assays for antibodies that indicate and quantify risk for future development of autoimmune type 1 diabetes have been optimized and standardized. The immunohistochemical assay of islet cell antibodies (ICAs) detects antibodies that react with an array of antigens in slices of pancreas islet tissues. More recent biochemical assays detect antibodies that react with specific antigens (e.g., glutamic acid decarboxylase [GAD], insulin, and ICA125/IAA). These biochemical assays may detect the antibodies identified by the ICA assay, suggesting that the immunohistochemical method may become superfluous. The predictive powers of ICAs and biochemical antibodies are well defined in first-degree relatives (FDRs) of people with type 1 diabetes, but they are less well known in the general population, in which the great majority of cases of type 1 diabetes arise. Screening for these antibodies, particularly ICAs, has identified the FDRs who are now participating in trials of secondary intervention therapies that may prevent progression to overt diabetes by arresting or retarding pancreatic β-cell damage that is mediated by the autoimmune process (1).

In addition to secondary intervention trials in nondiabetic people with active autoimmune disease, tertiary intervention trials in people with newly diagnosed type 1 diabetes have been undertaken (2). The rationale for intervention at this stage of disease rests on the evidence of the association between residual β-cell function and relatively good metabolic control during “remission phase” type 1 diabetes, and it depends on acceptance of the enhancement of metabolic control as a surrogate for clinical benefit (3,4). Because of the risks that have been associated with experimental tertiary interventions, and because experience with them has demonstrated a need for long-term therapy to maintain effect, such interventions have not led to clinical applications. However, with the development of immunomodulatory treatments that contain allo- and autoimmune responses in humans with whole-pancreas or isolated islet grafts, and with efforts to develop tolerance-promoting treatments, interest in tertiary interventions in recent-onset type 1 diabetes has been renewed.

In this issue, Decochez et al. (5) report that the levels of ICAs in the sera of people at diagnosis of clinical type 1 diabetes can predict the rate of decline in β-cell function. Multivariate analysis showed that plasma C-peptide levels 2 years later were inversely correlated with ICA levels at entry, with high statistical significance, without regard to co-incident levels or numbers of biochemical antibodies. The subjects of the study consisted of people with clinical type 1 diabetes who were consecutively entered into the Belgian Diabetes Registry as they presented. All of the subjects were <40 years of age at presentation, and their clinical characteristics were typical of patients diagnosed with type 1 diabetes. Diabetes-related antibodies were present in the blood in 93% of the subjects. The assays had excellent performance characteristics, and they were standardized according to established international reference systems. The strengths of this study include its technical quality and the fact that, in spite of its quite modest scale, its subjects can be regarded as an acceptable sample of the population in the catchment area of the registry. The authors conclude that high titers of ICAs identify a group of patients with type 1 diabetes at high risk of rapid loss of residual β-cell function. They suggest that use of ICAs is important in selecting subjects for trials of potential β-cell-preserving interventions. They further suggest that the ICA assay measures clinically relevant antibodies that are not detected in currently available biochemical assays.

In discussion of these conclusions, it is necessary to consider whether they are consistent with other findings. It is also important to consider which outcome measures can provide adequate assessment of the efficacy of interventions in terms of the effects on both the autoimmune disease process and the clinical disease in relation to potential benefit.

Several earlier studies on the relationship between the presence of ICAs at diagnosis and the subsequent course of β-cell function have been reported, along with inconsistencies among the findings that may be related to their relatively small scales and variable methods (5). The largest study of the relationship of diabetes-related autoantibodies to the course of β-cell function came from Finland (6). The data indicated that multiple biochemical antibody positivity was associated with relatively rapid reduction in β-cell function in the 747 subjects in this study. ICAs were also assayed and titrated, but the statistical analysis did not provide assessment of the possible independent risk associated with the presence of ICAs. In tertiary intervention studies with cyclosporin (7), the presence of ICAs (which were not titrated) did not predict the response to immunosuppression in terms of either clinical remission or serial assessments of β-cell function. Further observations in a representative subset of subjects in this trial have a bearing on the mechanistic interpretation of the results of assessing ICAs, GAD antibodies, and antibodies to exogenous insulin in such studies (8). Although cyclosporin inhibited the humoral immune response to pancreas islets in terms of ICA titers, decrements in ICA titers were not useful in monitoring the efficacy of immunosuppression for induction of remission. In studies of the effect of cyclosporin on GAD autoantibodies, the antibody levels did not change in both cyclosporin-treated and placebo-treated groups over a 12-month
The predictive value of diabetes-related antibodies for the rapid loss of β-cell function may be clarified with the accumulation of data in current natural history studies in populations of FDRs of type 1 diabetic subjects, and in control subjects of current and future intervention studies. Concerning the outcome measures to be used as indexes of benefit in intervention studies of overt type 1 diabetes, it is important to recognize that results suggestive of amelioration of the autoimmune disease process or (in terms of insulin dosage or β-cell function) the metabolic disease process are not sufficient for demonstration of clinical benefit. Evidence of clinical benefit from the intervention probably requires, at least, a demonstration of enhanced metabolic control with the implication of reducing future morbidity (2). Therefore, such trials should be planned on this basis. For this purpose, studies should target optimized metabolic control in all subjects. In tertiary intervention trials in overt type 1 diabetes, this approach should involve intensive insulin therapy through an interval within which clinical benefit might be convincingly established only with unavoidable separation of the groups according to maintenance of glycemic control, as indicated by measures such as HbA1c levels.

Assessment of β-cell function under defined conditions and insulin dosage requirements with estimates of insulin sensitivity (4) could constitute secondary outcome measures of importance. These strictures should also apply to preventative studies that might be undertaken in other groups of subjects, including late-onset autoimmune type 1 diabetes, and young subjects in whom overt disease develops during planned primary prevention trials (9).

It is apparent from these considerations that technological advances must be pursued in the area of detecting the risk of progression of β-cell-destructive autoimmune disease. Whereas groups of people with a well-defined risk for developing type 1 diabetes can be identified by screening for biochemical antibody assays alone, assays of ICAs cannot yet be discarded, and attempts to improve these assays may be worthwhile. It is also clear, given the uncertain relationship of the humoral antibodies with disease activity at the β-cell level, that the development of assays for the functions of T-cells in type 1 diabetes must be pursued.

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