The Time Is Right for a New Classification System for Diabetes: Rationale and Implications of the β-Cell–Centric Classification Schema

Stanley S. Schwartz,[1] Solomon Epstein,[2] Barbara E. Corkey,[3] Struan F.A. Grant,[4] James R. Gavin III,[5] and Richard B. Aguilar[6]

The current classification system presents challenges to the diagnosis and treatment of patients with diabetes mellitus (DM), in part due to its conflicting and confounding definitions of type 1 DM, type 2 DM, and latent autoimmune diabetes of adults (LADA). The current schema also lacks a foundation that readily incorporates advances in our understanding of the disease and its treatment. For appropriate and coherent therapy, we propose an alternate classification system. The β-cell–centric classification of DM is a new approach that obviates the inherent and unintended confusions of the current system. The β-cell–centric model presupposes that all DM originates from a final common denominator—the abnormal pancreatic β-cell. It recognizes that interactions between genetically predisposed β-cells with a number of factors, including insulin resistance (IR), susceptibility to environmental influences, and immune dysregulation/inflammation, lead to the range of hyperglycemic phenotypes within the spectrum of DM. Individually or in concert, and often self-perpetuating, these factors contribute to β-cell stress, dysfunction, or loss through at least 11 distinct pathways. Available, yet underutilized, treatments provide rational choices for personalized therapies that target the individual mediating pathways of hyperglycemia at work in any given patient, without the risk of drug-related hypoglycemia or weight gain or imposing further burden on the β-cells. This article issues an urgent call for the review of the current DM classification system toward the consensus on a new, more useful system.

A CLASSIFICATION SYSTEM THAT HAS PETERED OUT?

The essential function of a classification system is as a navigation tool that helps direct research, evaluate outcomes, establish guidelines for best practices for prevention and care, and educate on all of the above. Diabetes mellitus (DM) subtypes as currently categorized, however, do not fit into our contemporary understanding of the phenotypes of diabetes (1–6). The inherent challenges of the current system, together with the limited knowledge that existed at the time of the crafting of the current system, yielded definitions for type 1 DM, type 2 DM, and latent autoimmune diabetes in adults (LADA) that are not distinct and are ambiguous and imprecise.

Discovery of the role played by autoimmunity in the pathogenesis of type 1 DM created the assumption that type 1 DM and type 2 DM possess unique etiologies, disease courses, and, consequently, treatment approaches. There exists, however, overlap among even the most "typical" patient cases. Patients presenting with otherwise

[1]Main Line Health, Wynnewood, PA, and University of Pennsylvania, Philadelphia, PA
[2]Division of Endocrinology, Diabetes and Bone Disease, Department of Medicine, Mount Sinai Hospital, New York, NY
[3]Department of Medicine, Boston University School of Medicine, Boston, MA
[4]Division of Human Genetics and Center for Applied Genomics, Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
[5]Emory University School of Medicine, Atlanta, GA
[6]Diabetes Nation, Sisters, OR

Corresponding author: Stanley S. Schwartz, stschwar@gmail.com.

classic insulin resistance (IR)-associated type 2 DM may display hallmarks of type 1 DM. Similarly, obesity-related IR may be observed in patients presenting with "textbook" type 1 DM (7). The late presentation of type 1 DM provides a particular challenge for the current classification system, in which this subtype of DM is generally termed LADA. Leading diabetes organizations have not arrived at a common definition for LADA (5). There has been little consensus as to whether this phenotype constitutes a form of type 2 DM with early or fast destruction of β-cells, a late manifestation of type 1 DM (8), or a distinct entity with its own genetic footprint (5). Indeed, current parameters are inadequate to clearly distinguish any of the subforms of DM (Fig. 1). Discussions and critiques of the current DM classification system are found in the literature (1–6).

The use of IR to define type 2 DM similarly needs consideration. The fact that many obese patients with IR do not develop DM indicates that IR is insufficient to cause type 2 DM without predisposing factors that affect β-cell function (9).

