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REVIEWS

Review

A Unified Pathophysiological Construct of Diabetes and its Complications

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Advances in understanding diabetes mellitus (DM) through basic and clinical research have helped clarify and reunify a disease state fragmented into numerous etiologies and subtypes. It is now understood that a common pathophysiology drives the diabetic state throughout its natural history and across its varied clinical presentations, a pathophysiology involving metabolic insults, oxidative damage, and vicious cycles that aggravate and intensify organ dysfunction and damage. This new understanding of the disease requires that we revisit existing diagnostics and treatment approaches, which were built upon outmoded assumptions. 'The Common Pathophysiologic Origins of Diabetes Mellitus and its Complications Construct' is presented as a more accurate, foundational, and translatable construct of DM that helps make sense of the hitherto ambiguous findings of long-term outcome studies.

Introduction: Redefining a Fragmented Disease

Outmoded diagnostic guidelines and lexicon about DM have arisen from the overlaying of successive research advances. DM was divided into 'type 1 DM', 'type 2 DM', and, subsequently, 'latent autoimmune diabetes of adults (LADA)' for type 1 DM clinical presentation in older patients who did not fit into either category of the first two categories. Early research discoveries described subforms of DM arising from distinct etiologies. A call to action has been issued by numerous workers for a revamping of the diagnostics of DM [1–7] (reviewed in-depth in [1]), and leading diabetes associations concur [8]. The partitioning of complications into **microvascular disease** (see Glossary) and **macrovascular disease** is another example that directly impacts processes of care by implying that these arise through different mechanisms, and, should be managed differently.

Introduced in the February 2016 issue of *Diabetes Care*, our β **Cell-Centric Model** of DM [1] presents a schema that aligns diabetes etiology with the updated body of knowledge. We hope that the construct described herein accomplishes the same for diabetes complications by more accurately characterizing the pathophysiological mechanisms common to both disease causation and diabetes-related complications.

The Pathophysiology of Dysglycemia: A Novel Schema

The β Cell-Centric Model presupposes that all persistent dysglycemia originates from a final common denominator: a damaged or dysfunctional β cell. It is still sometimes believed that one subtype of DM is more privy to genetic influences, while another is more privy to life style. In reality, all arise from the same processes: genetically predisposed β cells that are acted upon by factors including nutrient excess and other environmental influences (including the gut biome),

Trends

All cells implicated in DM and its complications undergo the same metabolic insults and injury (Common origin of DM).

Existing diagnostics and treatment algorithms for subtypes, including type 1 DM, type 2 DM, and latent autoimmune diabetes of adults (LADA), frustrate care.

There is also no functional or therapeutic distinction between 'microvascular' and 'macrovascular' disease, although differences in cardiovascular (CV) effects of various antidiabetes agents are evidenced.

In the clinic, this means that we need only regard a single disease; one that can best be addressed by early, aggressive glucose lowering and by targeting the individual mediating pathways of hyperglycemia operative in any specific patient (β Cell-Centric Model).

Patient risks and predispositions, drug mode of action, and 'intelligently' designed combined regimens are our current best means of reducing adverse outcomes.

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insulin resistance (IR), immune dysregulation and inflammation, comorbidities, and intracellular fuel excess resulting from an insufficiency of insulin or its effects (**glucolipotoxicity**) [1]. A vicious cycle ensues that aggravates and intensifies the dysfunction and damage (Figure 1). This mechanism explains all phenotypes seen across the spectrum of DM, regardless of current categorization.

This model shifts the focus from marginally translatable designations (i.e., type 1 DM, LADA, and type 2 DM) to the mediating pathways of hyperglycemia at work in a given patient (the Egregious Eleven) [1] (Figure 2). Importantly, this approach allows tailored care. Some of the 11 mediating pathways of hyperglycemia are now known to contribute to β cell dysfunction (liver, muscle, adipose tissue, brain, colon/biome, and immune dysregulation/inflammation), while others result from β cell dysfunction through downstream effects (reduced insulin, decreased incretin effect, α cell defects, stomach/small intestine via reduced amylin, and kidney). Most are treatable, whereas others are likely to be treatable in the future. The Egregious Eleven extends the eight established pathways (Figure 2) with recently understood contributors, including colon/biome, and stomach/small intestine. The immune system/inflammation interplays with most systems of the body; organs contributing to hyperglycemia are no exception. In addition to being involved in cross-talk with, and a likely contributor, to IR, chronic inflammation poses a threat to the cardiovascular (CV) and other systems. In β cells, the stress of increased demand for insulin produces the inflammasome, a protein complex that promotes potentially injurious compounds, such as IL-1β. Anti-inflammatory agents are in development as treatments for DM.

