HHS Public Access

Author manuscript

Endocrinol Metab Clin North Am. Author manuscript; available in PMC 2019 March 01.

Published in final edited form as:

Endocrinol Metab Clin North Am. 2018 March ; 47(1): 33–50. doi:10.1016/j.ecl.2017.10.001.

Prediabetes and Cardiovascular Disease: Pathophysiology and Interventions for Prevention and Risk Reduction

Ben Brannick, MD [Chief Clinical Endocrinology Fellow] and **Sam Dagogo-Jack, MD [Professor of Medicine and Director]**

Division of Endocrinology, Diabetes & Metabolism, University of Tennessee Health Science Center, Memphis, Tennessee, USA

Synopsis

Prediabetes is a state characterized by impaired fasting glucose or impaired glucose tolerance. This review discusses the pathophysiology and macrovascular complications of prediabetes. The pathophysiologic defects underlying prediabetes include insulin resistance, alpha- and beta-cell dysfunction, increased lipolysis, inflammation, and suboptimal incretin effect. Recent studies have revealed that the long-term complications of diabetes manifest in some people with prediabetes; these complications include microvascular and macrovascular disorders. Finally, we present an overview of randomized control trials aimed at preventing progression from prediabetes to type 2 diabetes and discuss their implications for macrovascular risk reduction.

Keywords

Impaired fasting glucose; impaired glucose tolerance; prediabetes complications; cardiovascular disease; macrovascular

Introduction

Type 2 diabetes mellitus (T2DM) is one of the major causes of premature morbidity and mortality worldwide with the World Health Organization (WHO) reporting that one in ten adults worldwide had T2DM in 2014.[1] In the United States, one out of every five health care dollars is spent on diabetes related healthcare.[2] Diabetes Mellitus also imposes a huge drain in developing countries on national health budgets comprising on average at least 5% of their total health expenditures on diabetes in 2010.[3] Of these, macrovascular complications are the largest contributor to the direct and indirect costs of diabetes.[4] The development of T2DM is punctuated by an interlude of prediabetes, itself a toxic state that is associated with the development of macrovascular complications.

Corresponding Author: Sam Dagogo-Jack, MD, Division of Endocrinology, Diabetes & Metabolism, University of Tennessee Health Science Center, 920 Madison Avenue Suite 300A, Memphis, TN 38163 USA, Tel.: (901) 448-5318, sdj@uthsc.edu.

Authors' contributions: SD-J, as senior author, created the design and content of this manuscript. Both SD-J and BB drafted, revised and produced the final version of the manuscript.

Diagnosis and Burden of Prediabetes

The prelude to diabetes is prediabetes in what can be described as a continuum from normoglycemia through worsening dysglycemia. Prediabetes is defined specifically as impaired glucose tolerance and/or impaired fasting glucose.[5] According to the American Diabetes Association (ADA) impaired glucose tolerance (IGT) is defined as a 2-hour plasma glucose value in the 75-gram oral glucose tolerance test (OGTT) of 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L).[6] Impaired fasting glucose (IFG) is defined as a fasting plasma glucose of 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L).[6] Finally prediabetes can also be defined as a hemoglobin A1c (HbA1c) of 5.7% –6.4% (39–46 mmol/mol).[6,7] It bears stressing that the ADA criteria stipulate normal glucose tolerance (NGT) as a fasting glucose level less of than 100mg/dl and a 2-hr post-load OGTT plasma glucose level of less than 140mg/dl. In regards to using HbA1c as a diagnosis of prediabetes, it must be stressed that there are many well characterized “pitfalls” such as anemia, chronic kidney disease, and other systemic illness and hematological disorders that disrupt the reliability of HbA1c as an integrated measure of mean plasma glucose.[8–12] In particular, racial and ethnic differences in the relationship between blood glucose values and HbA1c call for caution when utilizing HbA1c levels for the diagnosis of prediabetes. 8–14 It is always prudent to confirm diagnosis with actual blood glucose measurement before instituting therapeutic measures.[8] Estimates by the Centers for Disease Control and Prevention (CDC) in the United States indicated that there were ~29 million adults with diabetes and 86 million with prediabetes in 2014.[15,16] Worldwide, there are more than 400 million people with prediabetes and projections indicate that more than 470 million people will have prediabetes by 2030.[17] In addition, many studies from across the globe have pointed out that the risk of many co-morbidities are the same in diabetes and prediabetes and affect all age groups.[18–23]

Pathophysiological Defects in Prediabetes

The known pathophysiological defects that underlie T2DM are being increasingly recognized in the prediabetic state.[24–28] The natural progression of dysglycemia involves increasing insulin resistance and loss of pancreatic β-cell function.[29] Significant defects in insulin action and secretion are consistently demonstrable in the prediabetic state of IGT.[30–32] Several cross-sectional studies and a few longitudinal studies have carefully documented the various defects leading to prediabetes and T2DM.[33–35]