CLASSIFICATION SCHEMA CAN RAISE BARRIERS TO OPTIMAL PATIENT CARE

The current classification schema imposes unintended constraints on individualized medicine. Patients diagnosed with LADA who retain endogenous insulin production may receive "default" insulin

therapy as treatment of choice. This decision is guided largely by the categorization of LADA within type 1 DM, despite the capacity for endogenous insulin production. Treatment options that do not pose the risks of hypoglycemia or weight gain might be both useful and preferable for LADA but are typically not considered beyond use in type 2 DM (10). Incretins and sodium–glucose cotransporter 2 (SGLT-2) inhibitors are examples of newer agents that have demonstrated potential and are being rigorously evaluated in the treatment of type 1 DM and LADA (10–17).
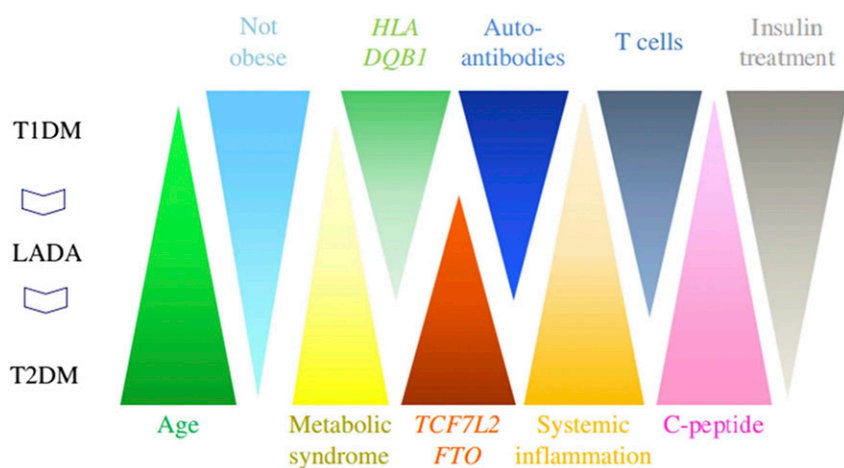
The categorization of LADA within type 1 DM also leads to myopia on the part of insurers. Medications that could be logical choices as adjunctive or alternative therapies to insulin for candidate patients with LADA are not designated as approved processes of care under the current classification system and accordingly are not covered by insurers.

We believe that there is little rationale for limiting choice of therapy solely on the current definitions of type 1 DM, type 2 DM, and LADA. We propose that choice of therapy should be based on the particular mediating pathway(s) of hyperglycemia present in each individual patient, as will be discussed. Only large clinical trials can fully validate the best use of various agents across the spectrum of DM. In the interim, however, an evidence-based practice approach can allow for broader utility in routine care. Metformin and pioglitazone may be safe and efficacious adjunctive

therapies regardless of the current diagnostic category, as may be incretins (11,15,17–23) and SGLT-2 inhibitors (14,24–26). It is reasonable that broader use of existing agents would extend to the management of maturity-onset diabetes of the young (23,27), as well as stress-related and steroid-induced DM.

