(386, 387, 404, 405). Combining HLA and non-HLA polymorphisms in genetic risk scores has improved the selection of individuals at risk of type 1 diabetes into prevention clinical trials.

EMERGING CONSIDERATIONS AND KNOWLEDGE GAPS/ RESEARCH NEEDS

The sequencing of the human genome and the formation of consortia demonstrate advances in the identification of the genetic bases for monogenic type 1 as well as type 2 diabetes. This progress should ultimately result in family counseling, prognostic information, and the selection of optimal treatment (403, 406, 407). The prospect of genotyping is to identify pathophysiological variants and provide personalized medicine.

Autoimmune Markers

DESCRIPTION/INTRODUCTION/TERMINOLOGY

The pathogenesis of type 1 diabetes is strongly associated with several immune abnormalities most prominently islet autoantibodies, but also co-occurrence of other organ-specific autoimmune diseases such as autoimmune thyroid disease and celiac disease. The islet autoantibodies are directed against insulin (IAA), GAD65 (GADA), insulinoma-associated antigen (IA-2A) or zinc transporter ZnT8 (ZnT8A) and predict type 1 diabetes. In children with only 1 persistent islet autoantibody, the risk of diabetes within 10 years is 15% while 2 or more islet autoantibodies predict type 1 diabetes in 70% within 10 years (408, 409). The islet autoantibody biomarkers are useful to predict and classify type 1 diabetes.

USE/RATIONALE

Recommendation: Standardized islet autoantibody tests are recommended for classification of diabetes in adults in whom there is phenotypic overlap between type 1 and type 2 diabetes and uncertainty as to the type of diabetes. GPP

Recommendation: Islet autoantibodies are not recommended for routine diagnosis of diabetes. B (low)

Recommendation: Longitudinal follow-up of subjects with 2 or more islet autoantibodies is recommended to stage diabetes into stage 1: two or more islet autoantibodies, normoglycemia, no symptoms; stage 2: two or more islet autoantibodies, dysglycemia, no symptoms; and stage 3: two or more islet autoantibodies, diabetes and symptoms. GPP

Recommendation: Standardized islet autoantibody tests are recommended in prospective research studies of children at increased genetic risk of type 1 diabetes following HLA typing at birth or in first degree relatives of individuals with type 1 diabetes. B (low)

Although several islet autoantibodies have been detected in individuals with type 1 diabetes, and these have prognostic value in individuals at high risk of type 1 diabetes, routine measurement of islet autoantibodies has limited use outside of clinical studies (410). Currently islet autoantibodies are not used in routine management of diabetes. This section will focus on the pragmatic aspects of clinical laboratory testing for islet autoantibodies.

Diagnosis. The clinical onset of type 1 diabetes is related to the loss of the functional beta-cell mass. In most people with type 1 diabetes, the loss of function is associated with an autoimmune attack (411). This is termed type 1A or immune-mediated diabetes. As further discussed under Analytical Considerations, quantitative assays of specific autoantibodies have generally replaced the islet cell antibody (ICA) test, which is indirect immunofluorescence on frozen sections of human pancreas. Islet autoantibodies comprise autoantibodies to (*a*) islet cell cytoplasm (ICA), (*b*) native insulin, termed IAA (412), (*c*) GADA (413–415), (*d*) islet antigen-2, IA-2A (414) and IA-2βA (also known as phogrin) (416), and (*e*) 3 variants of the ZnT8 transporter (ZnT8A) (417, 418). Autoantibody markers are usually present in 85% to 90% of individuals with type 1 diabetes when fasting hyperglycemia is initially detected (2). Autoimmune destruction of the islet beta cells has multiple genetic predispositions and is thought to be initiated by environmental influences, such as certain enteroviruses. The ensuing autoimmunity may be present for months or years prior to the appearance of 2 or more islet autoantibodies without either dysglycemia or symptoms (Stage 1) and the subsequent development of dysglycemia (Stage 2), followed by the onset of hyperglycemia and symptoms of diabetes (Stage 3) (see Table 9). After years of type 1 diabetes, the autoantibodies tend to fall below detection limits, but GADA usually remains increased. Insulin treatment precludes the analysis of IAA as it takes only about 11 days before insulin antibodies are induced. People with type 1A diabetes have a significantly increased risk of other autoimmune disorders, including celiac disease, Graves disease, thyroiditis, Addison disease, and atrophic gastritis along with pernicious anemia. As many as 1 in 4 females with type 1 diabetes have autoimmune thyroid disease while 1 in 280 individuals develop adrenal autoantibodies and adrenal insufficiency (419). A small subset of people with type