

DYSGLYCEMIA-BASED CHRONIC DISEASE: AN AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS POSITION STATEMENT

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This document represents the official position of the American Association of Clinical Endocrinologists and the American College of Endocrinology. Where there were no randomized controlled trials or specific U.S. FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Position statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician.

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ABSTRACT

The American Association of Clinical Endocrinologists (AACE) has created a dysglycemia-based chronic disease (DBCD) multimorbidity care model consisting of four distinct stages along the insulin resistance-prediabetes-type 2 diabetes (T2D) spectrum that are actionable in a preventive care paradigm to reduce the potential impact of T2D, cardiometabolic risk, and cardiovascular events. The controversy of whether there is value, cost-effectiveness, or clinical benefit of diagnosing and/or managing the prediabetes state is resolved by regarding the problem, not in isolation, but as an intermediate stage in the continuum of a progressive chronic disease with opportunities for multiple concurrent prevention strategies. In this context, stage 1 represents “insulin resistance,” stage 2 “prediabetes,” stage 3 “type 2 diabetes,” and stage 4 “vascular complications.” This model encourages earliest intervention focusing on structured lifestyle change. Further scientific research may eventually reclassify stage 2 DBCD prediabetes from a predisease to a true disease state. This position statement is consistent with a portfolio of AACE endocrine disease

care models, including adiposity-based chronic disease, that prioritize patient-centered care, evidence-based medicine, complexity, multimorbid chronic disease, the current health care environment, and a societal mandate for a higher value attributed to good health. Ultimately, transformative changes in diagnostic coding and reimbursement structures for prediabetes and T2D can provide improvements in population-based endocrine health care. (**Endocr Pract.** 2018;24:995-1011)

Abbreviations:

A1C = hemoglobin A1c; **AACE** = American Association of Clinical Endocrinologists; **ABCD** = adiposity-based chronic disease; **CVD** = cardiovascular disease; **DBCD** = dysglycemia-based chronic disease; **FPG** = fasting plasma glucose; **GLP-1** = glucagon-like peptide-1; **MetS** = metabolic syndrome; **T2D** = type 2 diabetes

THE PREDIABETES PROBLEM

The earliest record of diabetes dates back to the Egyptian physician “Hesy-Ra” around 3000 BC (1). Through the years, diabetes has been diagnosed by physical symptoms (e.g., excessive thirst and urination [1]), the presence of overt glycosuria, numerical values representing blood glucose levels over two standard deviations from the mean (2,3), glucose levels based on an epidemiologic association with the development of retinopathy (4), time-averaged measures of dysglycemia for 2 weeks (e.g., glycated protein [fructosamine]) or 2-months (e.g., hemoglobin A1c [A1C]), novel markers and their combinations (5-7), the application of continuous glucose monitoring (CGM) to optimize glycemic control (8), and even genetic variants (9). According to the 2014 National Diabetes Statistics Report by the Centers for Disease Control and Prevention, type 2 diabetes (T2D) accounted for about 90 to 95% of the 29.1 million people of all ages diagnosed and undiagnosed with diabetes in the U.S., with another 86 million people over age 18 years with prediabetes, of which 15 to 30% developed T2D within 5 years (10). However, in the most recent 2017 National Diabetes Statistics Report, these numbers increased and were 30.3 million U.S. residents of all ages (9.4% of the population) with diabetes and 84.1 million age 18 and over (33.9% of the population) with prediabetes (11).

According to a recent analysis using data from the U.S. National Health and Nutrition Examination Surveys (NHANES; 1988-2014), patients with prediabetes have increased prevalence rates of hypertension, dyslipidemia, chronic kidney disease, and cardiovascular disease (CVD) risk (12). Since intervention once a patient develops T2D is more costly, both economically and in terms of disease burden, and lifestyle interventions introduced as early as possibly in the natural history of the disease can be effective

tive and durable, there is high impact and opportunity associated with a diagnosis of prediabetes (12-18). However, what is particularly alarming is that in 2015, 23.8% of patients with diabetes (7.2 million persons) and 88.4% of patients with prediabetes (74.3 million persons) did not even know they had the condition (11). Generally speaking, this problem of “unawareness” amplifies the impact of chronic disease and emphasizes the importance of identifying specific causes, interventional strategies (including all types of prevention), and implementation tactics. In sum, the critical question is whether making the diagnosis of “prediabetes” can improve health?

Prediabetes was first described in 1956 in the perspective of gestational diabetes (18) but is now a construct in clinical medicine that identifies people at higher risk for T2D, hypertension, and CVD than the general population. Prediabetes is diagnosed based on fasting plasma glucose (FPG), standardized 2-hour postchallenge glucose testing, or A1C levels, though diagnostic cutoffs may vary (19-21). The concept of prediabetes hinges on a preventive care approach to chronic disease, in which people with a “predisease” are identified by a positive screening test, with the explicit intent to intervene. At the population level, the intended result of the intervention would result in decreased incidence and prevalence rates, costs, and detriment on quality-of-life metrics (22). Hence, those with overweight are at higher risk for obesity, prehypertension for hypertension, metabolic syndrome (MetS) for CVD, and so forth.

From a purely theoretical and idealistic standpoint, the advantages of detecting and intervening in people at-risk for a potentially debilitating chronic disease such as T2D makes sense, not only for the individual person but also for society as a whole (22,23). In the 15-year follow-up of the Diabetes Prevention Program Outcomes Study (24), those patients with prediabetes randomized to lifestyle intervention had significant reduction in T2D development. Moreover, among all patients in the study, there was a 28% lower prevalence of microvascular complications in those not developing T2D (24). Unfortunately, from a purely pragmatic standpoint, the actual effects of this type of population-based intervention may prove expensive due to the high prevalence rate of prediabetes, the small number of individuals destined to develop clinically significant T2D, and lack of anticipated level of benefit for all people in the current prediabetes diagnostic category (25). The problem is even deeper. The current paradigm of diabetes care is plagued by patient adherence problems, inertia among health care professionals adopting contemporary clinical practice guidelines, and a lack of reverent, consistent, and universal insurance coverage for diagnostics, lifestyle medicine, and pharmaceuticals, all prompting the need for a new approach involving patient-centered and preventive care (26). In other words, the current management of patients with prediabetes should be challenged,

with diagnostic criteria reworked, logistics of care re-engineered, and the pathophysiologic basis re-examined (27).