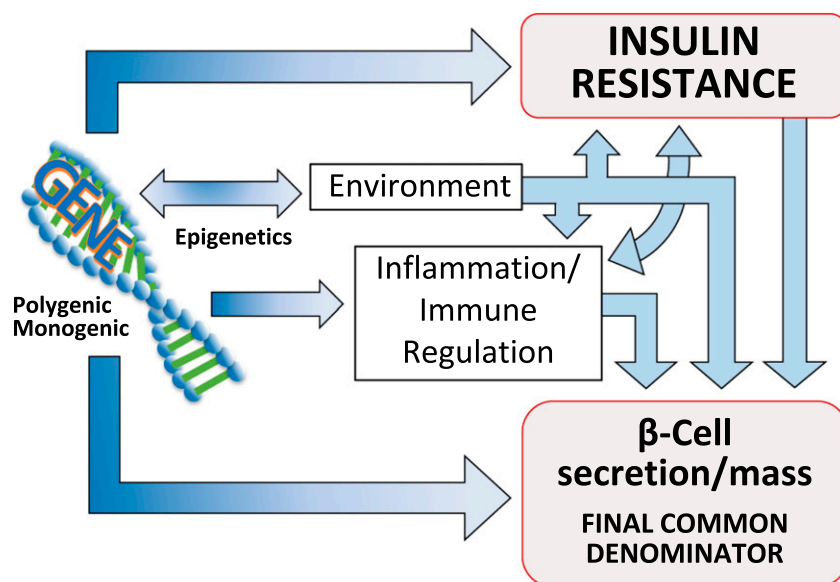## β-CELL–CENTRIC CONSTRUCT: A POTENTIAL MODEL FOR THE CLASSIFICATION OF DM

Given the above discussion, the issue is not "what is LADA" or any clinical presentation of DM under the current system. The issue is the mechanisms and rate of destruction of β-cells at work in all DM. We present a model that provides a more logical approach to classifying DM: the β-cell–centric classification of DM. In this schema, the abnormal β-cell is recognized as the primary defect in DM. The β-cell–centric classification system recognizes the interplay of genetics, IR, environmental factors, and inflammation/immune system on the function and mass of β-cells (Fig. 2). Importantly, this model is universal for the characterization of DM. The β-cell–centric concept can be applied to DM arising in genetically predisposed β-cells, as well as in strongly genetic IR syndromes, such as the Rabson-Mendenhall syndrome (28), which may exhaust nongenetically predisposed β-cells. Finally, the β-cell–centric classification of all DM supports best practices in the management of DM by identifying mediating pathways of hyperglycemia that are operative in each patient and directing treatment to those specific dysfunctions.

The β-Cell: At the Root and Crossroads of Multiple Mediating Pathways of Hyperglycemia

The β-cell–centric construct suggests a more logical rationale to the eight core defects described by the ominous octet (29). Our model recognizes a total of 11 interlocking pathways that contribute to hyperglycemia (Fig. 3A). These mediating pathways of hyperglycemia are induced by the translation of genetic predispositions to IR, susceptibility to environmental influences, or immune dysregulation and inflammation to genetically predisposed, dysfunctional β-cells. The β-cell construct can incorporate newly discovered pathways to

Figure 1—Qualitative illustration of the spectrum of factors associated with different forms of DM, including the variable age at onset, lack of obesity, metabolic syndrome, genetic associations, different forms of immune changes, C-peptide secretion, and the need for insulin therapy. T1DM, type 1 DM; T2DM, type 2 diabetes. Adapted with permission from Leslie et al. (1).

Figure 2—Genetic determinants influence IR (whether centrally or peripherally induced), loss of β-cell function and mass, environmental triggers (such as viruses, endocrine disruptors, food advanced glycosylation end products, gut biome), and immune modulation and inflammation. Singly or, more commonly, in various combinations, these factors converge on the genetically susceptible β-cell, impinge on β-cell function and biology, and orchestrate the shift from normoglycemia to hyperglycemia. As this process takes place regardless of subtype of DM, the dysfunctional β-cell is the final common denominator in all DM.

dysglycemia as these evolve, such as emerging research linking osteocalcin levels to A1C and HOMA of β-cell function status (30).

The mediating pathways of hyperglycemia that contribute to β-cell dysfunction include liver, muscle, and adipose tissue (organs associated with IR) and brain, colon, and immune dysregulation. This damage results in downstream hyperglycemia arising from increased glucagon secretion, as well as a reduction in insulin production, incretin effect, and amylin levels. Even mild hyperglycemia resulting from β-cell dysfunction can upregulate SGLT-2 protein in the kidney, which further contributes to hyperglycemia (31). Hyperglycemia, regardless of its source, leads to glucotoxicity, which further impairs β-cell function. In a given patient, the specific mediating pathways of hyperglycemia at work are variable, though likely to involve multiple pathways (Fig. 3A).

Three additional mediating pathways of hyperglycemia to those of the ominous octet (29) have been identified. Systemic low-grade inflammation is observed in type 2 DM, type 1 DM, and LADA (32,33) and has been shown to accompany the endoplasmic stress imposed by increased metabolic demand for insulin (34). Early studies show

incretins exert anti-inflammatory effects (35,36), which may account in part for their benefit. Inflammation is being clinically evaluated as a therapeutic target. It would be of interest if a recent 1-year trial reporting the ability of a dipeptidyl peptidase 4 inhibitor to delay the progression of disease in LADA patients (17) proved durable and reproducible.

