Preventive Interventions for Type 1 Diabetes: History, Appraisal and Prospects

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ABSTRACT

Putative therapeutic interventions with hypothetical clinical benefit in overt type 1 diabetes, or in the pre-clinical condition with evidence of the active autoimmune process, or in people at risk for the disease by virtue of family history with or without genotypic evidence of increased risk, have now been undertaken. These are summarized and appraised in this narrative review, which deals in historical order, the Diabetes Control and Complications Trial (DCCT) and its epidemiological follow-up, the Canadian-European Randomized Trial of Cyclosporin in Recent-Onset Type 1 Diabetes (CERT), the Diabetes Prevention Trial Type 1 (DPT1), the European Nicotinamide Diabetes Intervention Trial and its Canadian component (ENDIT-CANENDIT), and the Trial to Reduce Insulin-Dependent Diabetes in the Genetically at Risk (TRIGR) now in progress in Europe, North America and Australia. It is suggested that the experience justifies continuing exploration of potential clinical interventions, in each stage of the history of autoimmune type 1 diabetes. It is emphasized that this endeavour mandates long-term follow-up, with assessment of outcomes, to be compared with those of contemporary standard of care management of the disease. In discussion, potential novel interventions are considered, and it is concluded that it is reasonable to expect that these studies will eventually yield results providing platforms for the development of preventive or curative treatments for type 1 diabetes.

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RÉSUMÉ

Des interventions thérapeutiques ayant des bienfaits cliniques hypothétiques sur le diabète de type 1 avéré, sur l'état préclinique associé à l'activité du processus auto-immun ou chez des personnes exposées à la maladie en raison d'antécédents familiaux, que des preuves génotypiques d'un risque accru soient présentes ou non, sont maintenant utilisées. Ces interventions sont résumées et évaluées dans cette analyse narrative qui constitue un survol historique de l'essai DCCT (*Diabetes Control and Complications Trial*) et de son suivi épidémiologique, de l'essai CERT (*Canadian-European Randomized Trial of Cyclosporin in Recent-Onset Type 1 Diabetes*), de l'essai DPT1 (*Diabetes Prevention Trial Type 1*), de l'essai ENDIT-CANENDIT (*European Nicotinamide Diabetes Intervention Trial* et son volet canadien) et de l'essai TRIGR (*Trial to Reduce Insulin-Dependent Diabetes in the Genetically at Risk*) maintenant en cours en Europe, en Amérique du Nord et en Australie. On avance que l'expérience justifie la poursuite de l'exploration d'interventions cliniques possibles à chaque stade de l'évolution du diabète auto-immun de type 1. On appuie sur le fait que cette exploration exige un suivi à long terme, au cours duquel on évalue les résultats et les compare à ceux des normes contemporaines en matière de gestion de la maladie. On évalue des interventions novatrices possibles et conclut qu'il est raisonnable de s'attendre à ce que ces études donnent un jour des résultats qui serviront d'assise au développement de traitements préventifs et curatifs du diabète de type 1.

MOTS CLÉS

Diabète auto-immun, complications du diabète, prévention, évolution

KEYWORDS

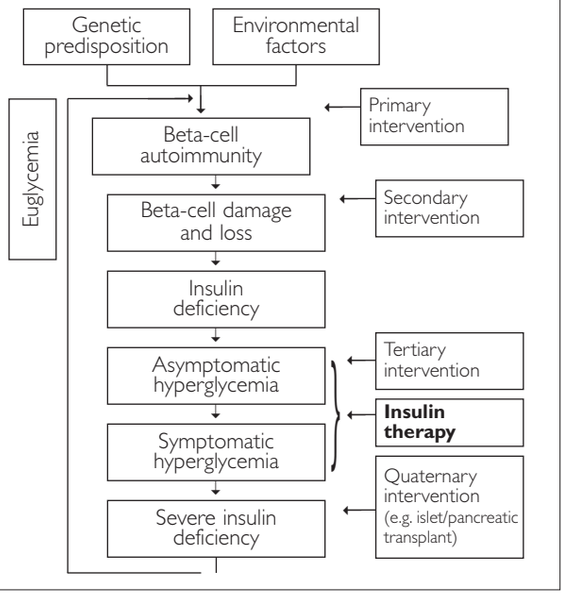
Autoimmune diabetes, diabetes complications, prevention, progression

