Dysglycemia-based Chronic Disease—Diabetes Re-worked

Jeffrey I Mechanick[1]

1. Divisions of Cardiology and Endocrinology, Diabetes and Bone Disease, Icahn School of Medicine at Mount Sinai, New York City, NY, US

DOI: https://doi.org/10.17925/USE.2018.14.2.77

Type 2 diabetes (T2D) is a complex, chronic disease with a significant quality of life burden for affected individuals, as well as socio-economic burdens on a population scale. Efforts to mitigate morbidity, mortality, and risks for other acute and chronic diseases have been compromised by a traditional chronic disease model that focuses on tertiary prevention (i.e., waiting until the disease is fully manifest and in many cases with severe complications). More specifically, the role for prevention at an earlier "prediabetes" stage has been questioned. A re-examination of the biology and clinical data on T2D pathogenesis can modulate the way we think about T2D. The new Dysglycemia-Based Chronic Disease (DBCD) model addresses these challenges by positioning T2D and prediabetes along a continuous spectrum from insulin resistance to prediabetes to T2D to vascular complications. It is hoped that by conceptualizing T2D in the DBCD framework, health care professionals can provide more efficient, cost-effective care.

Keywords

Diabetes, prediabetes, insulin resistance, dysglycemia, cardiovascular disease, chronic disease

Disclosures: Professor Mechanick received honoraria for lectures from Abbott Nutrition International.

Review Process: Double-blind peer review.

Authorship: All named authors meet the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

Received: October 10, 2018

Accepted: November 2, 2018

Citation: *US Endocrinology.* 2018;14(2):77–9

Corresponding Author: Jeffrey I. Mechanick, The Mount Sinai Hospital, 1 Gustave L. Levy Place, Box 1030, New York, NY 10029 USA. E: jeffreymechanick@gmail.com

Support: No funding received for publication of this article.

Diabetes afflicts 9.4% of the US population with about 90–95% having type 2 diabetes (T2D) and another 33.9% of the US population having prediabetes (2017 data).[1] In 2015, it was estimated that 23.8% of patients with diabetes and 88.4% of patients with prediabetes did not even know they had the condition.[1] This diabetes and prediabetes unawareness prompts several key questions:

- What is the impact of this chronic disease unawareness on individual and population health, and can that impact be mitigated through earlier diagnosis and intervention?
- What is the biological basis for successful targeted action?
- What would this new framework for T2D care actually look like?

Impact of type 2 diabetes and prediabetes unawareness

Approximately 70% of patients with prediabetes have a lifetime risk of converting to T2D,[2–4] so primary prevention is a critical component of any comprehensive risk mitigation strategy. Interventions that improve insulin sensitivity can prevent T2D in at-risk patients through weight loss, healthy eating patterns, increased physical activity, and various diabetes medications (e.g., metformin, thiazolidinediones, and incretin-based therapies).[5–9]

Patients with prediabetes also have significant cardiovascular disease (CVD) risk factors: 51.2% with dyslipidemia, 36.6% hypertension, 24.3% tobacco use, and a 10-year cardiovascular (CV) event risk of 5.7%.[10,11] Prediabetes is independently associated with microvascular disease (due to hyperglycemia and not associated with CV risk scores), which can evolve into T2D-associated CVD.[12] Huang et al. determined relative risks in patients with prediabetes: 1.13–1.30 for composite CVD, 1.10–1.20 for coronary heart disease, 1.06–1.20 for stroke, and 1.13–1.32 for all-cause mortality.[11] So, secondary prevention of CVD is also a critical component in this overall strategy. When patients are unaware of the diagnosis of prediabetes, primary and secondary prevention strategies cannot be implemented, and therefore T2D and CVD are not averted.

Do appropriate interventions mitigate risk? First, there is progression of T2D-related complications without interventions.[13–16] Second, there is reduction of cardiometabolic risk with lifestyle and weight loss interventions.[17–23] Third, there are decreased health care expenditures with interventions.[24–30] With this emerging evidence base affirming benefits of early intervention, the next question is why are these maneuvers not more aggressively applied well before a patient is diagnosed with T2D? The key may be translating this compelling information into concrete, teachable, actionable steps that are also feasible in our very onerous health care system.