Changes in gut microbiota may contribute to the diabetic state (37–40). Gut microbiota has been shown to be associated with type 1 DM, type 2 DM, and obesity and has been proposed to help explain the observation that only a portion of overweight individuals develop frank DM (38,39). Probiotics and prebiotics may address this mediator of hyperglycemia.

Reductions in amylin production in the diabetic state are a consequence of β-cell dysfunction. Decreased amylin levels lead to accelerated gastric emptying and increased glucose absorption in the small intestine, with corresponding increases in postprandial glucose levels. This pathway of hyperglycemia could theoretically be addressed, at least in part, by the ability of incretins to slow gastric emptying.
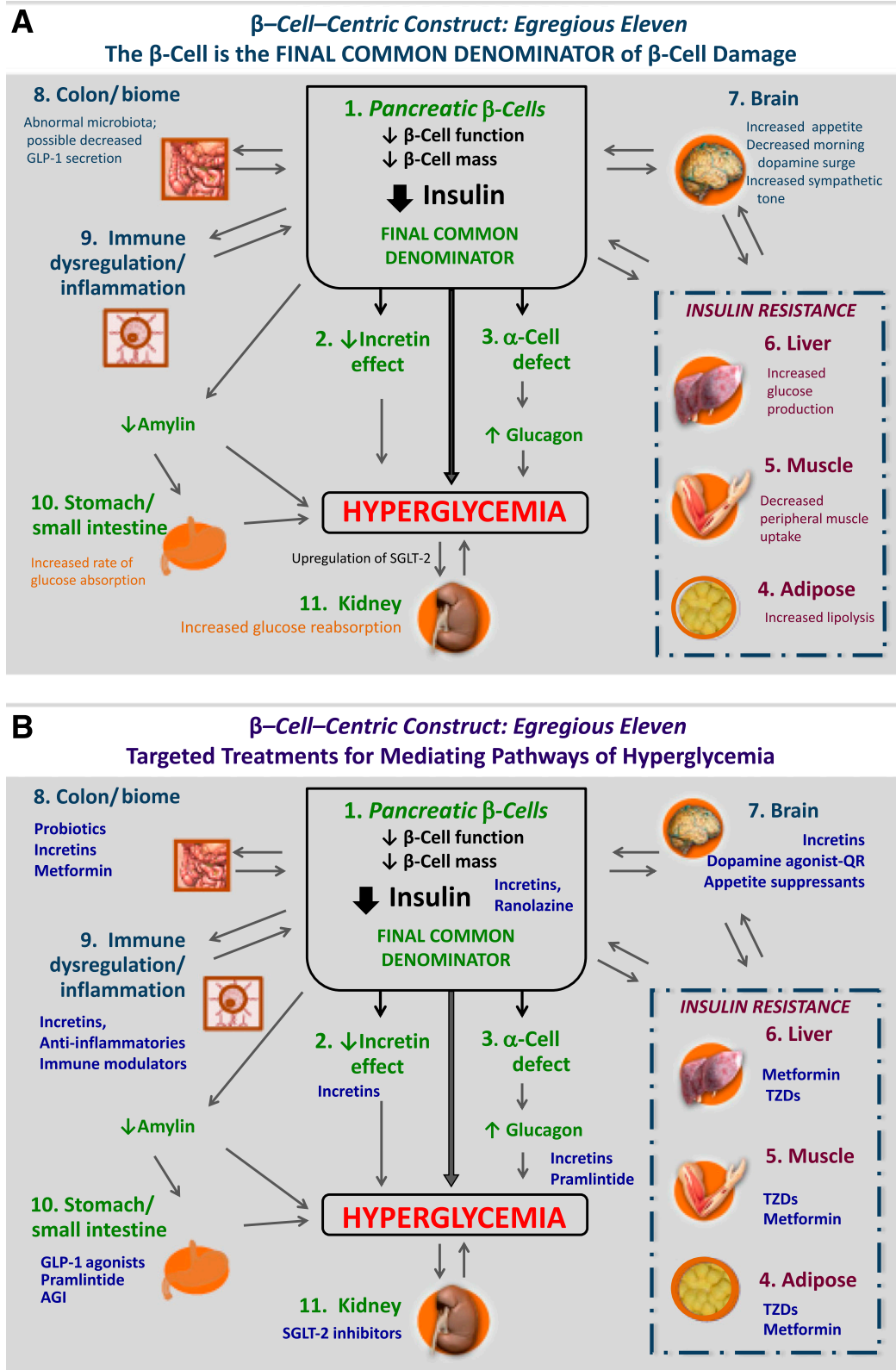
A key premise is that the mediating pathways of hyperglycemia are common