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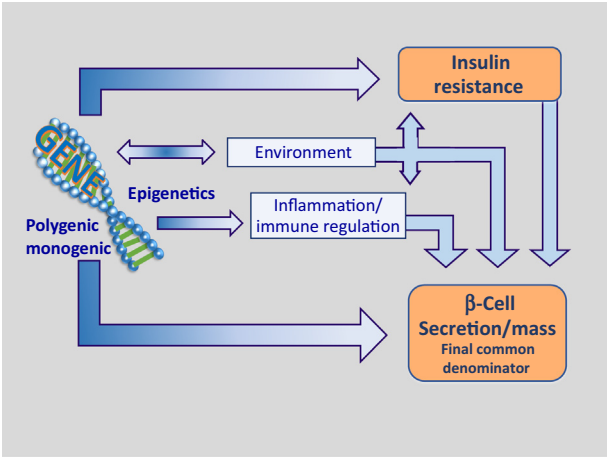

Figure 1. Genetic Determinants Influence Insulin Resistance (IR; i.e., the Inability of Cells to Respond Normally to Insulin, Including Centrally Induced IR, and Peripheral IR) and Possible Contributions from Factors such as Stress Hormones, the Gut Biome, Loss of β-Cell Function and Mass, Environmental Triggers (such as Viruses, Endocrine Disruptors, and Food Advanced Glycosylation Endproducts), and Immune Modulation and Inflammation. Singly or, more commonly, in various combinations, these factors converge on the genetically susceptible β cell, impinge on its function and biology, and orchestrate the shift from normoglycemia to hyperglycemia. Given that this process occurs regardless of the diabetes mellitus (DM) subtype, the dysfunctional β cell is the final common denominator in all DM. Reproduced, with permission, from [1].