The American Association of Clinical Endocrinologists (AACE) has long supported clinical intervention in patients with prediabetes (28-30), together with evidence-based optimization of care for patients with diabetes, obesity, and related metabolic disorders (31-34). With respect to obesity, AACE has recently proposed a new Adiposity-Based Chronic Disease (ABCD) diagnostic term (35) and a complications-centric obesity care model. Now, within a larger framework of comprehensive cardiometabolic risk, this thinking extends to dysglycemia.

AACE recognizes the dilemma confronting prediabetes as an actionable diagnosis for intervention and resolves this difficulty by redefining the context of prediabetes and T2D within an evidentiary structure for *Dysglycemia-Based Chronic Disease* (DBCD). Rather than strongly arguing that DBCD should immediately be part of our lexicon, AACE takes the position that popular and recognizable terms, such as prediabetes, T2D, and MetS, fit squarely within a DBCD framework as evolving manifestations of a chronic disease. Therefore, research, education, and clinical practice processes should re-orient toward effective prevention and treatment at all stages in this chronic disease model. More to the point, that despite objections and controversy already anchored in the literature (36,37), AACE takes the firm stance that patients with prediabetes fall within the progressive spectrum of DBCD (insulin resistance-prediabetes-T2D) and are well-suited for structured lifestyle and/or pharmaco-therapeutic preventive measures. Notably, this effort to better reconcile prediabetes within a larger framework of cardiometabolic health is shared by others, where the targets are precise, classification is rational, and early intervention improves clinical outcomes (38,39).

THE GENERAL CONTEXT OF DBCD WITHIN THE NEXUS OF ABCD AND CARDIOMETABOLIC DISEASE

The essential component of DBCD is insulin resistance. When insulin secretion is unable to compensate for insulin resistance, the result is hyperglycemia and eventual prediabetes, identified on the basis of impaired FPG or impaired 2-hour postchallenge plasma glucose during an oral glucose tolerance test (40). Since up to 70% of patients with prediabetes have a lifetime risk of converting to T2D (40,41) (74% of individuals at age 45 [42]), primary prevention of T2D is paramount. Also, since those with prediabetes have significant CVD risk factors (36.6% with hypertension, 51.2% dyslipidemia, 24.3% tobacco use, and 5 to 7% 10-year cardiovascular event risk), secondary prevention is paramount by using effective diagnostic tests and treatments to reduce these risks and prevent CVD as early as possible (12,43).

There are three aspects to reducing the impact of prediabetes using primary and secondary prevention strategies. The first aspect is to prevent T2D. Progression to T2D can be prevented with interventions that improve insulin sensitivity, such as weight loss, healthy eating patterns, regular and sustained physical activity, and/or the use of diabetes medications (e.g., metformin, thiazolidinediones, and incretin-based therapies) (37,44-47). Left unchecked, prediabetes will progress to T2D in a majority of patients, while some others will continue with prediabetes or revert to normal glucose tolerance (48,49). While normoglycemia may be temporary with ultimate return of progressive glucose intolerance, individuals who revert to normal glucose tolerance are at diminished risk of T2D compared to those with stable prediabetes but remain at greater risk of T2D compared with those entirely without DBCD, particularly if there are other metabolic risk factors present or if they meet criteria for MetS (48,49). The second aspect is to prevent CVD. Prediabetes represents a state of clustered CVD risk factors, accelerated atherosclerosis, and increased risk for CVD events. Epidemiologically, elevated postprandial plasma glucose levels are more associated with increased CVD risk than FPG levels, particularly in women (50). Aggressive management of CVD risk factors is warranted in patients with prediabetes, though the exact degree and nature of intervention, as well as the subpopulations best served by this approach, remain unclear (38). The third aspect is to prevent T2D-related complications. The degree of dysglycemia in prediabetes is sufficient to cause microvascular complications of diabetes in some patients, as demonstrated in the Diabetes Prevention Program, where up to 10% of patients developed background retinopathy or neuropathy (51). Thus, in addition to CVD risk factor management, improvement of glycemic status in the prediabetes stage should be a specific target, though again, the exact degree and nature of improvement remains unclear.

Insulin resistance in association with overweight/obesity gives rise to MetS, which may or may not be accompanied by prediabetes (23). In this way, the natural history of DBCD intersects the natural history of ABCD at the level of insulin resistance, which involves abnormalities in the amount, distribution, and/or function of adipose tissue (35). The abnormal adipocyte secretome can affect the cardiometabolic nexus of disease manifestations, including prediabetes, MetS, nonalcoholic fatty liver disease, T2D, and CVD (52). In these patients, there is an infiltration of inflammatory macrophages in adipose tissue; dysregulated secretion of adipokines; impaired lipid storage leading to redistribution of lipid to the intra-abdominal compartment, liver, and muscle cells; and an exacerbation of insulin resistance (53-55). Hence, in those patients who develop prediabetes, ABCD is essentially indistinguishable from DBCD. However, not all patients with ABCD have DBCD. ABCD can also involve an augmentation in

adipose tissue mass without abnormalities in adipose tissue function. These patients are insulin sensitive with little or no increase in risk for T2D and CVD (55-58); however, the increase in adipose mass predisposes to biomechanical complications such as osteoarthritis, sleep apnea, urinary stress incontinence, and dysmobility/disability, in addition to some forms of cancer. Weight gain on an insulin-resistant background can exacerbate adipose tissue dysfunction and the cardiometabolic disease process (56-58), producing MetS and/or prediabetes and leading to T2D. However, weight gain on an insulin-sensitive background may confer minimal or no increase in risk for T2D and CVD, at least for the short term (56-58), but may still predispose to the biomechanical complications of ABCD on the basis of increased adipose tissue mass.