Findings from Longitudinal Assessment of Insulin Action and Secretion

A landmark longitudinal study that tracked high risk subjects from the stage of NGT to prediabetes reported that the transition to prediabetes was associated with an increase in body weight, increase in insulin resistance, and a decline in the endogenous insulin secretion (beta-cell dysfunction).[29] The study further demonstrated that progression from prediabetes to T2DM was accompanied by a worsening of weight gain, insulin resistance, and beta-cell dysfunction.[29] Thus the salient finding from the longitudinal observation was that insulin resistance and beta-cell failure co-evolve simultaneously rather than sequentially, as was previously believed. Individuals who maintained NGT status, despite weight gain and associated insulin resistance, were those who mounted a robust endogenous insulin secretory response.[29] Thus, if beta-cells cannot overcome insulin resistance, dysglycemia ensues. A

supportive post-mortem study reported ~40% deficit in relative β-cell volume among individuals with prediabetes compared to those with normal fasting glucose concentrations.[35]

Lipolysis, Incretin, Alpha Cell, and Inflammation in Prediabetes

Further defects in the prediabetic state include increased lipolysis, decreased endogenous levels of glucagon-like peptide 1 (GLP-1), and impaired postprandial suppression of glucagon secretion by the alpha-cells of the pancreas.[36–40] Additionally, as listed in Table 1, aberrant expression of proinflammatory cytokines adds to the toxic milieu of prediabetes. For instance, low adiponectin levels have been demonstrated to be predictive of progression from NGT to prediabetes, and from prediabetes to T2DM.[39,41] Elevated levels of molecular markers such as intercellular adhesion molecule-1 (ICAM-1) and tumor necrosis factor-α (TNF-α) have been reported.[42] Figure 1 shows the recognized pathophysiological defects in T2DM, highlighting those that have also been described in prediabetes.[43–44]

Emerging insights regarding the gut microbiome and its association with cardiometabolic disorders, such as obesity, diabetes, dyslipidemia, etc., have relevance to prediabetes. Recently, a disturbed gut microbiota expressed as gut dysbiosis (an intestinal physical barrier abnormality) has been associated with the progression and maintenance of obesity, T2DM, cardiovascular disease (CVD) and the metabolic syndrome.[45–50] Future research into this area will help shed light onto the proximal chronology of the associated between gut dysbiosis and early dysglycemia/prediabetes.

Predictors of Glycemic Progression to Prediabetes/T2DM

Conversion from Prediabetes to T2DM

An analysis of six prospective studies on progression from prediabetes to T2DM revealed the following features: (1) baseline fasting plasma glucose (FPG) and the 2-h OGTT glucose values were positively associated with diabetes risk; (2) the rate of progression from prediabetes to T2DM was exponential among subjects in the top quartile of baseline FPG but increased linearly with increasing 2-h OGTT glucose levels; (3) incident diabetes occurred at higher rates in Hispanic, Mexican-Americans, Pima, and Nauruan populations than among other ethnicities such as Caucasians; (4) increased BMI predicted T2DM risk in low risk populations but not in populations with the highest incidence of T2DM.[51,52] Of note, weight gain significantly predicted the risk of incident T2DM in African-Americans in the Atherosclerosis Risk in Communities study.[53]

Normoglycemia to Prediabetes Transition

Longitudinal studies in subjects from a high-risk population (PIMA Indians) with baseline NGT indicated that weight gain, insulin resistance, and progressive loss of insulin secretory response to glucose predicted transition from NGT to IGT (prediabetes).[29,53] The longitudinal mean weight change in NGT → NGT subjects (nonprogressors) vs. NGT → IGT progressors was 2.6 kg vs. 5.2 kg during a 6-year follow-up period.[24]

In the Baltimore Longitudinal Study of Aging (BLSA), 62% of the initially NGT participants progressed to prediabetes during 10 years of follow-up, yielding an annualized rate of prediabetes 6.2% in the BLSA.[54]

In the Pathobiology of Prediabetes in a Biracial Cohort (POP-ABC) study, initially normoglycemic African American and European American offspring of parents with T2DM were followed longitudinally for the primary outcome of incident prediabetes (IFG or IGT). During a mean 2.62 years of follow-up 101 of 343 POP-ABC participants developed incident prediabetes, yielding an annualized rate of ~11%.[55] Compared to nonprogressors, POP-ABC participants who developed incident prediabetes were older, more likely to be male, had higher baseline BMI and fat mass, lower levels of physical activity (adjusted for food habits), lower measures of insulin sensitivity, disposition index; serum adiponectin and HDL cholesterol levels, and higher triglyceride levels.[41,55–57]

Macrovascular Complications of Prediabetes

The macrovascular disorders associated with prediabetes include CVD, stroke, and peripheral vascular disease. As figure 2 depicts, these disorders are established in patients with T2DM, but their initiation and progression are well recognized to occur during the prediabetes stage.[58–61] In fact, the traditional CVD risk factors (dyslipidemia, obesity, hypertension) are quite prevalent among individuals with prediabetes.[62–67]

