EDITORIAL (SEE BALASUBRAMANYAM ET AL., P. 2575)

Ketosis-Prone Type 2 Diabetes

Time to revise the classification of diabetes

Diabetic ketoacidosis (DKA) is the most serious hyperglycemic emergency in patients with diabetes. DKA is reported to be responsible for >100,000 hospital admissions per year in the U.S. (1) and is present in 25–40% of children and adolescents with newly diagnosed diabetes (2) and in 4–9% of all hospital discharge summaries among adult patients with diabetes (3,4). DKA has long been considered a key clinical feature of type 1 diabetes, an autoimmune disorder characterized by severe and irreversible insulin deficiency. In recent years, however, an increasing number of ketoacidosis cases without precipitating cause have also been reported in children, adolescents, and adult subjects with type 2 diabetes (5–7). These subjects are usually obese and have a strong family history of diabetes and a low prevalence of autoimmune markers. At presentation, they have impairment of both insulin secretion and insulin action, but aggressive diabetes management results in significant improvement in β-cell function and insulin sensitivity sufficient to allow discontinuation of insulin therapy within a few months of treatment (7–9). Upon discontinuation of insulin, the period of near-normoglycemic remission may last for a few months to several years (10–13). This clinical presentation has been reported primarily in Africans and African Americans (6,7,14–16) and also in other minority ethnic groups (12,17,18). This variant of type 2 diabetes has been referred to in the literature as idiopathic type 1 diabetes, atypical diabetes, Flatbush diabetes, diabetes type 1 (1/2) (somewhere between type 1 and type 2 diabetes), and more recently as ketosis-prone type 2 diabetes (9).

In this issue of *Diabetes Care*, Balasubramayam et al. (19) compared the accuracy of four published classification schemes that have attempted to predict long-term β-cell function and insulin independence in patients with DKA. Each of these classification schemes takes into consideration the clinical features, body weight, insulin secretion, and presence of autoimmune markers of β-cell destruction (7,8,12,20). These investigators analyzed data from 294 consecutive patients with DKA (45% African American, 40% Hispanic, 14% Caucasian, and 1% Asian) who were followed for a mean duration of 31 months (range 12–60 months) after an episode of DKA. β-Cell function was determined within 2 weeks of resolution of the index DKA episode and after 6–12 months. Positive β-cell function was defined by a fasting C-peptide >1.0 ng/ml or a peak C-peptide response >1.5 ng/ml after glucagon stimulation test (1 mg i.v.). β-Cell autoantibodies (glutamic acid decarboxylase [GAD] and IA-2) were measured shortly after presentation. They proposed a new Aβ classification scheme based on the presence or absence of β-cell autoantibodies and the β-cell function to predict whether patients with DKA will have preserved β-cell function and long-term insulin independence. The proposed Aβ classification scheme divided patients with DKA into four groups. Patients with autoimmune disease with absent (A+β−) or preserved (A+β+) β-cell function and those without autoimmune diabetes with absent (A−β−) or preserved (A−β+) β-cell function. This classification was found to have a sensitivity of 99.4%, specificity of 95.9%, positive predictive value of 97.1%, and negative predictive value of 99.2% in predicting whether patients with DKA will have preserved β-cell function and long-term insulin independence. The high predictive value was driven mainly by the presence of β-cell function following the resolution of DKA rather than the presence of autoimmune markers. Patients with negative β-cell function, with or without autoimmune markers, have clinical and biochemical characteristics of type 1 diabetes, i.e., they require exogenous insulin to preserve life (12). Less than 1% of the subjects classified initially as β− showed improvement in β-cell function during follow-up.

Patients with β-cell function despite autoimmune markers (A+β+) represent 7% of newly diagnosed patients with DKA. Some A+β+ patients have long-term preservation of β-cell function, but about half of them follow a clinical course that resembles type 1 diabetes, with progressive deterioration of β-cell function, and require exogenous insulin therapy (12). At presentation, A+β+ subjects have been shown to have lower basal and stimulated insulin secretion than those without antibodies (A−β+) and are more likely to relapse into hyperglycemia (21,22). These subjects could be classified as having latent autoimmune diabetes of the adult (23–26) or slowly progressing type 1 diabetes (27,28). During follow-up, most patients with latent autoimmune diabetes display features of insulin dependence including propensity toward developing ketosis and complete β-cell failure (24,29).