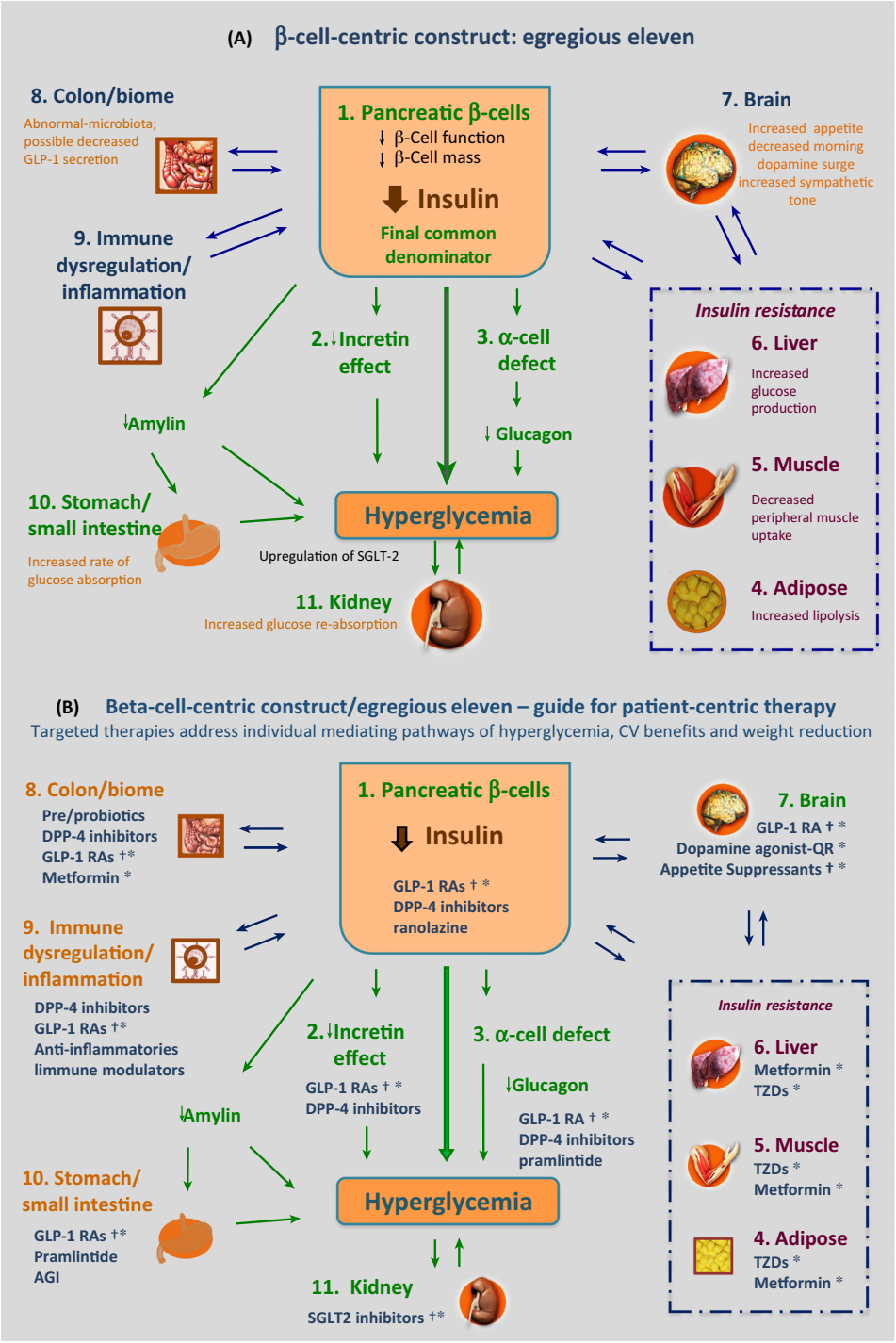

Figure 2. The Time Is Right for a New Classification System for Diabetes: Rationale and Implications of the β-cell–Centric Classification Schema. This schema highlights that, in contrast to current diagnostics that divide diabetes mellitus (DM) into categories including type 1 DM, type 2 DM, maturity-onset diabetes of the young (MODY) and latent autoimmune diabetes of adults (LADA), there is, in fact, a single and core defect in the disease, and this defect resides with the dysfunctional β cell. (A) The β Cell-Centric Model: The Egregious Eleven. Dysfunction of the β cells is the final common denominator in DM. Eleven currently known mediating pathways of hyperglycemia are shown. Many of these contribute to β cell dysfunction [liver, muscle, adipose tissue (shown in maroon to depict an additional association with insulin resistance; IR), brain, colon/biome, and immune dysregulation/inflammation (all shown in blue)], and others result from β cell dysfunction through downstream effects [reduced insulin, decreased incretin effect, α cell defect, stomach/

(See figure legend on the bottom of the next page.)

Glossary

β Cell-Centric Model: a model that describes how all persistent dysglycemia originates from a final common denominator: a damaged or dysfunctional β cell. Genetically predisposed β cells are acted upon by factors including nutrient excess and other environmental influences (including the gut biome), insulin resistance (IR), immune dysregulation and inflammation, comorbidities, and from the resulting insufficiency of insulin or its effect, intracellular fuel excess (glucolipotoxicity).

Common Origins of Diabetes and its Complications Construct: a model that describes a common pathophysiology drives the diabetic state throughout its natural history and across its varied clinical presentations. Through reiterative pathways, all cells implicated in diabetes and diabetes-related complications undergo the same metabolic insults, oxidative damage, and vicious cycles that aggravate and intensify organ dysfunction and damage.

Egregious Eleven: 11 known mediating pathways of hyperglycemia: β cells, incretin effects, α-cell defects, adipose, muscle, liver, brain, colon/biome, immune regulation/inflammation, stomach/small intestine, and kidney (expanded from what was commonly known as the 'Ominous Octet').

Glucolipotoxicity: cumulative dysfunction caused by elevated glucose and fatty acid levels on pancreatic β cell function and survival.

Keen's Model for Diabetes-Related Complications: a model that describes all diabetes-related complications result from the interaction of an abnormal metabolic state engendered by β cell dysfunction with the presence (or absence) of several other factors: genetic susceptibility to damage, environmental factors, and comorbidities.

Macrovascular disease: cardiovascular conditions, such as ischemic heart disease, peripheral vascular disease, and cerebrovascular disease, that may develop as diabetes-related complications and lead to organ and tissue damage; the most common cause of death for patients with diabetes.

Metabolic memory: a phenomenon of vascular stressors from a glycemic

Extending the Principles of the β Cell-Centric Model to Diabetes-Related Complications

Clues to the true nature of DM complications emerged nearly two decades ago and explained why some patients with poor glycemic control have many complications, while others do not. It was shown that all diabetes-related complications arise from a common pathway. The interaction of an abnormal metabolic state engendered by β cell dysfunction with the presence (or absence) of several other factors (genetic susceptibility to damage, environmental factors, and comorbidities) is represented by the unifying mechanism of hyperglycemia-induced cellular damage, with oxidative stress and reactive oxygen species (ROS) as key arbitrators [9]. Elucidation of the common mechanism of cell damage in DM put to rest any misconceptions that microvascular disease and macrovascular disease constitute distinct disease entities [10,11] (Figure 3).

ROS cause strand breaks in nuclear DNA, and activate downstream pathways that lead to cellular damage. This mechanism is at work in vascular endothelial cells just as it is in glomeruli and retina, for example, as well as neurons, which are nonvascular cells [10] (Figure 4).

Accordingly, it should be understood that microvascular and macrovascular complications are privy to the same physiological pressures of hyperglycemia. Similarly, complications are not DM subtype dependent, that is, are not driven by distinct processes in type 1 DM complications versus type 2 DM complications.

The Common Origins of Diabetes and its Complications Construct: A Synthesis

The premise of this paper is that all complications result from a set of reiterative processes across the entire disease state of 'diabetes'; that is, the drivers of complications constitute the same pressures and processes that damage β cells; namely, the interplay between genetic predisposition, environmental cues, IR, immune dysregulation and inflammation, intracellular fuel excess, and comorbidities (such as hypertension and hyperlipidemia) [9,12]. A vicious cycle ensues that hastens and worsens the systemic imbalances and damage to susceptible cells.