Cardiovascular Disease

A recent meta-analysis based on 35 studies reported data for the association between myocardial infarction and congestive heart failure as well as coronary artery disease and atherosclerosis have all been reported in individuals with prediabetes.[67–69] In the EPIC-Norfolk study, a 1% increase in 27 HbA1c within the normal range was associated with increased 10-year cardiovascular mortality. The EPIC-Norfolk findings are in accord with data from the Paris Prospective Study cohort which 70 showed a doubling of CVD mortality in IGT subjects compared with NGT subjects. The finding of increased mortality is underscored by the fact that most patients with prediabetes harbor features of insulin resistance (metabolic) syndrome, including upper-body obesity, hypertriglyceridemia, decreased HDL cholesterol levels and hypertension, among others. Components of the metabolic syndrome often can be identified in prediabetic subjects several years before the diagnosis of [71,72] T2DM. These features translate into advanced atherosclerotic vascular changes which are often preceded by impairment of endothelium-dependent vasodilation, vascular smooth muscle dysfunction and increased arterial stiffness.[73]

A recent cross-sectional study reported a positive association between prediabetes and the prevalence of arterial stiffness, suggesting that early intervention on prediabetes control might prevent arterial stiffness.[74] Remarkably, the prediabetes state is associated a nearly 3-fold higher prevalence of unrecognized myocardial infarction compared with NGT status, as was demonstrated in the Multi-Ethnic Study of Atherosclerosis (MESA) study.[62]

More recently, a randomized controlled trial of 6522 patients with coronary artery disease and prediabetes found that while acarbose did not reduce the risk of major adverse cardiovascular events, it did reduce the incidence of diabetes.[75]

Stroke

Compared to NGT subjects, individuals with prediabetes have an increased risk of cerebrovascular diseases, including transient ischemic attack, stroke, and recurrent stroke.[65,76–79] A recent study by Tanaka and colleagues demonstrated that both diabetes and prediabetes were associated with poor early prognosis 30 days after acute ischemic stroke.[80] A study by Qiao et al. indicates that the 2-hr postload OGTT glucose level is a strong predictor of stroke and future cardiovascular disease.[81] In the recently published KORA-MRI study, among 400 subjects who underwent MRI, 103 subjects had prediabetes and 54 had established diabetes. Subjects with prediabetes had an increased risk for carotid plaque and adverse functional cardiac parameters.[82] In the IRIS trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or transient ischemic attack, treatment with pioglitazone significantly decreased the risks of stroke, myocardial infarction or development of T2DM as compared with placebo treament.[83,84]

Peripheral Vascular Disease

Prediabetes is common in patients with peripheral vascular disease; however, the exact mechanisms remain to be fully elucidated. The development of diabetes is independently associated with mortality in PVD patients in some but not all studies.[85,86]

Interactions among Prediabetes and CVD Risk Factors

Epidemiologic studies have shown that prediabetes is a strong predictor of CVD.[84–89] The studies include DECODE and Funagata Diabetes Study, among others.[88–91] In the San Antonio Heart Study, there was evidence that the risk for CVD starts to increase long before the onset of clinical diabetes.[92–94] Obesity and overweight, known risk factors for T2DM and prediabetes, have also been associated with CVD risk.[95–98] Overweight and obesity have been frequently associated with low-grade, chronic, systemic inflammation characterized by increased levels of pro-inflammatory markers including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), and C-reactive protein.[99] Also, overweight people with prediabetes often present with dyslipidemia (higher triglycerides and lower HDL cholesterol)[99–104] Hypertension is another CVD risk factor that has been examined in prediabetes.[105–109] The DREAM[105] and NAVIGATOR[106] studies assessed the effect of blood pressure control on the progression from prediabetes to T2DM. Similarly, the Diabetes Prevention Program investigators reported lower rates of incident hypertension among prediabetic individuals randomized to the intensive lifestyle arm as compared to the placebo arm.[107]

Intervention Studies to Prevent Progression from Prediabetes to T2DM and Development of CVD

Prevention of T2DM

Table 2 lists lifestyle and pharmacological intervention studies to prevent T2DM among individuals enrolled with prediabetes. Lifestyle intervention has clearly been demonstrated to decrease progression to T2DM.[106–111] The results of the DPP, Finnish Diabetes Prevention Study (FDPS), and other pertinent studies showed approximately 60% risk reduction for incident T2DM in the lifestyle arm compared to placebo.[112–116] In both the DPP and FDPS, every 1 kg decrease in weight in the lifestyle arm was associated with 15%–16% in future T2DM risk.[115,117–122]

There are also studies showing potential benefits from a variety of different pharmacotherapies.[122] Pioglitazone was found to decrease the risk of diabetes by ~70% in obese subjects with prediabetes in the ACT NOW study.[123] Table 2 lists pertinent randomized controlled trials from around the world that demonstrated significant decrease in progression of prediabetes to diabetes. These include the STOP-NIDDM (25% risk reduction), Xendos (45% risk reduction), DREAM (62% risk reduction), CANOE (26% risk reduction) and the Valsartan arm of the NAVIGATOR trial (14% risk reduction).[124–128] It must be noted, however, that in both the IDPP1 and the follow-up study IDPP2, pharmacologic intervention provided no additional benefit beyond lifestyle modification in subjects randomized to Lifestyle + Metformin or Lifestyle + Pioglitazone arms.[129,130] Furthermore, all the medications tested for diabetes prevention have had untoward adverse effects (sometimes severe), and attempts to withdraw the medications have resulted in glycemic rebound.[131–132] Given these limitations of pharmacotherapy, the current guidelines from the ADA recommend lifestyle modifications as first line approach for diabetes prevention.[6] Indications for possible use of metformin include women with a history of gestational diabetes and high-risk individuals unresponsive to optimal lifestyle modification.[6]

