critical factor in the initiation of autoimmunity; the majority of risk is found in the HLA class II region, with smaller effects of many other genes (see below).
2. Precipitating events such as exposure to environmental factors are then thought to initiate beta cell destruction. Despite intensive searches for environmental triggers, strongly conclusive evidence for any particular factor remains to be identified.

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1499-2671/$ – see front matter © 2014 Canadian Diabetes Association
http://dx.doi.org/10.1016/j.jcjd.2014.05.004

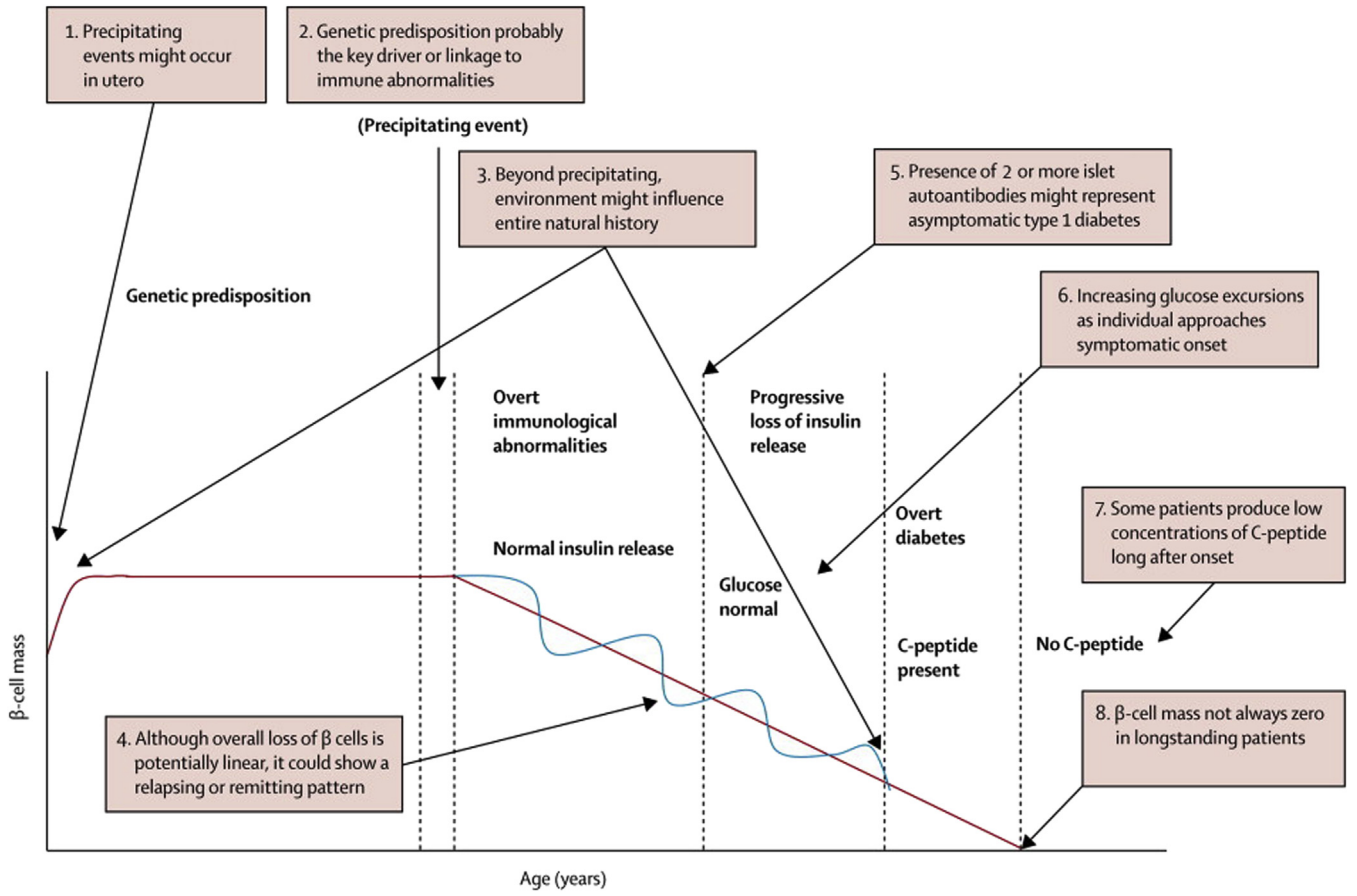

Figure 1. The natural history of type 1 diabetes. *Note:* Reprinted from reference 2, with permission from Elsevier.

3. Autoimmunity directed at beta cells is then found. The autoimmune attack is likely facilitated by immune dysregulation which may be due to genetic susceptibility factors. The immune response is thought to be mediated by T lymphocytes, but the most easily detected finding is the presence of islet autoantibodies.
4. With progressive loss of beta cells, the first metabolic abnormality, reduced insulin secretion in response to a glucose challenge, is found (3). Early glucose abnormalities such as impaired glucose tolerance during an oral glucose tolerance test then occur.
5. Ongoing loss of insulin secretion eventually leads to overt symptoms of diabetes, and the diagnosis is made. In most patients, a honeymoon phase with improved insulin secretion follows. Beta cell loss continues so that many individuals lose all insulin secretion, but recent evidence suggests that small amounts of insulin secretion may remain for many years after diagnosis (4).

Interventions targeting the loss of beta cells at all stages of the process have been carried out. These studies depend on the understanding of the epidemiology, genetics and prediction of type 1 diabetes.

Epidemiology

The incidence of type 1 diabetes varies widely on a global level. The highest reported incidence is in Finland, at 57.6 new cases per 100 000 people per year in those 0 to 14 years of age. Other European countries with high incidence are Sweden, Norway and the United Kingdom, all at >25 new cases per 100 000 people per year. Outside Europe, the countries that have large populations of those of European background with the highest incidence are Canada (25.9 per 100 000 per year) and Australia (22.5 per 100 000 per year). Of the non-European-ancestry countries, Saudi Arabia and Kuwait have the highest incidence, at 31.4 and 22.3, respectively. Most African, Asian and South American countries have lower incidence, at less than 8.5 cases per 100 00 per year (5). The overall incidence of diabetes is rising at approximately 3% per year, particularly in those with lower genetic susceptibility, indicating that the role of susceptibility genes is complex and is changing (6,7).

Genetics of type 1 diabetes

Type 1 diabetes is approximately 15 times more common in family members of those with type 1 diabetes, with a general population prevalence of approximately 0.3% and a family prevalence of approximately 6%, making family members the logical target population for studies of interventions to prevent diabetes (8,9). More than 40 genetic loci have been associated with type 1 diabetes, with the human leukocyte antigen (HLA) region accounting for approximately 50% of the genetic risk (10). The haplotypes most strongly associated with type 1 diabetes include: DRB1*03:01-DQA1*05:01-DQB1*02:01 (DR3) and DRB1 *04:01/02/04/05/08-DQA1*03:01-DQB1*03:02/04 (DR4) (11). The DRB1*15:01-DQA1*01:02-DQB1*06:02 (DR2) haplotype is dominantly and almost completely protective for type 1 diabetes, (11). Of the other associated regions, a region in the regulatory region of the insulin gene, the PTPN22 (protein tyrosine phosphatase