THE SPECIFIC CONTEXT OF DBCD AS THE INSULIN RESISTANCE-PREDIABETES-T2D SPECTRUM

Dysglycemia is loosely defined as any abnormality in glycemic status that is associated with disease, or the potential for disease, with the earliest citation in PubMed in 1951 (59). There is general consensus that both insulin resistance and pancreatic β -cell dysfunction are the key initiating physiologic events for development of T2D, conferred by complex interactions among genetic mutations and/or polymorphisms on a genomic scale, with epigenomic modifications and environmental factors (60). Recently, the role of pancreatic α -cell dysfunction and hyperglucagonemia has been investigated, wherein α -cells are stimulated by glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), and high glucagon levels stimulate hepatic glucose production (61). In fact, α -cells can influence pancreatic β -cell function by producing paracrine GLP-1 from proglucagon (62). Incretin resistance may also be a significant element of dysglycemia. This is evidenced by improvements in glycemic status after Roux-en-Y gastric bypass or biliopancreatic diversion, which are associated with sufficient rises in incretin levels that could overcome incretin resistance (63). Furthermore, reciprocal effects of β -cell function can reduce the number of α -cells, the relative α -cell/ β -cell distribution, and α -cell function (64).

At a molecular level, mitochondrial DNA methylation markers are associated with early stage (decreased insulin sensitivity) but not late-stage (abnormal FPG or A1C) dysglycemia (65). The pathophysiology of T2D is even more complex when the results of Lawlor et al (66) are considered, in which 248, 138, and 24 genes were identified that have differential expression in T2D versus nondiabetes from human β -, α -, and δ -cell single-cell transcriptomes, respectively.

The association of prediabetes with macrovascular disease, namely CVD, is well established among many

different patient populations and ethnicities (44,67-77). In the Maastricht Study, Sorenson et al (78) found that prediabetes is also independently associated with microvascular dysfunction, which may contribute to T2D-associated CVD. This microvascular disease association is due to hyperglycemia, which is often independent of the cardiovascular risk scores (78). Quantitatively, the effects on CVD risk of impaired fasting glucose, impaired glucose tolerance, and insulin resistance as part of the MetS vary in degree (23,79,80). Specifically, in a meta-analysis of prospective cohort studies, Huang et al (43) found that for those patients with prediabetes (defined by various impaired fasting glucose and impaired glucose tolerance criteria), the range of relative risks for composite CVD was 1.13 to 1.30, coronary heart disease 1.10 to 1.20, stroke 1.06 to 1.20, and all-cause mortality 1.13 to 1.32. Interestingly, in the Whitehall II Study, the incidence rate for major CVD events was greater for those patients with prediabetes diagnosed by A1C compared with either FPG or 2-hour postchallenge glucose (81).

Even so, the impact and relevance of prediabetes on CVD risk are supported by progression of diabetes-related complications without intervention (82-85), reduction of cardiometabolic risks with lifestyle and weight-loss interventions (44,86-92), and reduction in health care costs with interventions (93-99). In short, the question here is not whether glycemia-targeted interventions mitigate the

implied prediabetes-CVD causal association, but rather that recognition of the need to treat in earlier DBCD stages with comprehensive risk reduction strategies, namely, structured lifestyle interventions and weight-loss therapy, produces clinically significant outcome benefits (i.e., decreased incidence of T2D, MetS, and CVD).

The causality direction and underlying mechanism for the adiposity and prediabetes relationship continue to be elucidated. However, in support of the ABCD model, visceral (reflected by waist circumference and waist-to-hip ratio measurements) and intrahepatic adiposity are more strongly associated with prediabetes and T2D than general measures of adiposity (e.g., body mass index [BMI] and truncal fat) (100,101). Moreover, patients with prediabetes and overweight/obesity have more endothelial dysfunction (using the relative hyperemia index) than their normoglycemic, desirable-weight controls (102), consistent with a model of CVD risk involving complex interactions among adiposity, dysglycemia, and inflammation.

Interventions shown to be effective in preventing progression from prediabetes to T2D, such as exercise and weight loss, are well known to increase insulin sensitivity. The function of β -cells is altered in DBCD, with increases in the early stages of the disease to compensate for insulin resistance, followed by decreases that involve defects in glucose sensing, islet cell size, and insulin content in those individuals destined to progress to overt T2D (103-