Biological basis for targeted action

Insulin resistance can be associated with abnormal adiposity (amount, distribution, and function) as described by the recently published Adiposity-Based Chronic Disease (ABCD) model.[31] Insulin resistance is differentiated from prediabetes by the lack of any abnormalities in glycemic status (fasting, post-prandial, casual, post-challenge, or via hemoglobin A1c) in the former. Weight gain with insulin resistance can worsen adipocyte dysfunction and produce prediabetes, metabolic syndrome, T2D, and eventually CVD.[32–34] Insulin resistance and pancreatic β-cell dysfunction are the main initiating events for developing T2D. Other mechanisms involve pancreatic α-cell dysfunction (hyperglucagonemia), glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1,[35] and mitochondrial methylation factors.[36] In fact, there are 248, 138, and 24 genes from human β-, α-, and δ-cell transcriptomes respectively, with differential expression in T2D versus non-diabetes.[37]

A dynamic driver network for the important predisease-T2D transition mechanisms was outlined by Jin et al.[38] In this network, structured lifestyle change at critical time points can slow down disease progression and decrease T2D.[38] Notably, in those with a high genetic risk for coronary heart disease, a healthy lifestyle was associated with nearly 50% relative risk reduction.[39] Many of these biological and lifestyle effects vary in different ethnicities, such as Asian Indians who may have relatively more β-cell dysfunction and faster prediabetes to T2D conversion rates than Caucasians.[40]

The dysglycemia-based chronic disease framework

Dysglycemia can be viewed as any abnormality in glycemic status associated with disease or disease potential. The American Association of Clinical Endocrinologists (AACE) has recently created a new framework to optimize the care of patients with or at-risk for T2D termed Dysglycemia-Based Chronic Disease (DBCD).[41] The impetus for this new model can be summarized as follows:

- initial triggering by questions of whether the concept of "prediabetes" is helpful, based on concerns that notwithstanding earlier diagnosis and the potential for prevention tactics, this intervention would prove too costly for the small number of actual patients realizing benefit;[42] this problem is solved by validating prediabetes not as an entity in isolation, but rather as a necessary event along a spectrum with antecedent drivers and downstream consequences;
- recent AACE experience reworking chronic endocrine disease models in obesity;[41,43] and
- heightened awareness and need for a new T2D care model that is actionable and results in earlier diagnosis and prevention tactics, particularly incorporating early and pervasive structured lifestyle change.

The DBCD framework has the following structure: a continuous spectrum with four stages, preventive strategies, and specific actions:

- Stage One: molecular risk or insulin-resistance—amenable to primordial and primary prevention (emphasizing structured lifestyle change) to decrease risk for stages 2–4; requires initiative primarily with local community centers and governmental agencies for population-based programs (posted nutrition facts, distribution of educational materials, public service announcements, creation of sufficient, safe physical activity sites, tobacco cessation campaigns, etc.);
- Stage Two: biochemical cardiometabolic risk or prediabetes—continuation of primordial prevention programs in addition to primary and secondary prevention programs (structured lifestyle change and possibly medication) to decrease risk for stages 3 and 4; focused education for health care professionals (HCP), creation of comprehensive lifestyle medicine protocols with high-touch clinical settings and high-technology nudges (e.g., wearable technologies), innovative therapeutic environments that facilitate medical fitness and nutritional counseling with physician services, incorporation of sleep hygiene, community engagement, and behavioral medicine into lifestyle medicine centers;
- Stage Three: biochemical disease or T2D—continuation of primordial and primary prevention programs in addition to secondary and tertiary prevention programs (structured lifestyle change and, as needed, medication) to decrease the risk for stage 4; requires routine implementation of formal lifestyle medicine with and without pharmacotherapy, emphasis on comprehensive and complication-centric care, protocol-based tailoring of nutrition and physical activity recommendations based on specific disease severity and phenotype; and
- Stage Four: vascular complications or T2D with complications—continuation of primordial, primary, and secondary prevention programs in addition to tertiary prevention programs (structure lifestyle change with increasing medication and other procedures) to prevent further progression of disease, morbidity, and mortality; requires formal lifestyle medicine protocols that are interwoven with pharmacotherapy and procedures (e.g., renal and T2D nutritional recommendations for patients receiving hemodialysis; healthy eating counseling for patients having had bariatric surgery; comprehensive cardiac rehabilitation after coronary artery bypass surgery that also includes nutritional and behavioral counseling).