Prevention of CVD in Prediabetes

Long term follow-up of the Da Qing study demonstrated that diabetes prevention through lifestyle modification was associated with decreased cardiovascular and all-cause mortality after 23 years.[133] In the DPP, intensive lifestyle intervention that significantly decreased the risk of T2DM also reduced the need for antihypertensive medications.[107] The prevalence of hypertension in the DPP cohort at baseline was approximately 30% in the three comparison groups (placebo, metformin, lifestyle).[107] After 3 years of follow-up, the prevalence of hypertension was observed to have increased to approximately 40% in the placebo and metformin arms.[107] Surprisingly, the hypertension prevalence remained at the baseline rate of 30% in the intensive lifestyle group 3 years later.[107] Thus, lifestyle intervention designed to prevent T2DM also seems to have prevented incident hypertension in this initially prediabetic cohort.[107] The DPP investigators also reported that subjects assigned to intensive lifestyle intervention showed decreased blood pressure, increased HDL cholesterol levels, and lower triglyceride levels and a reduction in the more atherogenic small, dense LDL particles during approximately 3 years of follow-up.[107] Consonant with these findings, there

was a reduced need for lipid lowering medications in the DPP,[107, 109,110] as has been observed by others.[111–113,134,135]

The Mediterranean diet is appealing as a specific nutritional recommendation, based on convincing reports of its benefits on cardiometabolic endpoints. For example, results from the PREDIMED (PREvención con DIeta MEDiterránea) randomized nutrition intervention trial for the primary prevention of CVD showed a 40% reduction in the incidence of T2DM in participants assigned to a Mediterranean diet supplemented with extra-virgin olive oil compared with those assigned to a low-fat control diet.[136,137] Other reports on the Mediterranean diet showed concordant findings on cardiometabolic profile. Mediterranean-style diet has been shown to result in greater weight loss along with improvement in inflammatory markers compared with general lifestyle counseling (14kg vs. 3kg, $P < 0.001$).[138–141]

Besides the impact of lifestyle intervention on CVD risk factors, there is considerable interest in knowing whether prevention of diabetes also prevents related CVD. This has been a question under investigation by the Diabetes Prevention Program Outcome Study (DPPOS) research group. Analysis of regression patterns in the DPPOS showed that individuals whose blood glucose returned to normal experienced a 56% long-term reduction in diabetes incidence compared to those who remained dysglycemic.[109] Although CVD outcomes data collection is still in progress, additional inference from the DPPOS study would suggest that regression from prediabetes to normal may also be associated with decreased risk for CVD.[111,142]

Clinical Translation and Conclusion

Prediabetes is a toxic cardiometabolic state associated with increased risk for microvascular and macrovascular complications.[143] Physicians and healthcare providers should screen patients routinely for prediabetes and refer those with the condition for intensive lifestyle counseling. The goal is to achieve and maintain > 5% weight loss through caloric restriction and increased physical activity, similar to the DPP and kindred studies (Table 2).[6,34,63–64] Healthcare providers should endeavor to build strong ties within healthcare systems, communities, and payers, to increase the availability of evidence-based structured lifestyle programs.

In a recent survey 33.6% of outpatients (out of 1.16 million outpatient visits analyzed) had prediabetes, based on HbA1c results. Amazingly, < 1% of those patients whose HbA1c tests showed prediabetes were recognized and diagnosed as such by clinicians. Of the abysmally low numbers whose prediabetes status was properly captured in the clinical records, only 23% had documentation of treatment (lifestyle modification and/or metformin) in the medical record.[144] The prediabetes period presents an opportunity to intervene during the disease process. Primary care physicians, specialists, health systems and patients themselves all have an obligation to ensure that the opportunity for prevention is not missed.[145–149]

While it has long been known that diabetes confers significant cardiovascular risks, it is now becoming established that CVD risks precede diabetes and are evident in people with

prediabetes. Given the millions of people with prediabetes around the globe, the impact on cardiovascular health is staggering. However, identifying and intervening in the at-risk prediabetic populations requires education, increased awareness, care coordination, organization and novel reimbursement mechanisms at multiple levels (health systems, society and individual).

Acknowledgments

SD-J is supported, in part, by Grant R01 DK067269 from the National Institutes of Health.

Disclosure Statement

Dr. Brannick has nothing to disclose. Dr. Dagogo-Jack is supported, in part, by Grant R01 DK067269 from the National Institutes of Health.