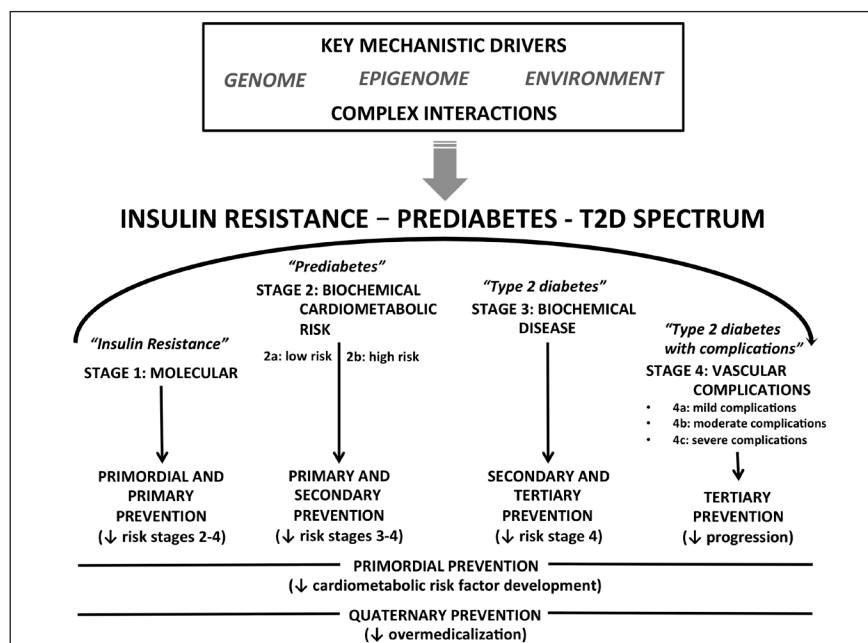


Fig. 1. Dysglycemia-based chronic disease and the insulin resistance-prediabetes-type 2 diabetes (T2D) spectrum. Prediabetes is Stage 2 in the dysglycemia spectrum, or dysglycemia-based chronic disease (i.e., DBCD) framework. Key mechanistic drivers are strong independent predictors of a particular outcome in a complex system (117). Primordial prevention—to decrease diabetes risk factors in the general population; primary prevention—to decrease conversion to T2D in patients with prediabetes; secondary prevention—to detect disease and decrease morbidity in patients with early asymptomatic T2D; tertiary prevention—to decrease progression of T2D related complications; and quaternary prevention—to decrease overmanagement/-medicalization of any patient along the spectrum. Each dysglycemia stage can be viewed as the basis, or low or high risk, for chronic cardiovascular disease along a cardiometabolic spectrum.

110). β -Cell dysfunction is particularly pronounced in certain ethnic populations with higher prevalence rates of prediabetes and T2D, such as Asian Indians (111). Mechanisms related to these changes are being clarified, for instance by studying *db/db* mice with high FPG but normal postchallenge plasma glucose levels, in which the exocytic machinery is altered (112). Importantly, exercise and weight loss improve β -cell function in patients with prediabetes (113). Also, in patients with prediabetes and overweight/obesity, treatment with liraglutide (1.8 mg/day) or other GLP-1 receptor agonists is associated with an increased insulin secretion rate and β -cell sensitivity to glucose (114,115).

While DBCD exists along a continuum, it is useful to identify distinct stages as the disease progresses to formulate an actionable preventive care plan. This model is designed as a starting point for a more comprehensive approach to T2D and CVD by recognizing that these outcomes are the culmination of a common and protracted disease process. The natural history and clinical progression of DBCD indicate that there are opportunities for primordial (reducing risk factors in populations), primary, secondary, tertiary, and even quaternary (reducing overmedicalization) prevention. While AACE (30) and the American Diabetes Association (41) have issued position statements regarding prediabetes, no medications have as yet been approved for this indication, and it has been controversial as to whether prediabetes should merit therapy as a disease entity (36,116). The proposed evidence-based 4-stage model outlined below emphasizes the context of prediabetes as a component in the progression of DBCD, with opportunities for various prevention modalities to reduce evolution to T2D, CVD, or both (Fig. 1) (117).

1. **Stage 1 DBCD “Insulin Resistance”:** starts at birth with genomic/epigenomic risk determinants for insulin resistance. Molecular risk for islet-cell dysfunction under chronic stress of insulin resistance may also be present. Specific molecular screening or aggressive case finding tests to detect risk are not yet commercially available. However, a significant family history of T2D, *in utero* exposure to gestational diabetes, detection of hyperinsulinemia, or abdominal obesity (i.e., ABCD characterized by abnormalities in fat distribution) are easily obtained markers for this earliest DBCD stage and can therefore prompt action. Those with insulin resistance are at higher risk of progressing along the DBCD continuum and merit primary disease prevention: structured lifestyle interventions that reduce cardiometabolic risk factors and later DBCD stage likelihoods, respectively. A molecular roadmap for this process was recently presented by Jin et al (118), who identified a dynamic driver network

governing the key predisease-T2D transition mechanisms. It is postulated that appropriate interventions (such as structured lifestyle change) at these critical time points could prevent or delay progression of disease (118). Along these lines, Khara et al (119) found that in patients with a high genetic (molecular) risk for coronary heart disease, a favorable (healthy) lifestyle was associated with a nearly 50% reduction in relative risk. Pragmatically, all individuals can benefit from population-based primordial disease prevention given the pervasive diabetogenic and obesogenic environment. Primordial prevention strategies include health messaging and public education that create a culture of wellness, in addition to legislation on local, state, and federal levels that transition unhealthy to healthy built environments and target obstetrical care to ameliorate the *in utero* environment and mitigate intergenerational disease transmission.

2. **Stage 2 DBCD “Prediabetes”:** the emergence of detectable biochemical elevations in blood glucose with or without CVD risk factors or MetS traits. Screening and/or aggressive case finding for dysglycemia are critical in this stage. Prediabetes is associated with a high risk of future T2D due to the combination of insulin resistance and islet-cell dysfunction and for CVD as a result of accelerated atherosclerosis. Population-based primordial prevention strategies are applicable in this stage. Primary prevention strategies are indicated for these individuals, such as structured lifestyle modifications resulting in weight loss and enhanced physical fitness, that improve metabolic and CVD risk factors and prevent progression to Stage 3 DBCD, or T2D (47,120-127). At present, *prediabetes* is still considered as a predisease, but with further scientific delineation, prediabetes may eventually meet criteria for a true disease state. Moreover, secondary prevention strategies are indicated for prediabetes incorporating early detection of T2D, as well as interventions to reduce the progression of CVD. Pragmatically, successful interventions (e.g., lifestyle alone versus lifestyle + pharmacotherapy) at Stage 2 DBCD Prediabetes can depend on risks for CVD, T2D, and other T2D complications. Cardiometabolic Disease Staging (55) can effectively stratify risk for future T2D. Alternatively, patients may be segregated into subtypes based on various FPG and/or A1C cutoffs (e.g., 110 mg/dL [128] and 6.0% [42 mmol/mol] [129], respectively):
 - Stage 2a: low-risk prediabetes (e.g., FPG <110 mg/dL and/or A1C <6.0% [42 mmol/

- mol]) managed with intensive lifestyle intervention alone, versus
- Stage 2b: high-risk prediabetes (e.g., FPG ≥ 110 mg/dL and/or A1C $\geq 6.0\%$) managed with intensive lifestyle intervention and *possibly* pharmacotherapy (which may be

no different than those modalities used to manage Stage 3 DBCD T2D and reduce risks for disease progression (e.g., blood pressure and lipid management [32]).