across prediabetes, type 1 DM, type 2 DM, and other currently defined forms of DM. Accordingly, we believe that the current antidiabetes armamentarium has broader applicability across the spectrum of DM than is currently utilized.

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 to use agents that will help patients reach target A1C levels without introducing drug-related hypoglycemia or weight gain. Despite the capacity of insulin therapy to manage glucotoxicity, there is a concern for β-cell damage due to IR that has been exacerbated by exogenous insulin-induced hyperinsulinemia and weight gain (41). Sulfonylureas have been shown to induce apoptosis of β-cells in culture (42,43). In contrast, early data on some newer agents are suggestive of β-cell–sparing abilities. An improvement of early and late β-cell response to glucose load has been reported with dipeptidyl peptidase 4 inhibitor treatment (18,21). Incretins have been shown, in preclinical evaluations, to halt apoptosis, stimulate proliferation of β-cells, increase insulin availability, improve α-cell response to insulin (44–46), and, in animal studies, preserve β-cells (47).

Genetic Influences on the β-Cell

The β-cell–centric model recognizes that the final common denominator of DM is the genetically predisposed, dysfunctional β-cell, which ultimately leads to compromised β-cell function, loss in β-cell mass, or depleted insulin content in the face of IR. These may include monogenic or polygenic defects that predispose to hyperinsulinemia, IR, more recently understood mechanisms such as inflammation by the immune system (48–51), susceptibility to environmental factors (37,51,52), or other physiological factors that increase demand on or otherwise damage β-cells such as elevated circulating lipids (37,53–55) (Fig. 2). As not all carriers of genes associated with DM develop DM, susceptibility likely relies on combinations of genetic abnormalities, environment, and lifestyle factors to exacerbate underlying genetic predispositions. Though research is nascent, implicated environmental factors have

A
β–Cell–Centric Construct: Egregious Eleven
The β-Cell is the FINAL COMMON DENOMINATOR of β-Cell Damage

8. Colon/biome
Abnormal microbiota;
possible decreased
GLP-1 secretion

7. Brain
Increased appetite
Decreased morning
dopamine surge
Increased sympathetic
tone

1. *Pancreatic β-Cells*
↓ β-Cell function
↓ β-Cell mass
Insulin
FINAL COMMON DENOMINATOR

9. Immune dysregulation/ inflammation

2. ↓Incretin effect

3. α-Cell defect

↑ Glucagon

↓Amylin

10. Stomach/ small intestine
Increased rate of
glucose absorption

HYPERGLYCEMIA
Upregulation of SGLT-2

11. Kidney
Increased glucose reabsorption

INSULIN RESISTANCE

6. Liver
Increased glucose production

5. Muscle
Decreased peripheral muscle uptake

4. Adipose
Increased lipolysis

B
β–Cell–Centric Construct: Egregious Eleven
Targeted Treatments for Mediating Pathways of Hyperglycemia

8. Colon/biome
Probiotics
Incretins
Metformin

7. Brain
Incretins
Dopamine agonist-QR
Appetite suppressants

1. *Pancreatic β-Cells*
↓ β-Cell function
↓ β-Cell mass
Insulin
FINAL COMMON DENOMINATOR
Incretins,
Ranolazine

