What is the best way to distinguish type 1 and 2 diabetes?

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EVIDENCE-BASED ANSWER

No clinical characteristic or diagnostic test is available to readily distinguish type 1 from type 2 diabetes mellitus. Although C-peptide levels, autoantibodies, and adiponectin-to-leptin ratios show some utility, they do not yet have a standard diagnostic role; research on the pathophysiology of diabetes suggests that the classic type 1 and type 2 distinctions may not be appropriate for all patients1 (strength of recommendation: **C**, based on expert opinion).

CLINICAL COMMENTARY

Focus on attaining optimal diabetes control goals as recommended by the ADA

Not long ago, clinicians were advised to avoid the terms *type 1* and *type 2* diabetes, because they were not very helpful in clinical management of our patients. Instead, it was suggested that we use *insulin-dependent* or *non-insulin-dependent*. The rationale is that for patients with diabetes, there is an absolute insulin deficiency due to premature beta-cell failure in type 1 diabetes, as well as a relative insulin deficiency due to insulin resistance in type 2. In addition, studies also suggest that a majority of patients with type 2 diabetes would require some form of exogenous insulin therapy after a duration of 8 to 10 years of their disease. Therefore, distinguishing between types 1 and 2 is neither clinically helpful nor cost-effective, as suggested by current review of the literature. Instead, clinicians should focus on attaining optimal diabetic control goals as recommended by the practice guidelines of management of diabetes mellitus from the ADA. Furthermore, it was also recognized that one of the hurdles of failure to reach the target goal of HbA_{1C} <7.0, among patients with type 2 diabetes is the delayed use of exogenous insulin therapy. Therefore, it is imperative for clinicians to discuss with each patient with a new diagnosis of diabetes, the natural progression of its disease process and its potential need and benefit of exogenous insulin therapy in the near future.

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Evidence summary

Onset of diabetes in childhood with ketoacidosis and insulin dependency has traditionally been sufficient to diagnose type 1 diabetes, while onset in older, obese patients with primary insulin resistance suggested type 2 diabetes. Unfortunately, features of type 1 and type 2 diabetes may be present in the same patient, making differentiation difficult. No diagnostic studies in the literature were identified that definitively demonstrate how to separate type 1 from type 2 diabetes.

A patient's age may suggest, but does not reliably distinguish, diabetes types. A study of 569 new-onset type 1 and type 2 diabetic children and adolescents showed that older age was only weakly associated with type 2 diagnosis (odds ratio [OR]= 1.4 for each 1-year increment in age; 95% confidence interval [CI], 1.3–1.6).[2] In fact, newly diagnosed 12-year-old children have an equal incidence of type 1 as type 2 diabetes. Likewise, adults with type 2 phenotype (no initial insulin requirement) can present with positive autoantibodies typically found in younger type 1 patients. Older patients who fit this profile have

been classified as type 1.5 diabetes or latent autoimmune disease in adults (LADA).[3]

A history of diabetic ketoacidosis (DKA) also does not reliably distinguish between types 1 and 2. A retrospective chart review gathered data on adults over 18 years of age who were admitted for DKA in a urban US hospital. Many patients with DKA were subsequently diagnosed with type 2 diabetes. Rates of type 2 diabetes in patients with DKA varied by race: 47% of Hispanics, 44% of African Americans, and 17% of Caucasians had type 2 diabetes.[4]

The overlapping presence of autoantibodies in both types of diabetes limits their use (**TABLE**). Autoantibodies do predict an earlier need for insulin. One prevalence study of 101 type 2 adult patients found 20% were positive for glutamic acid decarboxylase autoantibody (GADAb), which was positively associated with insulin dependence at 4 years postdiagnosis (OR=5.8; 95% CI, 1.8–18.9).[5] Eighty percent of patients with autoantibodies required insulin compared with 41% of patients without autoantibodies. Another study in young adults with type 2 or unclassified diabetes from Sweden found 93% of patients who were GADAb+ required insulin at 3 years, compared with 51% who were GADAb– (OR=18.8; 95% CI, 1.8–191).[6]

One motivation to study autoantibody testing is a potential benefit in preserving pancreatic function. Kobayashi proposed treating those with autoantibody-positive diabetes (presumed type 1 or type 1.5) with insulin immediately, while initiating oral medications in those who test negative (presumed type 2 diabetes). This approach lacks significant patient-oriented outcome data, but his small RCT of 55 patients was encouraging. With a 3-year follow-up rate of 89%, early insulin use in GADAb+ patients preserved C-peptide levels and possibly prolonged pancreatic beta cell survival.[7] Insulin dependency, defined as needing insulin for survival, occurred in 47% of controls (who received oral sulfonylureas) and only 13% of patients receiving insulin (number needed to treat [NNT]= 4; P=.043).[7] The theoretical benefit is that if beta cell exhaustion can be delayed, endogenous insulin production could be maintained to assist prevention of damaging postprandial glucose spikes.

TABLE 1

Antibody markers and diabetes type

PREVALENCE OF ANY AUTOANTIBODY MARKER	PERCENT
Newly diagnosed type 1 (Caucasian)	73–90
Newly diagnosed type 1 (African or Asian)	50
Newly diagnosed type 2 (Caucasian)	3–22
Healthy individuals	1–2

Source: Wingfield et al 2004[1] and Maron et al 1996.[3]

Although daily variation in serum insulin levels limits its use, C-peptide levels show more promise. Random C-peptide levels were superior to fasting or glucagon stimulated levels in 1093 patients, who were followed for 3 years to confirm insulin requirements. Using a receiver operating characteristic (ROC) curve, the area under the curve for random C-peptide levels to distinguish diabetes types was 0.98 (95% CI, 0.97–0.99).[8] For patients under the optimal cutoff of 0.5 nmol/L, the positive predictive value was 96% for diagnosing type 1 and the likelihood ratio was 22.5.

Finally, the ratio of adiponectin to leptin hormone may show diagnostic merit. Adipocytes secrete adiponectin which acts as an insulin sensitizer, antiatherogenic and anti-inflammatory agent. Obesity and type 2 phenotype correlate with lower levels of adiponectin, but are associated with higher levels of leptin hormone, another molecule secreted by adipocytes. A recent case-control study of children aged 6 to 21 years analyzed adiponectin and leptin hormone levels in patients with classical type 1 and 2 diabetes, as determined by 2 pediatric endocrinologists; interestingly, 29% of the type 1 patients were autoantibody negative.[9] After plotting a ROC curve, they found the area under the curve was 0.97 (95% CI, 0.93–1.00). At an adiponectin-to-leptin ratio cutoff less than 0.7, they

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found the sensitivity to diagnose type 2 was 88% (95% CI, 64–99%), the specificity was 90% (95% CI, 77–97), and the likelihood ratio for a positive test was 8.8.[9]

Recommendations from others

The National Academy of Clinical Biochemistry and the American Association of Clinical Endocrinologists recommend against routine testing of insulin, C-peptide, autoantibodies and genetic markers.[1,10] Guidelines from the American Diabetes Association admit that many diabetic individuals do not easily fit into a distinct diagnostic category; however, they only provide criteria for the general diagnosis of diabetes, not specific criteria to distinguish type 1 from type 2.[11]

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Sports Medicine, American Medical Society for Sports Medicine, American Orthopedic Society for Sports Medicine, and the American Osteopathic Academy of Sports Medicine, published recommendations for PPEs. They suggested a detailed history (consisting of a 16-point questionnaire incorporating AHA recommendations for cardiovascular screening), limited medical exam, and a detailed musculoskeletal exam evaluating strength, flexibility, and stability of major joints.[7]

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