3. **Stage 3 DBCD “T2D”:** marked by biochemical elevations in blood glucose associated with statis-

DBCD stage	Clinical context	Pragmatic relevance and actions	Evidence base references
Stage I Molecular (Insulin Resistance)	(Epi)genetic Risk	Family history	131,132
	ABCD	Investigational molecular markers	133
	CMDS	Basal hyperinsulinemia	134
		Abnormal adiposity	23,35,55
		Policy/laws/education for a healthy built environment	135,136
		Lifestyle change	137,138
		Cardiometabolic health	139
Stage 2 Biochemical Cardiometabolic Risk (Prediabetes)	Abnormal IFG, IGT, A1C	Screen/manage other MetS components	23
	GDM	ILI	31,44,47,90,92,121-127,140
	PCOS	Consider pharmacological therapy with Stage 2b	31,141
		Cardiometabolic risk	23
Stage 3 Biochemical Disease (Type 2 Diabetes)	Abnormal IFG, IGT, A1C	ILI	26
		Pharmacological therapy if needed for glycemic target	26
		Cardiometabolic disease	23
Stage 4 Vascular Complications (Type 2 Diabetes with Complications)	T2D complications	ILI	26
		Pharmacological therapy for glycemic targets	26
		Pharmacological/procedural therapy for specific complications	26
		Consider procedure with risk factors to achieve glycemic targets and complication management	142
		Cardiometabolic event biomarkers	143

Abbreviations: A1C = hemoglobin A1c; ABCD = adiposity-based chronic disease; CMDS = cardiometabolic disease staging system; DBCD = dysglycemia-based chronic disease; IFG = impaired fasting glucose; GDM = gestational diabetes; IGT = impaired glucose tolerance; ILI = intensive lifestyle intervention; MetS = metabolic syndrome; PCOS = polycystic ovary syndrome; T2D = type 2 diabetes.

^aThe severity of T2D complications is provided using the CMDS and other published information. Intensive lifestyle intervention consists of weight loss and strength training (when needed to optimize body composition), physical activity, healthy eating patterns, improved sleep hygiene, stress reduction, tobacco cessation, etc. Pharmacologic agents associated with T2D risk reduction are: phentermine/topiramate (49-89%); metformin (26-77%); troglitazone (54-75%); pioglitazone (70%); rosiglitazone (55%); orlistat (45%); lorcaserin (38%); and acarbose (25%) (141).

tically increased risk for T2D-related complications amenable to secondary prevention strategies. Aggressive case finding for CVD and T2D complications is critical in this stage. In patients with T2D with nonvascular complications, tertiary prevention strategies are needed to prevent further morbidity. Population-based primordial prevention strategies, used to reduce risk in the general population, are also applicable in this stage.

4. **Stage 4 DBCD “Vascular Complications”:** defined by the clinical presence of T2D microvascular complications (e.g., retinopathy, nephropathy, and neuropathy) and/or T2D macrovascular disease events (e.g., myocardial infarction, stroke, amputation, and ischemic foot ulcer), representing end-stage DBCD. These forms of organ dysfunction require tertiary prevention, or treatment, to ameliorate or reduce further deterioration. In this process, complications are diagnosed and treatment approaches fashioned according to mortality risks:
 - Stage 4a: mild complications,
 - Stage 4b: moderate complications, and
 - Stage 4c: severe complications (130).

Population-based primordial prevention strategies are also applicable for stage 4 DBCD and can help reduce the emergence of new CVD risk factors.

Rather than using a continuous spectrum with blurred demarcations among pathologic states, the above discrete stages are parsed out for practical application with respect to clinical context, pragmatic relevance, and an evidence base (Table 1) (131-143). Each of the stages is also amenable to quaternary prevention, in which overmedicalization and iatrogenesis are minimized.

DYSGLYCEMIA-BASED CHRONIC DISEASE—A NEW MULTIMORBIDITY T2D MODEL

Chronic disease is generally regarded as a pathological condition lasting for more than 3 months (144). In order for a medical condition to be viewed within a preventive care model, 3 criteria should exist: (1) association with a significant amount of human suffering; (2) safe and effective, affordable, and validated screening tools; and (3) safe and effective, affordable, and validated interventions for each prevention type (145,146). Even when there is a single etiology, there are many downstream paths that branch out producing multiple sequelae, complications, and morbid events. With complex interactions occurring over varying time scales, a steady state can emerge that characterizes the multimorbid chronic disease state (144). This model becomes even more complicated when there are multiple initiating, interacting, and/or concurrent etiologies, such as

T2D, obesity, coronary artery disease, cancer, depression, inflammation, frailty, and/or medications. The complexity of chronic disease emphasizes the importance of psychosocial, economic, and behavioral interventions, research metrics related to patient-defined goals of care, community-based leadership, and service- and therapeutic-level integration (147-149). The model will also need to be context-adaptable for people of different cultures/ethnicities (e.g., prediabetes to T2D conversion rates are faster for patients of South Asian > African > European ancestries; and in Asians, β -cell dysfunction predominates over insulin resistance [149-153]), as well as socio-economic strata and ability/disability (e.g., using patient-centered medical homes to improve diabetes self-management education and support [154]). In a study by Eisenstat et al (155) primarily addressing insulin use, patients with prediabetes and T2D were followed by a coordinated team in a network of primary care physicians, using evidence-based recommendations addressing medical, behavioral, and nutrition/lifestyle components. Certain factors were identified that facilitated care: diverse stakeholder engagement and buy-in with the theoretical basis of the model, institutional alignment of priorities, and credits for participation and implementation (155). The close integration of pharmacists can also improve adherence factors in the care model (156).

Overall, a chronic care model incorporates the following elements:

- a prepared and informed patient,
- capable, knowledgeable, and skilled health care professionals,
- organization of health care services,
- self-care support,
- clinical decision support,
- clinical information systems,
- design of the service delivery system, and
- community resources (157,158).

