COMMENT ON STONE ET AL.

Atypical Diabetes: What Have We Learned and What Does the Future Hold? Diabetes Care 2024;47:770–781

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We thank Stone et al. (1) for their comprehensive review of atypical diabetes, across both pediatric and adult populations.

We have recently treated a number of lean, Caucasian, autoantibody-negative adults who presented with marked hyperglycemia, high HbA_{1c}, and detectable low C-peptide (lower end of the reference range or below) but without ketoacidosis. Their clinical phenotype is most similar to that of individuals with type 1 diabetes, given they have overt hyperglycemia and initially require insulin therapy. After several months, they can successfully discontinue insulin and achieve adequate glycemia with dietary modifications alone. Repeat C-peptide values have increased (intermediate measures within the reference range). For classification purposes, the characteristics of this group seem to be most akin to those of autoantibody-negative (A−) and β-cell function–positive (β+) ketosis-prone diabetes, although the individuals present without ketoacidosis and do not have overweight or obesity. We hypothesize that their more gradual β-cell decline is protective for ketoacidosis at presentation. The current American Diabetes Association (ADA) classification recognizes idiopathic diabetes with fluctuating insulin requirements, but this classification only applies to people of African or Asian ethnicity (2). Some may argue the characteristics of this group are suggestive of atypical type 2 diabetes, yet their C-peptide in the low-normal to intermediate range and lean, Caucasian phenotype suggest otherwise. We propose classifying this minority subgroup as autoantibody-negative type 1 diabetes in remission given their evident transient marked insulinopenia and potential need for recommencement of insulin (3).

The American Diabetes Association guidelines recommend that individuals with unclear diabetes classification undergo repeat C-peptide testing at 3 years and beyond postdiagnosis. While endocrinologists are increasingly appreciative of the pathophysiological processes that cause diabetes, as aptly illustrated in Fig. 1 (1), it can be difficult to relay this information to patients who are often seeking a clear diagnosis. Unclear classification also imparts uncertainty to the treating physician and has significant implications for management. In Australia, for example, eligibility for subsidized medications or continuous glucose monitoring is based on diabetes classification at diagnosis. Further, all autoantibody-negative individuals are excluded from type 1 diabetes trials in the absence of detectable circulating islet autoantibodies, dampening efforts to understand their etiology and investigate novel therapeutic options.

We share the future dream of precision diabetes and suspect those with atypical diabetes will benefit most from additional omics tools to guide personalized diagnostics and therapeutics. We look forward to seeing further outcomes of the Rare and Atypical Diabetes Network (RADIANT).

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