The DBCD framework will require further scientific substantiation to validate and better characterize the relative causal dependencies, perhaps in a more detailed probabilistic model. Furthermore, the major context of the DBCD is the prevention of CVD by comprehensively addressing cardiometabolic risk factors as early as possible. This framework could better inform and guide clinical decision-making in T2D care to improve outcomes at lower costs. New diagnostic coding systems for reimbursements along the entire DBCD spectrum, as also hoped for in obesity care based on the ABCD model, could be forthcoming. From a pragmatic standpoint, implementation of the DBCD framework would prompt structured lifestyle interventions in every patient, especially those in diabetogenic and obesogenic environments. Perhaps clinical practice settings will then have a higher level of preparedness with easy access to gyms, exercise physiologists, wearable technologies to monitor glycemic status, and nutritionists, behaviorists, and others who can leverage lifestyle optimization. ❑

1. Centers for Disease Control and Prevention. 2017 National Diabetes Statistics Report. Available at: www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf (accessed October 28, 2017).
2. Tabak AG, Herder C, Rathmann W, et al. Prediabetes: a high-risk state for diabetes development. *Lancet*. 2012;379:2279–90.
3. Nathan DM, Davidson MB, DeFronzo RA, et al.; American Diabetes Association. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care*. 2007;30:753–59.
4. Ligthart S, van Herpt TT, Leening MJ, et al. Lifetime risk of developing impaired glucose metabolism and eventual progression from prediabetes to type 2 diabetes: a prospective cohort study. *Lancet Diabetes Endocrinol*. 2016;4:44–51.
5. Grams J, Garvey WT. Weight loss and the prevention