9. Immune dysregulation/ inflammation
Incretins,
Anti-inflammatories
Immune modulators

2. ↓Incretin effect
Incretins

3. α-Cell defect
↑ Glucagon
Incretins
Pramlintide

↓Amylin

10. Stomach/ small intestine
GLP-1 agonists
Pramlintide
AGI

HYPERGLYCEMIA

11. Kidney
SGLT-2 inhibitors

INSULIN RESISTANCE

6. Liver
Metformin
TZDs

5. Muscle
TZDs
Metformin

4. Adipose
TZDs
Metformin

Figure 3—β-Cell–centric construct: the egregious eleven. Dysfunction of the β-cells is the final common denominator in DM. *A*: Eleven currently known mediating pathways of hyperglycemia are shown. Many of these contribute to β-cell dysfunction (liver, muscle, adipose tissue [shown in red to depict additional association with IR], brain, colon/biome, and immune dysregulation/inflammation [shown in blue]), and others result from β-cell dysfunction through downstream effects (reduced insulin, decreased incretin effect, α-cell defect, stomach/small intestine via reduced amylin, and kidney [shown in green]). *B*: Current targeted therapies for each of the current mediating pathways of hyperglycemia. GLP-1, glucagon-like peptide 1; QR, quick release.

included endocrine disruptors (56), food additives (52), abnormal gut biome (38,39,57), and ingested advanced glycation end products (58). There is also evidence that certain environmental factors may epigenetically alter the genotype in reproductive cells, producing inheritable DM factors in future generations (59,60) (Fig. 2).

Clinically evident DM ensues at or after the juncture when the combined gene–environment trigger reaches a tipping point for sufficient β-cell compromise to be expressed as phenotypic hyperglycemia. This fundamental concept applies to all forms of DM, substantiating that the final common denominator in DM is at the level of the β-cell.

In our model, as typical in obesity, IR is a monogenic or, more commonly, a polygenic disorder (59). Additional contributing factors to IR may include inflammation (48–51), changes in the gut microbiota (37–40), and brain-modulated changes in metabolism (51,61,62). Resulting hyperinsulinemia feeds back to the hypothalamus to further exacerbate peripheral IR (61,62). Downstream effects of IR cause detriment to β-cell function by mechanisms that may include inflammatory cytokines, adipocytokines, lipotoxicity, and decreased adiponectin, potentially representing a physiological scenario similar to that induced by hyperinsulinemia (63,64).

β-CELL–CENTRIC SCHEMA AND INDIVIDUALIZED CARE

We propose that the β-cell–centric model is a conceptual framework that could help optimize processes of care for DM. A1C, fasting blood glucose, and postprandial glucose testing remain the basis of DM diagnosis and monitoring. Precision medicine in the treatment of DM could be realized by additional diagnostic testing that could include C-peptide (1), islet cell antibodies or other markers of inflammation (1,65), measures of IR, improved assays for β-cell mass, and markers of environmental damage and by the development of markers for the various mediating pathways of hyperglycemia.

We uphold that there is, and will increasingly be, a place for genotyping in DM standard of care. Pharmacogenomics could help direct patient-level care (66–69) and holds the potential to spur on research through the development of DM gene banks for analyzing genetic distinctions between type 1 DM, LADA, type 2 DM, and maturity-onset diabetes of the young. The cost for genotyping has become increasingly affordable.

Lifestyle modification is the starting point for intervention in prediabetes and DM as is normalization of dyslipidemia, given the links of prolonged lipid exposure with β-cell dysfunction (9,53–55). Our approach advocates intervention early in the process of β-cell dysfunction. It is intuitively obvious that the constellation of mediating pathways of hyperglycemia in frank DM is likely the same as those in prediabetes. Pharmacotherapy for prediabetes should be considered if lifestyle approaches do not produce normoglycemia. Preferential use of agents with proven or strong evidence for β-cell preservation is logical (70).

The optimal strategy is to use the least number of agents to target the greatest number of mediating pathways of hyperglycemia operative in the given patient. It would use regimens that stabilize hyperglycemia across multiple causes, act synergistically to reduce cardiovascular and other risk factors, and preserve β-cells. Figure 3*B* illustrates the mediating pathways of hyperglycemia addressed by various available agents and provides a logic for the selection of complementary modes of action in combination therapy.

Our approach for using combination therapy is consistent with the recommendations within the 2015 American Diabetes Association (71) and 2015 American Association of Clinical Endocrinologists (72) guidelines. We advocate the introduction of combination therapy early in the pharmacological management of the disease. Critically, we avoid stratifying first-, second-, and third-line treatment sequencing. This stratification establishes undue competition between classes, which should more rightly be viewed as complementary options rather than salvage therapy after inevitable treatment failure (19,73).