References

1. World Health Organization. World Health Organization. Geneva (Switzerland): 2016. Global status report on noncommunicable diseases 2016.
2. Dall TM, Yang W, Halder P, et al. The Economic Burden of Elevated Blood Glucose Levels in 2012. Diabetes Care. 2014; 37:3172–3179. [PubMed: 25414388]
3. Zhang P, Zhang X, Brown J, et al. Global healthcare expenditure on diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010; 87:293–301. [PubMed: 20171754]
4. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care. 2013 Apr; 36(4):1033–46. [PubMed: 23468086]
5. DeFronzo RA, Abdul-Ghani M. Assessment treatment of cardiovascular risk in prediabetes: impaired glucose tolerance impaired fasting glucose. Am J Cardiol. 2011; 108:3B–24B.
6. American Diabetes Association. Standards of Medical Care in Diabetes-2017. Diabetes Care. 40:S11–24. [PubMed: 27979889]
7. World Health Organization (WHO) Consultation. Definition and diagnosis of diabetes and intermediate hyperglycaemia. World Health Organization Geneva; Switzerland: 2006. (Available at: http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf.) Accessed March 10, 2017
8. Dagogo-Jack S. Pitfalls in the use of HbA1(c) as a diagnostic test: the ethnic conundrum. Nat Rev Endocrinol. 2010; 6:589–593. [PubMed: 20680035]
9. Chapp-Jumbo E, Edeoga C, Wan J, Dagogo-Jack S. Ethnic disparity in hemoglobin A1c levels among normoglycemic offspring of parents with type 2 diabetes. Endocr Pract. 2012; 18:356–362. [PubMed: 22138077]
10. Ebenibo S, Edeoga C, Wan J, Dagogo-Jack S. Glucoregulatory function among African Americans and European Americans with normal or pre-diabetic hemoglobin A1c levels. Metabolism. 2014; 63:767–72. [PubMed: 24641885]
11. Herman WH, Dungan KM, Wolffenbuttel BH, Buse JB, Fahrbach JL, Jiang H, Martin S. Racial and ethnic differences in mean plasma glucose, hemoglobin A1c, and 15-anhydroglucitol in over 2000 patients with type 2 diabetes. J Clin Endocrinol Metab. 2009 May; 94(5):1689–94. [PubMed: 19276235]
12. Soranzo N. Genetic determinants of variability in glycated hemoglobin (HbA(1c)) in humans: review of recentprogress and prospects for use in diabetes care. Curr Diab Rep. 2011 Dec; 11(6): 562–9. [PubMed: 21975967]
13. Herman WH. Are There Clinical Implications of Racial Differences in HbA1c? Yes, to Not Consider Can Do Great Harm! Diabetes Care. 2016 Aug; 39(8):1458–61. [PubMed: 27457636]
14. Wolffenbuttel BH, Herman WH, Gross JL, Dharmalingam M, Jiang HH, Hardin DS. Ethnic differences in glycemic markers in patients with type 2 diabetes. Diabetes Care. 2013 Oct; 36(10): 2931–6. [PubMed: 23757434]

15. Centers for Disease Control and Prevention. National diabetes statistics report: estimates of diabetes and its burden in the United States, 2014. Atlanta: US Department of Health and Human Services; 2014.
16. International Diabetes Federation IDF diabetes atlas 2015. 7th. Brussels: International Diabetes Federation; 2015.
17. Middelbeek RJW, Abrahamson MJ. Diabetes, prediabetes, and glycemic control in the United States: challenges and opportunities. Ann Intern Med. 2014; 160:572–573. [PubMed: 24733201]
18. Hu D, Fu P, Xie J, et al. MS for the InterASIA Collaborative Group. Increasing prevalence and low awareness, treatment and control of diabetes mellitus among Chinese adults: the InterASIA study. Diabetes Res Clin Pract. 2008; 81:250–257. [PubMed: 18495287]
19. Faeh D, William J, Tappy L, Ravussian E, Bovet P. Prevalence, awareness and control of diabetes in the Seychelles and relationship with excess body weight. BMC Public Health. 2007; 7:163. [PubMed: 17640380]
20. Saadi H, Carruthers SG, Nagelkerke N, et al. Prevalence of diabetes mellitus and its complications in a population-based sample in Al Ain, United Arab Emirates. Diabetes Res Clin Pract. 2007:369–377. [PubMed: 17532085]
21. Echouffo-Tcheugui JB, Dagogo-Jack S. Preventing diabetes mellitus in developing countries. Nat Rev Endocrinol. 2012; 8:557–562. [PubMed: 22488646]
22. Dagogo-Jack S. Predicting diabetes: our relentless quest for genomic nuggets. Diabetes Care. 2012; 35:193–195. [PubMed: 22275439]
23. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet. 2012; 379:2279–2290. [PubMed: 22683128]
24. Defronzo RA, Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009; 58:773–795. [PubMed: 19336687]
25. Cerasi E, Luft R. The prediabetic state, its nature and consequences–a look toward the future. Diabetes. 1972; 21:685–694. [PubMed: 5054335]
26. Halban PA, Polonsky KS, Bowden DW, et al. Beta-cell failure in type 2 diabetes: postulated mechanisms and prospects for prevention and treatment. Diabetes Care. 2014; 37:1751–1758. [PubMed: 24812433]
27. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease mortality in adults: the European Prospective Investigation. Ann Intern Med. 2004; 141:413–420. [PubMed: 15381514]
28. Ford ES, Zhao G, Li C. Pre-diabetes the risk for cardiovascular disease: a systematic review of the evidence. J Am Coll Cardiol. 2010; 55:1310–1317. [PubMed: 20338491]
29. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest. 1999; 104:787–794. [PubMed: 10491414]
30. Kitabchi AE, Temprosa M, Knowler WC, et al. The Diabetes Prevention Program Research Group. Role of insulin secretion and sensitivity in the evolution of type 2 diabetes in the diabetes prevention program: effects of lifestyle intervention and metformin. Diabetes. 2005; 54:2404–2414. [PubMed: 16046308]
31. Eschwege E, Richard JL, Thibult N, et al. Coronary heart disease mortality in relation with diabetes, blood glucose and plasma insulin levels. The Paris Prospective Study, ten years later. Horm Metab Res Suppl. 1985; 15:41–46. [PubMed: 3908280]
32. DeFronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM. A balanced overview. Diabetes Care. 1992; 15:318–368. [PubMed: 1532777]
33. Mitrakou A, Kelley D, Mokan M, et al. Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. N Engl J Med. 1992; 326:22–29. [PubMed: 1727062]
34. Meigs JB, D'Agostino RB Sr, Nathan DM, Rifai N, Wilson PW. Longitudinal association of glycemia and microalbuminuria: the Framingham Offspring Study. Diabetes Care. 2002; 25:977–983. [PubMed: 12032102]

35. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes. 2003; 52:102–110. [PubMed: 12502499]
36. Dagogo-Jack S, Askari H, Tykodi G. Glucoregulatory physiology in subjects with low-normal, high-normal, or impaired fasting glucose. J Clin Endocrinol Metab. 2009; 94:2031–2036. [PubMed: 19276238]
37. DeFronzo R, Kanat M, Abdul-Ghani M. Treatment of prediabetes. World J Diabetes. 2015; 6:1207–1222. [PubMed: 26464759]
38. Toft-Nielsen MB, Damholt MB, Madsbad S, et al. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. J Clin Endocrinol Metab. 2001; 86:3717–3723. [PubMed: 11502801]
39. Mather KJ, Funahashi T, Matsuzawa Y, et al. Diabetes Prevention Program. Adiponectin, change in adiponectin, and progression to diabetes in the Diabetes Prevention Program. Diabetes. 2008; 57:980–986. [PubMed: 18192541]
40. Mitrakou A, Kelley D, Mokan M, et al. Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. N Engl J Med. 1992; 326:22–29. [PubMed: 1727062]
41. Jiang Y, Owei I, Wan J, Ebenibo S, Dagogo-Jack S. Adiponectin levels predict prediabetes risk: The Pathobiology of Prediabetes in A Biracial Cohort (POP-ABC) study. BMJ Open Diabetes Res Care. 2016; 4(1):e000194.
42. Huang Z, Chen C, Li S, Kong F, Shan P, Huang W. Serum Markers of Endothelial Dysfunction and Inflammation Increase in Hypertension with Prediabetes Mellitus. Genet Test Mol Biomarkers. 2016; 20:322–327. [PubMed: 27167462]
43. Dagogo-Jack, S. Diabetes risks from prescription and nonprescription drugs. ADA press; Alexandria VA: 2016.
44. Lefèbvre PJ, Scheen AJ. The postprandial state risk of cardiovascular disease. Diabet Med. 1998; 4:S63–8.
45. von Toerne C, Huth C, de Las Heras Gala T, et al. MASP1, THBS1, GPLD1 and ApoA-IV are novel biomarkers associated with prediabetes: the KORA F4 study. Diabetologia. 2016; 9:1882–1892.
46. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006; 444:1027–1031. [PubMed: 17183312]
47. Cani PD, Neyrinck AM, Fava F, et al. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. Diabetologia. 2007; 50:2374–2383. [PubMed: 17823788]
48. Ridaura VK, Faith JJ, Rey FE, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013; 341:1241214. [PubMed: 24009397]
49. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013; 19:576–585. [PubMed: 23563705]
50. Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology. 2012; 143:913–916. [PubMed: 22728514]
51. Edelstein SL, Knowler WC, Bain RP, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. Diabetes. 1997; 46:701–710. [PubMed: 9075814]
52. Knowler WC, Bennett PH, Hamman RF, Miller M. Diabetes incidence prevalence in Pima Indians: a 19-fold greater incidence than in RochesterMinnesota. Am J Epidemiol. 1978; 108:497–505. [PubMed: 736028]
53. Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M. Incident type 2 diabetes mellitus in African American white adults: The Atherosclerosis Risk in Communities Study. JAMA. 2000; 283:2253–2259. [PubMed: 10807384]