According to a systematic review of randomized, controlled trials involving patients with T2D from the Medline and Cochrane Library electronic databases, Baptista et al (157) found that the use of isolated chronic care model elements may be insufficient to improve clinical outcomes, but incorporating all of the elements together may prove beneficial. Figure 2 depicts the AACE DBCD multimorbidity T2D chronic care model based on the template used for the AACE obesity chronic care model that incorporates these and other elements (33). Each component is important in this preventive paradigm, which may have the greatest potential in terms of prevention of morbidity and mortality when patients are actively engaged in intervention at stage 2 DBCD Prediabetes.

The AACE DBCD model will require both clinical and economic validation. Research will need to address each component with respect to establishing thresholds

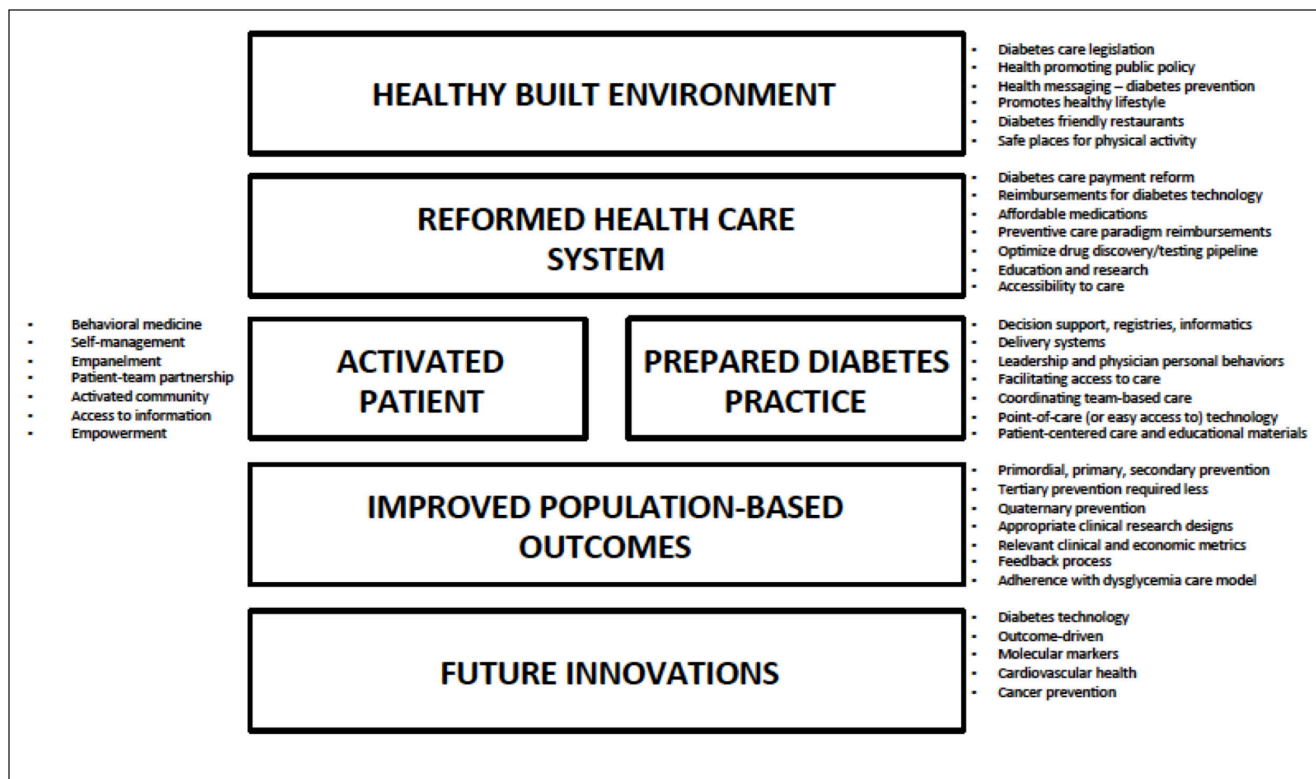


Fig. 2. American Association of Clinical Endocrinologists/American College of Endocrinology dysglycemia-based chronic disease multimorbidity type 2 diabetes care model. The built environment contextualizes diabetes care and consists of human-made entities. Decision support systems include electronic implementations of clinical practice guidelines. Delivery systems designs involve multidisciplinary care teams for glycemic control as well as complications. Empowerment is the process of linking patients with a diabetes care team and primary care physician, as well as serving as basis for performance metrics.

(molecular, biochemical, and clinical) for engagement and action, adhering with evidence-based management protocols appropriate for primary, secondary, and tertiary prevention, and incorporating suitable clinical outcome metrics. For instance, can transitions among the four stages and additional substages in the DCBD model be better demarcated using novel CGM technologies, cardiometabolic biomarkers, and metabolite/metabolomic biomarkers, along with revised fasting and postchallenge plasma glucose levels, judicious A1C testing, and self-monitoring of plasma glucose (132,159-161)? Can a FPG cutoff at 110 mg/dL (instead of 100 mg/dL) and/or A1C cutoff at 6.0% (42 mmol/mol) (instead of 5.7% [39 mmol/mol]) be used to discriminate a low-risk stage 2a (managed with lifestyle change) from a high-risk stage 2b (managed with lifestyle change and, if needed, pharmaceuticals) be validated (27,128,129,162)? The points here are that more research and analysis are needed to optimize these classifiers (163), rationally reduce unnecessary testing and pharmacotherapy (164), and improve lifestyle interventions for all subsets of the general population. Given the high prevalence of DBCD, risk stratification will be critically important from both the perspective of risk-benefit and cost-effectiveness in bringing more aggressive therapies to those patients at highest risk at each stage of preven-

tion/treatment. For example, using the Cardiometabolic Disease Staging system—a T2D risk stratification strategy employing the number of MetS traits and presence of prediabetes—demonstrates that a medicine-assisted weight-loss intervention can prevent T2D in high-risk individuals with lower numbers-needed-to-treat than in low-risk individuals (55,165,166).