The group of major interest includes those patients without autoimmunity but preserved β-cell function (A−β+). They represent 74% of adult patients with newly diagnosed diabetes presenting with DKA. Despite the presentation with severe metabolic decompensation, most patients showed clinical and biochemical characteristics of type 2 diabetes. Most A−β+ subjects had new-onset diabetes and were obese, middle-aged males with a strong family history of type 2 diabetes. In these patients, β-cell function is substantial when measured within 1–2 weeks of the index DKA and improves further when measured after 6–12 months (12). Several observational and prospective studies have reported that ~70% of such patients achieve near-normoglycemia remission within 10 weeks of follow-up (7,8,10) and that 40% of patients remained free of insulin injections 10 years after their first presentation (8).

The proposed Aβ classification has the disadvantage of requiring repeated measurements of glucagon-stimulated insulin secretion, which is costly and not easily accessible in clinical practice. The evaluation of insulin secretion in patients with diabetes is difficult and is complicated by the effect of hyperglycemia per se on insulin secretion (30,31). Characteristically, first-phase insulin secretory responses to an oral or intravenous glucose tolerance test are lost in patients with established diabetes and plasma glucose >140 mg/dl (32). In contrast, β-cell response to nonglucose secretagogues (e.g., glucagon, arginine, and β-adrenergic agonists) is often preserved in the presence of hyperglycemia (7,33). Among

nonglucose secretagogues, glucagon stimulation is most commonly used because this test is easy to use and provides a rapid and accurate determination of β-cell function in patients with recent episodes of hyperglycemia (8,12,14,34,35). For this test, C-peptide levels are measured before and within 10 min after the intravenous administration of glucagon (1 mg) (6,7,10). In agreement with this report, fasting C-peptide levels >1.0 ng/dl (0.33 nmol/l) and stimulated C-peptide levels >1.5 ng/dl (0.5 nmol/l) shortly after presentation is predictive of long-term remission (6–8,10,12,14, 36,37). Recent evidence suggests that a fasting C-peptide >1.0 ng/dl (0.33 nmol/l) within 2 weeks of presentation correlates well with the glucagon-stimulated C-peptide response in predicting long-term normoglycemic remission in subjects with a history of DKA (6–8,10,12,14,36,37).

The current classification and diagnosis of diabetes was developed by the National Diabetes Data Group (NDDG) of the U.S. in 1979 (38) and the second World Health Organization (WHO) Expert Committee on Diabetes in 1980 (39). Parallel international expert committees working under the sponsorship of the American Diabetes Association (ADA) and the WHO Consultation Committee proposed changes to the NDDG/WHO classification scheme in 1997 (40,41). The revised classification included type 1, with β-cell destruction and prone to ketoacidosis, type 2 that results from insulin resistance and relative (rather than absolute) insulin deficiency, gestational diabetes, and other types where the cause is associated with monogenetic defects in β-cell function, endocrinopathies, disorders of exocrine pancreas, drug- or chemical-induced diabetes, and other rare immune-mediated or genetic syndromes sometimes associated with diabetes. Patients with DKA are classified as having type 1a (autoimmune) or type 1b (idiopathic or nonautoimmune) diabetes. Type 1B or idiopathic diabetes includes patients prone to develop ketoacidosis with varying degrees of insulin deficiency, no evidence of autoimmunity, and in whom "an absolute requirement for insulin replacement therapy in affected patients may come and go" (20). The information presented by Balasubramayam et al. (19) indicates that despite the presentation with ketoacidosis, most patients with "idiopathic" diabetes have type 2 diabetes. In such patients, determination of autoimmune markers and measurement of basal or stimulated C-peptide levels shortly after admission predicts long-term β-cell function and long-term insulin independence.

Patients with ketosis-prone type 2 diabetes were once described as having "atypical diabetes;" however, increasing evidence indicates that this subtype of diabetes accounts for more than half of newly diagnosed black and Hispanic patients with DKA (3,6,17,42,43). These subjects are usually obese, have a strong family history of diabetes, have a low prevalence of autoimmune markers, and lack HLA genetic association (9). Most patients with ketosis-prone diabetes are able to discontinue insulin therapy within a few months of treatment. Thus, a newly diagnosed patient with ketoacidosis, in particular if overweight/obese from a minority ethnic group, is more likely to show clinical and immunologic features of type 2 rather than type 1 diabetes during follow-up. These data indicate that the current ADA/WHO classification should be revised to reclassify patients with idiopathic or type 1B diabetes as having "ketosis-prone type 2 diabetes."

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