and treatment of type 2 diabetes using lifestyle therapy, pharmacotherapy, and bariatric surgery: mechanisms of action. *Curr Obes Rep*. 2015;4:287–302.
6. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. Diabetes Prevention Program Research Group. *N Engl J Med*. 2002;346:393–403.
7. Garvey WT, Ryan DH, Henry R, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended-release. *Diabetes Care*. 2014;37:912–21.
8. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet*. 2017;389:1399–409.
9. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators: Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet*. 2006;368:1096–105.
10. Ali MK, Bullard KM, Saydah S, et al. Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988–2014. *Lancet Diabetes Endocrinol*. 2018;6:392–403.
11. Huang Y, Cai X, Mai W, et al. Association between prediabetes and risk of cardiovascular disease and all-cause mortality: systematic review and meta-analysis. *BMJ*. 2016;355:i5953. DOI: 10.1136/bmj.i5953.
12. Sörenson BM, Houben AJHN, Berendschot TTJM, et al. Hyperglycemia is the main mediator of prediabetes- and type 2 diabetes-associated impairment of microvascular function: the Maastricht study. *Diabetes Care*. 2017;40:e103–5.
13. Ratner R, Goldberg R, Haffner S, et al. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. *Diabetes Care*. 2005;28:888–94.
14. DECODE Study Group, European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? *Diabetes Care*. 2003;26:688–96.
15. Qiao Q, Jousilahti P, Eriksson J, et al. Predictive properties of impaired glucose tolerance for cardiovascular risk are not explained by the development of overt diabetes during follow-up. *Diabetes Care*. 2003;26:2910–4.
16. Rodriguez BL, Lau N, Burchfiel CM, et al. Glucose intolerance and 23-year risk of coronary heart disease and total mortality: the Honolulu Heart Program. *Diabetes Care*. 1999;22:1262–5.
17. Salimi Y, Fotouhi A, Mohammad K, et al. Causal effects of intensive lifestyle and metformin interventions on cardiovascular disease risk factors in pre-diabetic people: an application of G-estimation. *Arch Iran Med*. 2017;20:55–9.
18. Siddiqui F, Kurbasic A, Lindblad U, et al. Effects of a culturally adapted lifestyle intervention on cardio-metabolic outcomes: a randomized controlled trial in Iraqi immigrants to Sweden at high risk for type 2 diabetes. *Metabolism*. 2017;66:1–13.
19. Su W, Chen F, Dall TM, et al. Return on investment for digital behavioral counseling in patients with prediabetes and cardiovascular disease. *Prev Chronic Dis*. 2016;13:E13. DOI: 10.5888/pcd13.150357.
20. Nanditha A, Ram J, Snehalatha C, et al. Early improvement predicts reduced risk of incident diabetes and improved cardiovascular risk in prediabetic Asian Indian men participating in a 2-year lifestyle intervention program. *Diabetes Care*. 2014;37:3009–15.
21. Lindström J, Ilanne-Parikka P, Peltonen M, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet*. 2006;368:1673–9.
22. Orchard TJ, Temprosa M, Goldberg R, et al. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med*. 2005;142:611–9.
23. Uusitupa M, Lindi V, Louheranta A, et al. Long-term improvement in insulin sensitivity by changing lifestyles of people with impaired glucose tolerance: 4-year results from the Finnish Diabetes Prevention Study. *Diabetes*. 2003;52:2532–8.
24. Ackermann RT, Marrero DG, Hicks KA, et al. An evaluation of cost sharing to finance a diet and physical activity intervention to prevent diabetes. *Diabetes Care*. 2006;29: 1237–41.
25. Dalziel K, Segal L. Time to give nutrition interventions a higher profile: a cost-effectiveness of 10 nutrition interventions. *Health Promot Int*. 2007;22:271–83.
26. Palmer AJ, Roze S, Valentine WJ, et al. Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modeling the long term health economic implications of the diabetes prevention program in Australia, France, Germany, Switzerland, and the United Kingdom. *Clin Ther*. 2004;26:304–21.
27. Lindgren P, Lindström J, Tuomilehto J, et al. DPS Study Group. Lifestyle intervention to prevent diabetes in men and women with impaired glucose tolerance is cost-effective. *Int J Technol Assess Health Care*. 2007;23:177–83.
28. Ramachandran A, Snehalatha C, Yamuna A, et al. Cost-effectiveness of the interventions in the primary prevention of diabetes among Asian Indians: within trial results of the Indian Diabetes Prevention Programme (IDPP). *Diabetes Care*. 2007;30:2548–52.
29. Diabetes Prevention Program Research Group. Within trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care*. 2003;26:2518–23.
30. Mudaliar U, Zabetian A, Goodman M, et al. Cardiometabolic risk factor changes observed in diabetes prevention programs in US settings: a systematic review and meta-analysis. *PLoS Med*. 2016;13:e1002095. DOI: 10.1371/journal.pmed.1002095.
31. Mechanick JI, Hurley DL, Garvey WT. Adiposity-based chronic disease as a new diagnostic term: the American Association of Clinical Endocrinologists and American College of Endocrinology position statement. *Endocr Pract*. 2017;23:372–8.
32. Stefan N, Kantartzis K, Machann J, et al. Identification and characterization of metabolically benign obesity in humans. *Arch Intern Med*. 2008;168:1609–16.
33. Wildman RP, Muntner P, Reynolds K, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999–2004). *Arch Intern Med*. 2008;168:1617–24.
34. Guo F, Garvey WT. Cardiometabolic disease risk in metabolically healthy and unhealthy obese: stability of metabolic health status in adults. *Obesity*. 2016;24:516–25.
35. Lund A, Bagger JI, Christensen M, et al. Glucagon and type 2 diabetes: the return of the alpha cell. *Curr Diab Rep*. 2014;14:555. DOI: 10.1007/s11892-014-0555-4.
36. Zheng LD, Linarelli LE, Brooke J, et al. Mitochondrial epigenetic changes link to increased diabetes risk and early-stage prediabetes indicator. *Oxid Med Cell Longev*. 2016;2016:5290638. DOI: 10.1155/2016/5290638.
37. Lawlor N, George J, Bolisetty M, et al. Single-cell transcriptomes identify human islet cell signatures and reveal cell-type-specific expression changes in type 2 diabetes. *Genome Res*. 2017;22:208–22.
38. Jin B, Liu R, Hao S, et al. Defining and characterizing the critical transition state prior to the type 2 diabetes disease. *PLoS ONE*. 2017;12(7):e0180937. DOI:10.1371/journal.pone.0180937.
39. Khera AV, Emdin CA, Drake I, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *New Engl J Med*. 2016;375:2349–58.
40. Gujral UP, Mohan V, Pradeepa R, et al. Ethnic variations in diabetes and prediabetes prevalence and the roles of insulin resistance and β-cell function: the CARRS and NHANES studies. *J Clin Transl Endocrinol*. 2016;4:19–27.
41. Mechanick JI, Garber AJ, Grunberger G, et al. Dysglycemia-based chronic disease: an American Association of Clinical Endocrinologists position statement. *Endocr Pract*. 2018;(In Press).
42. Yudkin JS, Montori VM. The epidemic of pre-diabetes: the medicine and the politics. *BMJ*. 2014;349:g4485. DOI: 10.1136/bmj.g4485.
43. Garvey WT, Garber AJ, Mechanick JI, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the 2014 advanced framework for a new diagnosis of obesity as a chronic disease. *Endocr Pract*. 2014;20:977–89.