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 appreciate the efforts by Schwartz et al. (1) to synthesize current scientific knowledge in a simple and lucid manner and hope that the following suggestions will help improve the utility of their proposed β-cell–centric classification.

It is less important to "classify" diabetes than it is to ensure appropriate treatment for the person with diabetes. This can be planned using a bipolar construct of the insulin-to-glucagon ratio (IGR) rather than a unipolar β-cell–centric model. A high IGR indicates insulin resistance and metabolic syndrome in a setting that can be termed "maladaptive anabolism." A low IGR, however, suggests a state of "catabolism" due to insulin deficiency (2). IGR and its phenotypic correlates can therefore be used to facilitate appropriate choice of therapy.

Changes in the IGR may be due to any of the "Egregious Eleven" factors noted by Schwartz et al. (1). It must be noted here that there is a bidirectional relationship of incretin and glucagon with the β-cell as opposed to the unidirectional arrow shown by the authors (1). Other determinants may include testosterone, vitamin D, and the renin–angiotensin system, which have been listed in the "Dirty Dozen," a list of 12 pathophysiological factors (including the "Ominous Octet") that contribute to the development of diabetes (3). Yet another claimant that can serve as the basis for classification of therapy is AMPK (adenosine monophosphate kinase), the direct or indirect target of many glucose-lowering therapies.

We appreciate the call for "therapeutic parsimony," i.e., using the least number of agents to target the greatest number of hyperglycemia-causing pathways. This cannot be done, however, by sacrificing safety. Encouraging use of noninsulin therapy in type 1 diabetes goes against this principle.

Although use of noninsulin therapy may be appropriate in select patients with type 2 diabetes with basal insulin inadequacy, it should not be promoted as "preferred" therapy in patients with a low IGR. Whether to use insulin as an add-on or a "substitution" for noninsulin agents should be determined by considerations of efficacy and tolerability. If noninsulin drugs are clearly inefficacious, insulin should be added, whereas it should be substituted if noninsulin drugs prove unsafe or are not tolerated.

We agree that "ideal treatment regimens should not be potentially detrimental to the long-term integrity of the β-cells" (1). Modern sulfonylureas, if used judiciously, are safe and effective drugs with low risk of β-cell apoptosis (4), good cardiovascular safety, and no risk of increased mortality (5). It must also be noted that dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 receptor agonists act as insulin secretagogues, albeit indirectly.

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