This update revolutionizes how we conceptualize DM. Partitioning DM into the current diagnostic subtypes, and siloed approaches to care, is no longer valid. Similarly, it would be baseless to assume that macrovascular complications are more refractory to prevention than microvascular complications. While there is still much to uncover about the etiology of DM (see Outstanding Questions), we now have most of the pieces of the puzzle of cellular dysregulation wrought by chronic hyperglycemia. Lacking are models to conceptualize the disease within this new schema. This gap led us, as workers from various disciplines, to bring together respective knowledge and derive the model presented herein to describe the disease based on the evidenced, reiterative processes inherent to all derivations of DM and its broader physiological consequences.

The first resultant abnormal metabolic state is fuel excess (glucolipotoxicity), which induces and exacerbates β cell dysfunction. Second is oxidative stress due to this fuel excess, which is acted upon by numerous influencers, including IR (i.e., the inability of the cells to respond normally to insulin), and other cardiometabolic players (hypertension, overweight, smoking,

small intestine via reduced amylin, and kidney (shown in green)]. (B) Use of the Egregious Eleven as a guide for patient-centric therapy. Targeted therapies for each of the current mediating pathways of hyperglycemia, weight reduction, and cardiovascular (CV) benefits based on β Cell-Centric Model. Abbreviations: AGI, Alpha-glucosidase inhibitors; DPP-4, Dipeptidylpeptidase-4; GLP-1RA, glucagon-like peptide 1 receptor agonists; QR, quick release; SGLT2, Sodium-glucose co-transporter 2; TZDs, thiazolidinediones. †, weight-reducing agent; * potential CV benefit shown for at least one member of the class. Adapted, with permission, from [1].

environment in the diabetic state that persists after normoglycemia is reestablished. Hyperglycemia (or hypoglycemia) appears to be 'remembered' by those tissues implicated in the diabetic state, such as the kidney, eyes, and heart; evidenced in long-term follow-up studies on patients who received intensive therapy in large-scale trials. Metabolic memory is assumed to be regulated by epigenetic modifications.

Microvascular disease: retinopathy, nephropathy, and neuropathy that may develop as diabetes-related complications and lead to organ and tissue damage.

Oxidative stress: imbalance between the systemic manifestation of reactive oxygen species (ROS) and the ability of a biological system to either readily detoxify the reactive intermediates (ROS) or repair the resulting damage.

Reactive oxygen species (ROS): chemically reactive chemical species containing oxygen, such as peroxides, superoxide, hydroxyl radical, and singlet oxygen. ROS are a natural byproduct of the metabolism of oxygen. They have an important role in cell signaling and homeostasis. However, during times of environmental stress, elevated ROS can cause significant damage to cell structures. Cumulatively, this is known as oxidative stress.

Redox metabolome: proposed by Barbara Corkey and Orian Shirihai as master controller of tissue responses to changes in metabolism. It constitutes an elaborate and extensive tissue-to-tissue communication system orchestrated by ROS and related molecules. Disruption of the temporal and spatial redox metabolome during oxidative stress is a central process of system failure and disease.

Unifying mechanism of hyperglycemia-induced cellular damage: a model proposed by Michael Brownlee to highlight that oxidative stress and ROS are the key arbitrators of damage across all organs implicated in diabetes-related complications. A common mechanism of cell damage in DM puts to rest any misconceptions that microvascular disease and macrovascular disease constitute distinct disease entities.