54. Meigs JB, Muller DC, Nathan DM, Blake DR, Andres R. Baltimore Longitudinal Study of Aging. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. Diabetes. 2003; 52:1475–1484. [PubMed: 12765960]
55. Dagogo-Jack S, Edeoga C, Ebenibo S, Nyenwe E, Wan J, Pathobiology of Prediabetes in a Biracial Cohort (POP-ABC) Research Group. Lack of racial disparity in incident prediabetes and glycemic progression among black and white offspring of parents with type 2 diabetes: the pathobiology of prediabetes in a biracial cohort (POP-ABC) study. J Clin Endocrinol Metab. 2014; 99:E1078–1087. [PubMed: 24628558]
56. Boucher AB, Adesanya EA, Owei I, et al. Dietary habits and leisure-time physical activity in relation to adiposity dyslipidemia and incident dysglycemia in the pathobiology of prediabetes in a biracial cohort study. Metabolism. 2015; 64:1060–1067. [PubMed: 26116207]
57. Owei I, Umekwe N, Wan J, Dagogo-Jack S. Plasma lipid levels predict dysglycemia in a biracial cohort of nondiabetic subjects: potential mechanisms. Exp Biol Med (Maywood). 2016; 241:1961–1967. [PubMed: 27430991]
58. Selvin E, Lazo M, Chen Y, et al. Diabetes mellitus, prediabetes, and incidence of subclinical myocardial damage. Circulation. 2014; 130:1374–1382. [PubMed: 25149362]
59. Balkau B, Eschwège E, Papoz L, et al. Risk factors for early death in non-insulin dependent diabetes and men with known glucose tolerance status. BMJ. 1993; 307:295–299. [PubMed: 8374376]
60. Dagogo-Jack S, Egbuonu N, Edeoga C. Principles and practice on non-pharmacological interventions to reduce cardiometabolic risk. Med Princ Pract. 2010; 19:167–175. [PubMed: 20357497]
61. Nyenwe EA, Dagogo-Jack S. Metabolic syndrome prediabetes and the science of primary prevention. Minerva Endocrinol. 2011; 36:129–145. [PubMed: 21519322]
62. Stacey RB, Leaverton PE, Schocken DD, Peregoy JA, Bertoni AG. Prediabetes the association with unrecognized myocardial infarction in the multi-ethnic study of atherosclerosis. Am Heart J. 2015; 170:923–928. [PubMed: 26542500]
63. Hu FB, Stampfer MJ, Haffner SM, Solomon CG, Willett WC, Manson JE. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. Diabetes Care. 2002; 25:1129–1134. [PubMed: 12087009]
64. Coutinho M, Gerstein HC, Wang Y, et al. Analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care. 1999; 22:233–240. [PubMed: 10333939]
65. Smith NL, Barzilay JI, Shaffer D, et al. Fasting and 2-hour post challenge serum glucose measures and risk of incident cardiovascular events in the elderly: The Cardiovascular Health Study. Arch Intern Med. 2002; 162:209–216. [PubMed: 11802755]
66. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all-cause mortality: systematic review and meta-analysis. BMJ. 2016; 355:i5953. [PubMed: 27881363]
67. Bonora E, Kiechl S, Willeit J, et al. Carotid atherosclerosis and coronary heart disease in the metabolic syndrome: prospective data from the Bruneck study. Diabetes Care. 2003; 26:1251–1257. [PubMed: 12663606]
68. Tai ES, Goh SY, Lee JJ, et al. Lowering the criterion for impaired fasting glucose: impact on disease prevalence and associated risk of diabetes and ischemic heart disease. Diabetes Care. 2004; 27:1728–1734. [PubMed: 15220254]
69. Rijkelijkhuizen J, Nijpels J, Heine R, Bouter L, Stehouwer C, Dekker J. High risk of cardiovascular mortality in individuals with impaired fasting glucose is explained by conversion to diabetes: the Hoorn study. Diabetes Care. 2007; 30:332–336. [PubMed: 17259503]
70. Balkau B, Eschwège E, Papoz L, et al. Risk factors for early death in non-insulin dependent diabetes and men with known glucose tolerance status. BMJ. 1993; 307:295–299. [PubMed: 8374376]
71. Dagogo-Jack S, Egbuonu N, Edeoga C. Principles and practice on non-pharmacological interventions to reduce cardiometabolic risk. Med Princ Pract. 2010; 19:167–175. [PubMed: 20357497]