The ideal treatment regimens should not be potentially detrimental to the long-term integrity of the β-cells. Specifically, sulfonylureas and glinides should be ardently avoided. Any benefits associated with sulfonylureas and glinides (including low cost) are not enduring and are far outweighed by their attendant risks (and associated treatment costs) of hypoglycemia and weight gain, high rate of treatment failure and subsequent enhanced requirements for antihyperglycemic management, potential for β-cell exhaustion (42), increased risk of cardiovascular events (74), and potential for increased risk of mortality (75,76). Fortunately, there are a large number of classes now available that do not pose these risks. Empagliflozin has been recently shown to reduce cardiovascular outcomes and mortality in type 2 DM, while reducing weight and posing a low risk for hypoglycemia (24).

Newer agents present alternatives to insulin therapy, including in patients with "advanced" type 2 DM with residual insulin production. Insulin therapy induces hypoglycemia, weight gain, and a range of adverse consequences of hyperinsulinemia with both short- and long-term outcomes (77–85). Newer antidiabetes classes may be used to delay insulin therapy in candidate patients with endogenous insulin production (19). In patients requiring basal insulin, clinical research on novel combinations of classes, such as pramlintide (86) and incretins (19,22), may reduce or eliminate the need for bolus insulin. Bolus insulin accounts for most of the hypoglycemia seen with basal–bolus insulin therapy (87). When insulin therapy is needed, we suggest it be incorporated as add-on therapy rather than as substitution for noninsulin antidiabetes agents. Outcomes research is needed to fully evaluate various combination therapeutic approaches, as well as the potential of newer agents to address drivers of β-cell dysfunction and loss.

The principles of the β-cell–centric model provide a rationale for adjunctive therapy with noninsulin regimens in patients with type 1 DM (7,12–16). Thiazolidinedione (TZD) therapy in patients with type 1 DM presenting with IR, for example, is appropriate and can be beneficial (17). Clinical trials in type 1 DM show that incretins (20) or SGLT-2 inhibitors (25,88) as adjunctive therapy to exogenous insulin appear to reduce plasma glucose variability.

FURTHER EXPERIMENTAL AND TRANSLATIONAL RESEARCH

This article highlights the need to replot the classification of DM, recognizing the β-cell as the final common denominator

of glucose dysregulation and the mediating pathways of hyperglycemia surrounding the β-cell as the basis for treatment decisions. A β-cell–focused schema can integrate knowledge to date and incorporate new discoveries. It can provide sage advice for preferential use of pharmacological interventions that address the mechanisms of hyperglycemia operative in an individual patient, avoid hypoglycemia and weight gain, and appear to be β-cell sparing. Preferred therapies will be those that affect multiple mediators of hyperglycemia. Novel anti-inflammation agents currently in phase 2 and 3 clinical development should be evaluated for safety and efficacy, and we should further explore suggestions that this approach could effectively treat, reverse, or even prevent DM with an inflammatory component (89).

The β-cell–centric classification schema was envisioned as a stimulus to guide basic research, as well as clinical and translational research. It is hoped to help direct research on the genes involved in DM, the functions that these genes serve, the mechanisms that lead to β-cell damage, the downstream effects of reduced β-cell function, and any novel mechanisms of β-cell pathophysiology. Also needed is research toward improved diagnostic markers for the development of DM.

The β-cell–centric model can be readily retrofitted into the terminology of the existing classification system. However, we submit that an entirely new nomenclature may likely best fulfill the imperative of bringing the classification in line with the known etiology and disease course.

A CALL TO ACTION

For all the above-stated reasons, we urge that the time is right to convene a committee of diabetes community leaders and researchers to reevaluate the current outmoded DM classification system. Members of the American Diabetes Association, American Association of Clinical Endocrinologists, European Association for the Study of Diabetes, International Diabetes Federation, and World Health Organization should come together to address this immense, but vital, task toward delivering state-of-the-art, optimal patient care and directing future research.

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