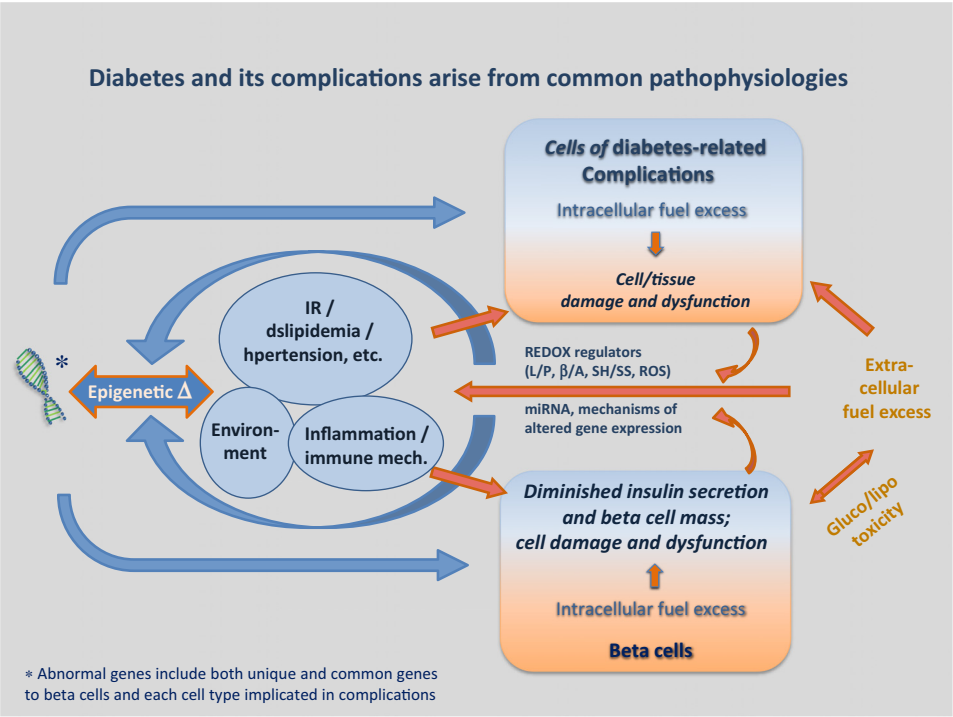

Figure 3. Diabetes and its Complications Arise from Common Etiopathophysiologies. The primary underlying mediator of diabetes-related complications is the damage wrought by hyperglycemia and other excess fuels engendered by reduced insulin or a reduced insulin effect due to abnormal β cell function. The development and progression of any given complication depends on the interplay between genetic predisposition, environmental cues, insulin resistance (IR), immune dysregulation and inflammation, intracellular fuel excess, and comorbidities (such as hypertension and hyperlipidemia).

etc.); nutrient excess; environmental cues; and, immune dysfunction and inflammation. Genetic predispositions determine the likelihood of individual diabetes-related complications, just as the genetic predisposition of β cells determines β cell exhaustion and damage. Dozens, even hundreds, of susceptibility loci map to the diabetic state, allowing for a multitude of potential contributing genes and gene interactions [13–15]. Some loci track β cell function with complication risk, others with the risk factors of complications, such as hypertension, obesity, and inflammation [13]. The appearance, timing, and severity of each complication in a given patient are largely determined by these factors. Retinopathy is predictive of CV disease (CVD), imposing as much as a fivefold relative risk of CV events (reviewed in [12]). Microalbuminuria can presage CVD in both type 1 DM and type 2 DM [16], and ischemic stroke by more than fourfold in patients with type 1 DM [17]. Susceptibility can be high enough for kidney, eye, or CV complications to ensue in patients with prediabetes [18,19].

Given that common etiopathophysiologies drive the entirety of DM, the phenotypic presentation of long-term complications mirrors that of DM at large. At some juncture, tissue and organ damage exceeds reparative capacity. The closing of the therapeutic window is an important pearl to take into the clinic: treat early and treat aggressively.

The above helps us make sense of the high rates of complications in some patients and low rates in others, even in the face of tightly controlled glucose levels. The refractory nature of

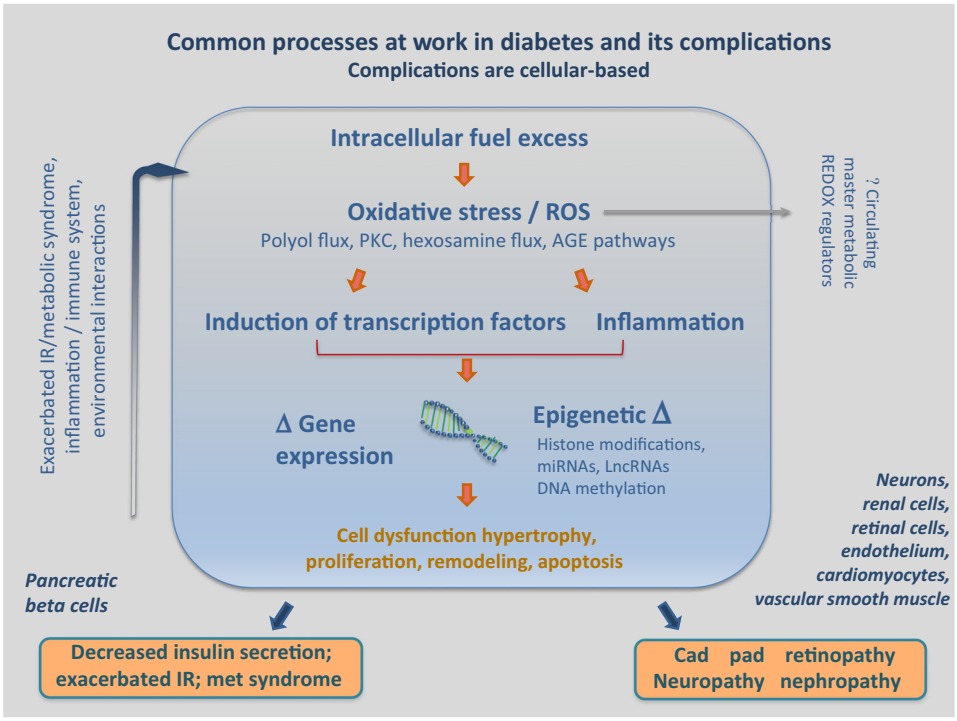

Figure 4. Common Processes at Work in all Target (Vulnerable) Cells Implicated in Diabetes. Chronic exposure to hyperglycemia and glucolipotoxicity from excess fuel leads to the release of reactive oxygen species (ROS). This activates pathways including polyol flux, advanced glycation end-product (AGE) formation, activation of protein kinase C (PKC), and hexosamine flux, resulting in inflammation. These trigger signaling pathways, induction of transcription factors, gene transcription, and epigenetic modifications, such as histone modifications, DNA methylation, noncoding RNA in miRNAs, and long noncoding RNAs (lncRNAs). Gene transcription favors cell hypertrophy, proliferation, remodeling, and apoptotic signaling, which physiologically manifest as coronary artery disease (CAD), peripheral artery disease (PAD), retinopathy, neuropathy, and kidney impairment (reviewed in [24]). Systemic effects include the exacerbation of the diabetic state, especially as insulin secretion from the laboring β cells decreases and as cardiovascular (CV) function is compromised. The possibility of a redox metabolome with circulating master metabolic REDOX regulators to coordinate responses across cell types has been proposed by Corkey and Shirihai [26] and Jones and Helmut [27].

