RESPONSE TO COMMENT ON SCHWARTZ ET AL.

The Time Is Right for a New Classification System for Diabetes: Rationale and Implications of the β-Cell–Centric Classification Schema. Diabetes Care 2016;39:179–186

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We thank Drs. Kalra and and Baruah for their comments (1) on our article (2) in an effort improve the utility of our proposed β-cell–centric classification.

We agree that "treatment" is more important than "classification." We find it frustrating that governments and insurers often think otherwise, limiting therapies of choice on the basis of labels of diabetes mellitus (DM) that are not optimally useful. Thus a "precision medicine" classification system that identifies specific causes of hyperglycemia and their corresponding therapies augurs for payment coverage parity across the range of glucose-lowering medications for patients with any form of DM.

Although the insulin-to-glucagon ratio (IGR) construct is interesting and could serve as a "marker" to help choose between various therapies in our approach, our construct is broader. It allows for the realization that a given individual may have other mechanisms of β-cell dysfunction (e.g., inflammation/immune dysfunction, environmental causes). This allows for wider consideration of therapies for any individual patient compared with using an IGR approach.

We acknowledge in the text that additional mechanisms of hyperglycemia will likely be identified. A benefit of the "Egregious Eleven" organizing principle is that it can readily accommodate new mediating pathways of hyperglycemia as they emerge.

We respectfully disagree that noninsulin therapy is illogical or categorically unsafe in type 1 DM. The ideal treatment paradigm would be one that uses the least number of agents possible to target the greatest number of mediating pathways of hyperglycemia operative in the given patient. It is prudent, we believe, to address insulin resistance and other mechanisms of hyperglycemia that may exist in these insulin-deficient patients. Moreover, use of noninsulin therapies in the management of type 1 DM is supported by several recent discussions, e.g., the study by Bode and Garg (3).

In the patient with type 2 DM, there are no precise markers of residual β-cell mass, and a low IGR may reflect abnormal β-cell function rather than inadequate mass. We feel justified in preferring noninsulin therapies that have the potential of preserving β-cell function versus the use of exogenous insulin therapy in the non–ketotic-prone patient. Exogenous insulin with its requisite hyperinsulinism results in increased weight with hypertriglyceridemia and cytokines, which are believed to reduce β-cell function, induce other comorbidities (4), and pose undue hypoglycemic risks (5).

As the authors note, we purposely kept sulfonylureas off our list of therapeutic agents. Multiple studies show sulfonylureas have marked reduction in efficacy after 1 year, possibly related to apoptosis (6). Moreover, real-world studies, e.g., the study by Pantalone et al. (7), show marked increased adverse events. It seems altogether possible that this class would not pass current U.S. Food and Drug Administration or European Medicines Agency requirements for cardiovascular safety.

We look forward to further opportunities to discuss our approach in order to arrive at a consensus that provides the best care to all patients with diabetes.

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Pharmaceuticals and AstraZeneca; and has served on the speakers' bureaus of AstraZeneca, Janssen, and Boehringer Ingelheim/Eli Lilly and Co. R.B.A. sits on the advisory board and speakers' bureaus of Eli Lilly and Co., Boehringer Ingelheim, Janssen, and Takeda. No other potential conflicts of interest relevant to this article were reported.

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