INTRODUCTION

Evidence accumulating since the discovery of insulin shows that available therapies can ameliorate the morbidity and mortality of type 1 diabetes. This encourages belief that interventions will be found to prevent the onset and further ameliorate the consequences of the disease. Such interventions can be regarded as "primary" if they are effective in the interval preceding detectability of the disease process; as "secondary" if effective in the presence of disease activity in the asymptomatic and euglycemic preclinical phase; or as "tertiary" in overt diabetes. The staging of the disease, with corresponding orders of intervention, is illustrated in Figure 1, which also identifies "quaternary" interventions as those involving replacement of organs or tissues after effective destruction by the disease, including pancreas and islet transplantation, which may lead to recycling through the stages.

Tertiary intervention trials have now yielded results with major clinical impact. Studies of intensive insulin treatment programs have resulted in new clinical guidelines that mandate targeting euglycemia in overt diabetes, while studies of immunomodulatory therapies have also yielded results with important therapeutic implications. Clinical trials of potential secondary preventive treatments for type 1 diabetes have now been reported; the findings refute the hypotheses tested, but carry important clinical implications. Most recently, the first randomized, controlled trial of a primary preventive intervention has demonstrated the feasibility of nutritional intervention in healthy newborns at higher-than-background risk of type 1 diabetes.

Figure 1. Type 1 diabetes: stages of disease and intervention



The backgrounds and histories of potential therapies that have come to assessment in randomized, controlled clinical trials are reviewed here, and synopses of trials that have been completed, or have completed recruitment and intervention, are also given, with outcomes where available. These endeavours have identified models of experimental intervention for each stage of the disease, and are appraised and discussed in historical order.

TERTIARY INTERVENTIONS

Effects of insulin

Clinical experience with insulin yielded the first indication that the process leading to type 1 diabetes might respond to treatment. This perception arose from the recognition of "partial remission" in recent-onset type 1 diabetes, manifested as a decline in the daily insulin dose to a minimum at about 3 months after diagnosis, under clinical conditions (1). Much later, studies of continuing endogenous secretion of insulin, and of "sensitivity" to exogenous insulin, revealed mechanistic features of these remissions (2). It appeared that the reduction of the exogenous insulin dosage follows partial recovery of endogenous insulin secretion, accompanied by improvement in insulin sensitivity. These changes are associated with improvement in glycemic control, reflected in a nadir of blood levels of glycosylated hemoglobin (A1C), but are reversed as relapse follows through intervals ranging from months to years with continuing standard care.

The clinical importance of residual beta-cell function in remission-phase type 1 diabetes was illustrated during the Diabetes Control and Complications Trial (DCCT) of intensive insulin therapy (IIT), which can be regarded as a tertiary preventive intervention. Studies of residual insulin secretion showed that beta-cell function was better preserved in those receiving IIT than in those receiving conventional therapy (3), and this was associated with relative improvement of glycemic control in the IIT group. The DCCT, and the epidemiological follow-up of that trial (Epidemiology of Diabetes Interventions and Complications [EDIC]), demonstrated reductions of microvascular (4) and macrovascular (5) complications by approximately 50% in subjects treated with IIT, both effects strongly correlating with reduced A1C. These impressive benefits were first fully apparent by 2006 and now emphasize the importance of identifying means of achieving normal-range A1C levels (or other indices of glycemia) in type 1 diabetes. This systematic goal is not attainable with treatment according to present guidelines, and this demands attention.