complications, particularly CV complications, to intensive glucose lowering (as seen in secondary prevention trials, such as VADT [20,21], ADVANCE [22], and ACCORD [23]) can also be due to irreparable structural damage. CV outcomes also appear to be impacted by hypoglycemia, weight gain, and iatrogenic hyperinsulinemia (engendered by exogenous insulin therapy). In older patients or those with pre-existing CV disease, intensification of glucose-lowering agents or management of CV risk factors (e.g., lipid-lowering agents) can be expected to reverse progressive organ failure.

Molecular Mechanisms Due to Fuel Excess

As mentioned, oxidative stress/ROS ubiquitously mediate hyperglycemia-induced tissue damage, and are generated mainly by increased free fatty acid (FFA) oxidation [10,11]. Oxidative stress-mediated regulation cascades have been found to map to the 'epicenter' of type 2 DM genetic interaction networks, as well as to the development of complications [13–15].

The release of ROS activates pathways that include polyol flux, advanced glycation end-product (AGE) formation, activation of protein kinase C (PKC), and hexosamine flux, leading to inflammation. These trigger signaling pathways, induction of transcription factors, gene transcription, and epigenetic modifications, such as histone modifications, open chromatin, DNA

methylation, noncoding RNA in miRNAs, and long non-coding RNAs (lncRNAs). Gene transcription in the presence of ROS activation favors cell hypertrophy, proliferation, remodeling, and, apoptotic signaling. These changes become physiologically manifested as coronary artery disease (CAD), peripheral artery disease (PAD), retinopathy, neuropathy, and kidney impairment. (*reviewed in Pasquier et al. 2015* [24]. Functional effects also include the exacerbation of the diabetic state, especially as insulin secretion from the laboring beta-cells decreases, and, secondarily, CV function is compromised (Figure 4).

Although the central role of ROS is well known to researchers, it has not been uniformly incorporated into clinical education. This exemplifies the need for a ore serviceable construct to correctly conceptualize the disease (as we now understand it), and, properly interpret and better translate the results of clinical studies into more efficacious care.

In the face of persistent nutrient excess, oxidative stress shifts from an adaptive mechanism to a maladaptive one [25,26]. Cell types affected in DM are those least equipped to defend against intracellular hyperglycemia, FFA, and ROS, that is, β cells, along with retina, endothelium, cardiomyocytes, glomeruli, and neurons, which are all cells implicated in diabetes-related complications. In a vicious cycle, the damage caused by oxidative stress and ROS further exacerbates metabolic dysregulation [25,26]. A **redox metabolome** (or 'redox code') [27] has been proposed as a master controller of tissue responses to changes in metabolism. It constitutes an elaborate and extensive tissue-to-tissue communication system orchestrated by ROS and related molecules [26]. Disruption of the temporal and spatial redox metabolome during oxidative stress is a central process of system failure and disease [27].

Oxidative stress/ROS in diabetes has been shown to link to premature CV morbidity and mortality (reviewed in [28]). It has also been linked to heart failure independent of hypertension and CAD [28], atherosclerosis [29], cardiomyopathy, weakening of myocardial structure and function, inflammation, neovascularization, apoptosis, cardiac remodeling, and the hypercoagulable state [11,30].

β cells are particularly vulnerable to ROS: they have ultra-low levels of critical antioxidants, which are subject to further suppression in the face of sustained dysglycemia [31–33]. Oxidative and endoplasmic reticulum stress in the β cell leads to cell dysfunction, decreased insulin output, activated β cell islet inflammasomes [33–35], and the activation of apoptosis [33,36–38]. Epigenetic modifications are integral to the process, switching on or off cellular hypertrophy, proliferation, remodeling, and apoptosis (reviewed in [24]). More than 250 epigenetically regulated genes involved in glucose metabolism and adaptive survival have been identified by pancreatic DNA methylation profiling methodologies [39]. A key function of epigenetic regulation is the setting – and resetting – of '**metabolic memory**'. Metabolic memory can be observed in the clinical trial setting as 'legacy effects' – controlled hyperglycemia during the clinical trials that translate into reduced outcomes in 10-, 15-, or 20-year follow-up studies.