Various economic modeling methods have already demonstrated positive impact for chronic disease management (167,168), including T2D (169). Introducing communications technology has been shown to facilitate adoption of a diabetes chronic care model and use of self-management strategies, while also lowering costs (170). Future economic studies on T2D prevention will need to concentrate on context, scope, payment models, income levels, self-management support, and impact on the labor market (169-172). The economic model will also need validation for patients of different cultures and ethnicities, both of which are associated with differences in key mechanistic drivers, phenotypic expression of disease, and conversion rates among the DCBD stages (173-176).

Currently, treatment of DBCD often begins at the time of T2D diagnosis. The DBCD paradigm places insulin resistance, prediabetes, MetS, T2D, and CVD within the context of a single chronic disease based on scientific

data and a current understanding of common pathophysiologic mechanisms. The clinical implications are that initiation of therapy only at the time of Stage 3 DBCD T2D or Stage 4 DBCD Vascular Complications diagnosis is not an optimal care approach. Rather, initiating DBCD management at earlier Stage 1 DBCD Insulin Resistance or Stage 2 DBCD Prediabetes can more effectively reduce disease progression, symptom burden, unhealthy population metrics, and overall health care costs. In fact, there is considerable scientific evidence that validate earlier intervention in high-risk individuals, including prediabetes, to reduce CVD (177-180). This new paradigm brings into focus health policy, the built environment, lifestyle medicine, and a philosophical position to restrain overmedicalization. With the perspective that T2D is only one stage in a progressive chronic disease process, a complement of preventive care modalities could rationally be initiated at any stage in DBCD progression depending upon risk-benefit and overall impact on public health, disease burden, and quality of life.

CONCLUSION

Recognizing and managing prediabetes is a necessary component for an effective personalized and population-based T2D care plan. In order to substantiate this position, AACE has formulated a DBCD multimorbidity care model consisting of four distinct stages in the general context of ABCD and cardiometabolic health and specific context along the insulin resistance-prediabetes-T2D spectrum that are actionable in a preventive care paradigm. Thus, prediabetes is regarded as stage 2 in the DBCD framework. This re-interpretation of prediabetes is consistent with other approaches, such as the recent move away from a strict glucocentric definition of prediabetes (181) to the AACE complications-centric (instead of BMI-centric) framework for obesity care (33,35).

The controversy over whether there is value, cost-effectiveness, or clinical benefit in diagnosing and/or managing the prediabetes state is resolved by regarding the problem, not in isolation where the evidentiary basis of

prediabetes recognition and management are challenged, but rather as part of comprehensive attention to a progressive, prevalent, and impactful metabolic disease, on a host of scales, managed by multiple concurrent preventive medicine strategies. This AACE position is consistent with a portfolio of endocrine disease care models that prioritize patient-centered care, evidence-based medicine, care models for complex and multimorbid chronic disease, the current health care environment, and a societal mandate for high value and good health.

With the refinement of the ABCD and DBCD diagnostic terms and care models, AACE will continue to develop comparable activities to eventually construct an actionable global cardiometabolic-based chronic disease framework. For instance, just as ABCD and DBCD incorporate and are part of inflammatory networks, new models of blood pressure homeostasis incorporate polarization of interstitial macrophage populations, direct effects on sodium sequestration, and networking effects on renovascular mechanisms of hypertension (52,182). Hence, chronic disease models of adiposity, dysglycemia, dyslipidemia, hypertension, and inflammation converge onto a unified theory of cardiometabolic risk. Consequently, any controversy over whether prediabetes exists or not will be obviated within this larger framework purposed to prevent morbidity and mortality from composite cardiometabolic risks. Moreover, at some point in the future, the concept of lifetime T2D risk can be formulated based on DBCD prevalence rates to inform decision-making and gauge whether diabetes fate can be avoided or merely delayed. At present, the DBCD framework is not applicable to type 1 diabetes.

Tactically, as with the AACE ABCD framework, a new diagnostic coding system can be engineered for prediabetes and T2D within the DBCD framework that can translate these concepts into organized action. As with ABCD, one can envision a robust coding system cross-tabulating each DBCD stage with specific phenotypes and complications. With validation and the development of appropriate reimbursement structures, a distinct transformation in endocrine health care can be realized.

Glossary Term

Adiposity

Definition (glossary terms in bold)

related to the amount, distribution, or function of fat tissue, cells containing fat, and/or adipocytes

Adiposity-based chronic disease

a chronic disease state resulting from abnormal **adiposity**

Aggressive case finding

process of identifying persons most likely to have a **chronic disease** based on presence of risk factors, manifestations, and likely benefit from treatment

Alpha (α)-cell dysfunction

mechanisms related to abnormal glucagon secretion in pancreatic α -cells in the context of increased hepatic glucose production, regulation by GIP and GLP-1, and **type 2 diabetes** pathogenesis and natural history

Beta (β)-cell dysfunction

mechanisms related to abnormal insulin secretion in pancreatic β -cells in the context of **type 2 diabetes** pathogenesis and natural history

