COMMENTS AND RESPONSES

Accuracy and Predictive Value of Classification Schemes for Ketosis-Prone Diabetes

Response to Fernández et al.

Fernández et al. (1) report frequencies of ketosis-prone diabetic (KPD) patients with or without long-term β-cell function that differ markedly from ours (2) and suggest that the Aβ classification scheme is therefore inaccurate.

Ethnicity may affect the prevalence of KPD subtypes; insulin-dependent subtypes may predominate among Caucasians, as we previously reported (3) and as they also show. However, this does not mean that the Aβ scheme's accuracy in predicting long-term β-cell functional status differs across ethnic populations. Apparent differences may be due to other characteristics of the phenotypes selected for analysis. If we select within our heterogeneous cohort only patients with key characteristics similar to those in the cohort of Fernandez et al. (mean age at diagnosis 25.4 years and BMI 21.9 kg/m^2), we obtain a subset whose 12-month functional status is 22% β+ and 78% β−, i.e., frequencies very close to those in the cohort of Fernandez et al., despite comprising a much lower proportion of autoantibody-positive patients and very few Caucasians. Importantly, the Aβ scheme's accuracy in predicting long-term β-cell function remains excellent in this subset (sensitivity 95%, specificity 100%, positive likelihood ratio [LR] ∞, negative LR 0.05, and receiver operating characteristic area under the curve 0.975).

We question their analysis, which concludes that the Aβ scheme is inaccurate. To obtain 20% sensitivity from 8 β+ patients, 1.6 patients would have had β-cell function at 12 months and 6.4 patients would not. To obtain 80% specificity from 32 β− patients, 6.4 patients would have had β-cell function at 12 months and 25.6 patients would not. Fractional patients are impossible.

They report that eight patients were β+ at baseline and eight were β+ at 12 months. Are the two sets of eight patients identical? If so, the Aβ scheme has 100% sensitivity. If not, then of the 8 patients who were β+ at baseline, 6–7 would have lost β-cell function at 12 months, and, of the 32 who were β− at baseline, 6–7 would have regained β-cell function at 12 months. The frequency of β+ to β− conversion is plausible because the majority who were β+ at baseline would have had the A+β+ phenotype, which displays the most dynamic β-cell functional behavior (50% converting from β+ to β− [2,4]). The frequency of β− to β+ conversion appears implausible based on the experience of several KPD investigators. Is it possible that some β+ patients were misclassified as β− because β-cell function was tested too close to the DKA episode, when it was still suppressed because of acidosis or glucotoxicity?

Fernandez et al. suggest that KPD displays "epidemiological. . . heterogeneity." But neither they nor we performed nonbiased epidemiologic surveys; we both selected populations based on hospital admission for DKA, and the phenotypes thus selected vary with regard to the prevalence of autoimmune diabetes and the ethnic makeup (two distinct factors) in our communities. To analyze the epidemiology of KPD, one must establish a denominator of persons at risk for diabetes in the population and a numerator using some predictive, functional marker to identify those at risk for KPD. Autoantibody testing would provide a second level of discrimination. Until then, we can say little about epidemiologic heterogeneity.

ASHOK BALASUBRAMANYAM, MD[1,2]
MARIO MALDONADO, MD[1]

From the [1]Translational Metabolism Unit, Division of Diabetes, Endocrinology, and Metabolism, Baylor College of Medicine, Houston, Texas; and the [2]Endocrine Service, Ben Taub General Hospital, Houston, Texas.

Address correspondence to Ashok Balasubramanyam, MD, Translational Metabolism Unit, Division of Diabetes, Endocrinology, and Metabolism, Baylor College of Medicine, Room 700B, One Baylor Plaza, Houston, TX 77030. E-mail: ashokb@bcm.tmc.edu.

DOI: 10.2337/dc07-1028

References

1. Fernández C, Giménez M, Díaz G, Conget I: Accuracy and predictive value of classification schemes for ketosis-prone diabetes (Letter). *Diabetes Care* 30:e96, 2007. DOI: 10.2337/dc07-0400
2. Balasubramanyam A, Garza G, Rodriguez L, Hampe CS, Gaur L, Lernmark A, Maldonado MR: Accuracy and predictive value of classification schemes for ketosis-prone diabetes. *Diabetes Care* 29:2575–2579, 2006
3. Balasubramanyam A, Zern J, Hyman D, Pavlik V: New profiles of diabetic ketoacidosis: type 1 versus type 2 diabetes and the effect of ethnicity. *Arch Intern Med* 159:317–322, 1999
4. Maldonado M, Hampe CS, Gaur LK, D'Amico S, Iyer D, Hammerle LP, Bolgiano D, Rodriguez L, Rajan A, Lernmark A, Balasubramanyam A: Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and beta-cell functional classification, prospective analysis and clinical outcomes. *J Clin Endocrinol Metab* 88:5090–5098, 2003