The New Understanding of DM and What It Means to Managing Outcomes

The above evidence supports early and aggressive treatment for hyperglycemia as well as complications through diet and life-style changes, and pharmacotherapy, with the underlying pathophysiology of DM taken into account. This is regardless of clinical presentation as type 1 DM, LADA, type 2 DM, or the characteristically less-severe maturity-onset diabetes of the young (MODY, under current classifications), as well as the age of the patient or stage of disease. As described above, organ damage can approach or pass the 'point of no return' for repair. Hence, it behooves practitioners to treat proactively. The recently released STENO-2 Trial follow-up study [40] showed that aggressive therapies for diabetes and related

comorbidities (e.g., renin–angiotensin system blockers, aspirin, and lipid-lowering agents) translated into reduced CV events and mortality, with an approximate 8 years gain of life as a legacy effect over the 21-year follow-up. Of note, this benefit was regardless of the type of complication; reductions of approximately one-third to a half were reported across all complications [40]. This strongly advocates targeted combination treatments to improve the processes of care for the management of DM and its complications.

The β Cell-Centric Model illustrated that the specific mediating pathways of hyperglycemia at work in any given patient are targets for pharmacotherapy [1]. Most of the Egregious Eleven can be treated with currently available antidiabetic medication. The goal is to use the least number of agents that treat the greatest number of operative pathways of hyperglycemia. The potential to intelligently design combination regimens with complementary pleiotropic benefits should be considered (Figure 2B).

Pharmacotherapy to anticipate and prevent complications should receive the same attention as glucose lowering. Choice of 'CV-friendly' therapies should factor heavily in treatment decisions, and future guidelines. 'CV-unfriendly' agents vis-à-vis weight gain, hypoglycemia, and poorer outcomes should be avoided. A range of agents has been evidenced to improve outcomes in the face of surprisingly modest improvements in glucose control, while other treatments appear to worsen outcomes. The drug mode of action can directly and/or indirectly address the underlying pathophysiological processes that lead to, or abet, diabetes-related complications.

Traditional antidiabetic agents, including metformin and pioglitazone, and newer agents, such as empagliflozin (a SGLT2 inhibitor), liraglutide (a GLP-1 receptor agonist), and bromocriptine-QR (a dopamine agonist), have each been shown to improve CV outcomes and mortality in large-scale clinical studies. An impressive benefit was found with empagliflozin, which demonstrated a striking 30% decrease in CV events and mortality in patients with established CVD over the course of just 3 years [41]. This dramatic improvement was achieved in the face of additional glucose lowering of only approximately 0.5%. Mechanistically, empagliflozin increases urinary glucose excretion and induces weight loss, and has been shown to reduce oxidative stress, arterial stiffness, blood pressure, and endothelial dysfunction [41]. The off-target effect of liraglutide on reducing ROS and providing neuroprotection against ischemia-induced apoptosis (reviewed in [42]) may help account for the reduced incidence of stroke in the LEADER Study on liraglutide, although GLP-1 receptor agonists intercept a broad range of central and systemic metabolic regulators. The IRIS Study on pioglitazone showed that it reduced the incidence of stroke and myocardial infarctions. This agent has been found to improve IR and endothelial dysfunction, decrease inflammation and immune factors, and modify gene expression of a range of growth, vascular, and tissue factors [43,44]. Rosiglitazone alternately appears to worsen lipid profiles, perhaps explaining adverse CV outcomes with this drug. Bromocriptine-QR appears to improve sympathetic tone and reduce peripheral IR; it improved major adverse cardiac events (MACE) by 42% in one study [45]. Metformin has been found in several prevention studies to modestly improve CV and mortality outcomes, although its mode of action remains elusive.

Combination regimens and pharmacological approaches that address multiple dysfunctions can manage outcomes, as well as hyperglycemia, effectively. Most of the studies to date were reported for type 2 DM cohorts; for most agents, studies are maturing as adjunctive therapy in type 1 DM. Add-on therapy will allow forestalling the use of insulin, or dose-reducing insulin with non-insulin options. This is an intriguing possibility, because insulin has been shown to worsen CV and mortality in a variety of large-scale outcome studies [46–54] (M.E. Herman *et al.*, unpublished data, 2017). Older patients or those with pre-existing CV risk factors (as evaluated in secondary prevention studies) may be particularly vulnerable. In a recent large registry study

(~1.5 million-year follow-up) evaluating the relationship between insulin therapy and end-stage renal disease, increased risk was evident for all hemoglobin A1c levels, which suggests something unexpected: that insulin therapy, rather than the level of glucose control or stage of disease, can drive outcomes [55].

Peripheral administration of insulin obligatorily induces iatrogenic hyperinsulinemia, which, through a range of downstream effects, may compromise the vasculature and other systems [56]. The off-target effects of exogenous insulin include well-known actions such as weight gain and obesity, and acute hypoglycemia. Recurrent asymptomatic hypoglycemia has been estimated in nearly 50% of patients, and can have short- and long-term consequences [54,57,58]. Other actions of hyperinsulinemia include IR and type 2 DM, as well as endothelial dysfunction, atherosclerosis, hypertension, dyslipidemia, chronic inflammation [56], and even cancer (reviewed in [56]).