Biochemical risk	abnormal blood tests that are correlated with an increased risk for disease (e.g., specified fasting plasma glucose, 2-hour post challenge plasma glucose, or hemoglobin A1c levels that diagnose prediabetes)
Built environment	the human-made world, including buildings and other structures, sidewalks and running paths, elevators and stairs, and all other aspects of human-made surroundings for daily life; this does not include natural surroundings (e.g., climate, geography, or terrain) or culture (e.g., religion, socio-economics, or politics)
Cardiometabolic risk	term that encompasses both metabolic risk for diabetes and vascular risk for coronary heart disease and/or stroke due to common pathophysiologic processes. This can also be understood as a broader and more interpretative term that describes the aggregate risk for atherosclerotic cardiovascular disease based on component metabolic factors, such as adiposity and dysglycemia
Cardiovascular disease	diseases of the heart and/or blood vessels that include: coronary heart, rheumatic heart, congenital heart, cerebrovascular, and peripheral arterial disease, as well as deep vein thrombosis, pulmonary embolus, heart failure, arrhythmia, and other valvular problems
Chronic disease	a disease state that persists for 3 months or longer; generally associated with a complex array of predisposing biological, environmental, and cultural factors, clinical manifestations, and complication risks
Diabetes-related complications	end-organ dysfunction that results from diabetes (e.g., nephropathy, retinopathy, and neuropathy)
Diabetes (mellitus)	a chronic disease state characterized by abnormally high blood glucose levels and increased risk for premature mortality and diabetes-related complications , such as retinopathy and cardiovascular disease
Disease	a diagnosed medical condition that impairs normal function, has characteristic signs or symptoms, and causes harm or morbidity. At present, diabetes is considered a disease , but prediabetes is considered a predisease . Diseases are managed with secondary prevention or tertiary prevention strategies.
Dysglycemia	a more general term that includes all forms of diabetes (usually type 2 diabetes) and prediabetes , including states of increased molecular risk for diabetes
Dysglycemia-based chronic disease	a chronic disease state resulting from dysglycemia
Hyperglycemia	elevated plasma glucose, generally interpreted in a specific physiologic context, such as fasting, postprandial, postchallenge , stress, or pregnancy
Incretin resistance	a pathophysiologic state in which β -cells exhibit subnormal or absent insulin secretory responses to incretins and α -cells exhibit partial or unsuppressed glucagon secretory responses to incretins
Insulin resistance	a pathophysiologic state in which cells exhibit subnormal responses to insulin; generally understood in the context of hepatocytes and myocytes in type 2 diabetes , as an etiologic event producing hyperglycemia , exacerbated by hyperglucagonemia and α-cell dysfunction , and either independent or dependent on β-cell dysfunction
Intervention	an action that encompasses all types of prevention
Lifestyle	one's manner of living, generally consisting of attitudes, beliefs, practices, culture, and interactions with the natural and built environment
Lifestyle medicine	the nonpharmacologic and nonsurgical/nonprocedural management of chronic disease
Metabolic syndrome	cluster of specific and residual risks for cardiovascular disease ; depending on the consensus definition, specific risks include insulin resistance , obesity , hypertension, hypertriglyceridemia, and markers of vascular inflammation and thrombosis
Molecular Risk	a predisease state characterized by the association of statistical- or network-based genetic or molecular markers (classifiers) with an increased incidence or prevalence rate of a chronic disease state
Obesity	a term used to describe the chronic disease state associated with a body mass index at or over specific ethnicity-adjusted cutoffs (e.g., 30 kg/m ² for Caucasians) presumed to be due to an increased amount of adiposity
Overweight	a term used to describe the pre- obesity state associated with a body mass index at or over specific ethnicity-adjusted cutoffs (e.g., 25 kg/m ² for Caucasians) presumed to be due to an increased amount of adiposity

Postchallenge	describes the context for hyperglycemia when a plasma glucose level is measured a specified time after administration of a specified amount of glucose (e.g., 75 g of oral glucose and measuring plasma glucose 2 hours later; the “2-hour oral glucose tolerance test”)
Prediabetes	a predisease state characterized by one or more abnormal biochemical tests (e.g., fasting plasma glucose, postchallenge plasma glucose, or hemoglobin A1c) that are associated with increased incidence or prevalence of type 2 diabetes and cardiovascular disease
Predisease	a term describing an early stage of chronic disease , before the disease is diagnosed, and during which time screening or aggressive case finding may be performed, and primary prevention strategies implemented
Primary prevention	population- and individual-based strategies applied before a disease is diagnosed in order to prevent disease occurrence; this includes effective screening and aggressive case finding , primordial prevention tactics, and in some cases, the judicious use of pharmacotherapy
Primordial prevention	population-based strategies applied at all stages along the chronic disease spectrum to reduce the incidence and prevalence of risk factors for chronic disease(s) ; examples include beneficial changes in behavior, the built environment , socio-economics, and health care policy
Quaternary prevention	population- and individual-based strategies applied to all stages along the chronic disease spectrum to reduce over- medicalization; specifically decreasing adverse events, improving value, and encouraging ethical decision-making; emphasizes primordial , primary , and secondary prevention education and practice
Residual risk	the amount of risk for a chronic disease that remains once specific, known component risks have been reduced (e.g., the risk for cardiovascular disease after hypertension, obesity , insulin resistance , and dyslipidemia risks have been controlled in patients with metabolic syndrome)
Screening	process of identifying persons most likely to have a common chronic disease but without clinical risks or manifestations, based on the application of a test, where safe and cost-effective treatments are available
Secondary prevention	population- and individual-based strategy applied to diagnosed chronic disease states in early stages to reduce the general impact or morbidity of the disease ; modalities generally include regular medical examinations, effective diagnostic testing, lifestyle medicine , and when needed, pharmacotherapy
Tertiary prevention	population- and individual-based strategy applied to diagnosed chronic disease states in later stages to reduce the impact of specific symptoms and slow the progression of specific complications; this can be the costliest and most prevalent prevention modality, including relatively expensive pharmacotherapy and procedures, and is the principal target of quaternary prevention
Type 2 diabetes	a specific type of diabetes that results from α-cell dysfunction , β-cell dysfunction , and insulin resistance , generally characterized by insufficient insulin action to prevent hyperglycemia but sufficient insulin action to prevent ketoacidosis, except in later stages and/or atypical forms; associated with specific diabetes-related complications

DISCLOSURES

Dr. Mechanick received honoraria for lectures and program development from Abbott Nutrition. Dr. Garber is a consultant to Novo Nordisk and Intarcia Therapeutics. Dr. Grunberger reports research contracts with Novo Nordisk and Medtronic and is on the speakers bureau of Eli Lilly, Novo Nordisk, Sanofi, Janssen, Boehringer Ingelheim, and AstraZeneca. Dr. Handlesman reports research grants and consultant and speaker honoraria from Aegerion, Amarin, Amgen, AstraZeneca, Bristol-Myers-Squibb, Boehringer Ingelheim, BI-Lilly, Gan & Lee, Gilead, Grifols, Hamni, Intarcia, Janssen, Lexicon, Lilly, Merck, Mylan, Merck-Pfizer, Novo Nordisk, Regeneron, and Sanofi. Dr. Garvey

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