In some of the same studies in which insulin therapy worsened outcomes, metformin decreased CV events and mortality (such as in the DIGAMI-2 Study in patients with DM who presented with acute myocardial infarction) [46]. A similar trend was found in younger patients with less CVD in the United Kingdom Prospective Diabetes Study (UKPDS) type 2 DM cohort, who received long-term intensive glucose-lowering treatments early in their disease onset. Twice the CV benefit was achieved with metformin than with insulin [59]. In composite, these findings suggest that insulin therapy is not the most CV friendly of available options.

The Common Origins of Diabetes and its Complications Construct not only makes sense of the conflicting data of the outcomes of large clinical trials, but can also help predict the value of various treatment strategies for glycemic control and complication risk. Large patient registries can be mined for such answers. Tailored treatments and intelligently designed combination regimens should have a prominent place in standard practice.

Concluding Remarks

We envisioned the β Cell-Centric Model and Common Origins of Diabetes and its Complications Construct as a serviceable framework that builds on our contemporary scientific understanding of this enigmatic disease and its sequelae. It formalizes and expands seminal work presented herein by Keen [9], Evans and coworkers [36], Brownlee and Shah [11], Pasquier and coworkers [24], Corkey and Shirihai [26], and others. These models fill a gap in conceptualizing DM, and gives us pause to rethink traditional assumptions about the disease, and the best practices for managing it. The framework provides a universal pathophysiology across the diabetic state, applicable to β cells and all tissues and organs affected by complications. It is also a framework through which currently outdated classifications, guidelines, and treatment algorithms can be revised. It also highlights the need to develop antidiabetic treatments for inflammation and an aberrant gut biome, mediating pathways of hyperglycemia hitherto unaddressed pharmacologically. Finally, the framework highlights how remaining gaps in individualized care can be filled through the development of genomic, proteomic, and metabolic diagnostics (see Outstanding Questions), such as discovery and diagnostics for gut biome factors, markers and risk factors for the development of individual diabetes-related complications, and the utility of anti-inflammatory treatments.

Importantly, we believe that this framework fosters improved processes of care and precision medicine. It both identifies and builds treatment regimens based on the mediating pathways of hyperglycemia and risks of complications of any given patient at any stage of their disease. It recognizes that proactive, aggressive intervention with intelligently combined, multi-targeted treatments can represent best practices.

Outstanding Questions

Which specific genes, epigenetic mechanisms, regulatory networks, antibodies, and molecular mechanisms are involved in injury to, and demise of, β cells and other cells prone to damage within the diabetic process?

Which environmental factors influence the development and advancement of DM, including less addressed factors, such as the gut biome?

What are the roles of IR and inflammation in the diabetic disease process?

What are the physiological actions of individual antidiabetes agents and classes beyond glucose lowering?

How can we more precisely classify the various DM phenotypes, and do so within a serviceable and adaptable framework?

What are the most reliable and appropriate risk factors and early diagnostics for the development of DM?

What markers (genomic, proteomic, or metabolomic) for individual susceptibility can be developed for diabetes and its various complications?

How can we incorporate earlier and more aggressive management of dysglycemia in standard practice?

Which agents/regimens can delay, slow or prevent diabetes, that is, preserve the β cell?

Author Contributions

S.S.S. conceived the Common Pathophysiologic Origins of Diabetes Mellitus and its Complications Construct and crafted the first draft of this article. S.E., B.E.C., S.F.A.G., J.R.G., and R.B.A. critically reviewed, provided incisive input, edited, and approved the final version of the manuscript. R.A. additionally contributed graphic design. M.E.H. additionally contributed moderately to the synthesis of the larger construct, and substantially to the writing of the manuscript. S.S.S. is the guarantor of this work and, as such, takes responsibility for the genesis and general framing of the Common Pathophysiologic Origins of Diabetes Mellitus and its Complications Construct.

Disclaimer Statement

S.S.S. is a speaker and advisor to Novo Nordisk, Merck, Takeda, Johnson & Johnson, Astra-Zeneca/Bristol-Myers Squibb, Eli Lilly and Company, Boehringer Ingelheim/Eli Lilly and Company, and is a speaker for Eisai and GlaxoSmithKline. J.R.G. has received consultant fees from Abbott Diabetes Care, Intarcia Pharmaceuticals, Astra Zeneca, and Novo Nordisk; and has served on the advisory boards of Janssen Pharmaceuticals and Astra Zeneca, and on the speaker's bureaus of Astra Zeneca, Janssen, and Boehringer Ingelheim/Eli Lilly and Company. R.B.A. sits on the advisory board and speaker's bureaus of Eli Lilly and Company, Boehringer Ingelheim, Janssen, and Takeda. No potential conflicts of interest relevant to this article were reported.

Acknowledgments

S.S.S. and S.G. received funding from National Institute of Health, USA (NIH) grant R01 DK085212; S.G. received funding from Daniel B. Burke Endowed Chair for Diabetes Research; B.C. received funding from NIH Grants DK99618, DK56690, DK74778, and DK-35914. No funding was received by any of authors for this manuscript.

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