72. Dagogo-Jack, S. Endocrinology & metabolism: complications of diabetes mellitus. In: Singh, AK., editor. Scientific American medicine. Hamilton, ON: Decker Intellectual Properties; 2015.
73. Papa G, Degano C, Iurato MP, Licciardello C, Maiorana R, Finocchiaro C. Macrovascular complication phenotypes in type 2 diabetic patients. Cardiovasc Diabetol. 2013; 12:20. [PubMed: 23331854]
74. Wang J, Liu L, Zhou Y, et al. Increased fasting glucose and the prevalence of arterial stiffness: a cross-sectional study in Chinese adults. Neurol Res. 2014; 5:427–433.
75. Holman RR, Coleman RL, Chan JCN, et al. ACE Study Group. Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2017 Sep 12.:pii. S2213-8587(17)30309-1.
76. Roquer J, Rodríguez-Campello A, Cuadrado-Godia E, et al. Ischemic stroke in prediabetic patients. J Neurol. 2014; 261:1866–1870. [PubMed: 25022941]
77. Urabe T, Watada H, Okuma Y, et al. Prevalence of abnormal glucose metabolism and insulin resistance among subtypes of ischemic stroke in Japanese patients. Stroke. 2009; 40:1289–1295. [PubMed: 19164796]
78. Kernan WN, Viscoli CM, Inzucchi SE, et al. Prevalence of abnormal glucose tolerance following a transient ischemic attack or ischemic stroke. Arch Intern Med. 2005; 165:227–233. [PubMed: 15668371]
79. Matz K, Keresztes K, Tatschl C, et al. Disorders of glucose metabolism in acute stroke patients: an underrecognized problem. Diabetes Care. 2006; 29:792–797. [PubMed: 16567817]
80. Tanaka R, Ueno Y, Miyamoto N, et al. Impact of diabetes and prediabetes on the short-term prognosis in patients with acute ischemic stroke. J Neurol Sci. 2013; 332:45–50. [PubMed: 23810779]
81. Qiao Q, Pyörälä K, Pyörälä M, et al. Two hour glucose is a better risk predictor for incident coronary heart disease and cardiovascular mortality than fasting glucose. Eur Heart J. 2002; 23:1267–1275. [PubMed: 12175663]
82. Bamberg F, Hetterich H, Rospleszcz S, et al. Subclinical Disease Burden as Assessed by Whole-Body MRI in Subjects with Prediabetes, Subjects with Diabetes, and Normal Control Subjects from the General Population: The KORA-MRI Study. Diabetes. 2017; 1:158–169.
83. Holman RR, Coleman RL, Chan JCN, et al. IRIS Trial Investigators. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. N Engl J Med. 2016 Apr 7; 374(14):1321–31. [PubMed: 26886418]
84. Inzucchi SE, Viscoli CM, Young LH, Furie KL, Gorman M, Lovejoy AM, Dagogo-Jack S, Ismail-Beigi F, Korytkowski MT, Pratley RE, Schwartz GG, Kernan WN, IRIS Trial Investigators. Pioglitazone prevents diabetes in insulin-resistant patients with cerebrovascular disease. Diabetes Care. 2016; 39:1684–92. [PubMed: 27465265]
85. Golledge J, Quigley F, Velu R, Walker PJ, Moxon JV. Association of impaired fasting glucosediabetes and their management with the presentation outcome of peripheral artery disease: a cohort study. Cardiovasc Diabetol. 2014; 13:147. [PubMed: 25361884]
86. Kamalesh M, Shen J. Diabetes and peripheral arterial disease in men: trends in prevalence, mortality, and effect of concomitant coronary disease. Clin Cardiol. 2009; 32:442–446. [PubMed: 19685517]
87. DeFronzo RA, Abdul-Ghani M. Assessment treatment of cardiovascular risk in prediabetes: impaired glucose tolerance impairedfasting glucose. Am J Cardiol. 2011; 108:3B–24B.
88. The DECODE Study Group. Consequence of the new diagnostic criteria for diabetes in older men and women. Diabetes Care. 1999; 22:1667–1671. [PubMed: 10526732]
89. Zhang L, Qiao Q, Tuomilehto J, et al. DECODE Study Group. The impact of dyslipidaemia on cardiovascular mortality in individuals without a prior history of diabetes in the DECODE Study. Atherosclerosis. 2009; 206:298–302. [PubMed: 19303072]
90. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease but not impaired fasting glucose. The Funagata Diabetes Study. Diabetes Care. 1999; 22:920–924. [PubMed: 10372242]

91. Balkau B, Bertrais S, Ducimetière P, Eschwege E. Is there a glycemic threshold for mortality risk? Diabetes Care. 1999; 22:696–699. [PubMed: 10332668]
92. Resnick HE, Harris MI, Brock DB, Harris TB. American Diabetes Association diabetes diagnostic criteria advancing age and cardiovascular disease risk profiles: results from the Third National Health Nutrition Examination Survey. Diabetes Care. 2000; 23:176–80. [PubMed: 10868827]
93. De Marco M, de Simone G, Roman MJ, et al. Cardiac geometry and function in diabetic or prediabetic adolescents young adults: The Strong Heart Study. Diabetes Care. 2011; 34:2300–2305. [PubMed: 21873564]
94. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? JAMA. 1990; 263:2893–2898. [PubMed: 2338751]
95. Yan F, Cha E, Lee ET, Mayberry RM, Wang W, Umpierrez G. A Self-Assessment Tool for Screening Young Adults at Risk of Type 2 Diabetes Using Strong Heart Family Study Data. Diabetes Educ. 2016; 42:607–617. [PubMed: 27480523]
96. Romeo S, Maglio C, Burza MA, et al. Cardiovascular events after bariatric surgery in obese subjects with type 2 diabetes. Diabetes Care. 2012; 35:2613–2617. [PubMed: 22855732]
97. Franssen R, Monajemi H, Stroes ES, Kastelein JJ. Obesity and dyslipidemia. The Medical Clinics of North America. 2011; 95:893–902. [PubMed: 21855698]
98. Liu T. A Comparison of Biological and Physical Risk Factors for Cardiovascular Disease in Overweight/Obese Individuals with and Without Prediabetes. Clin Nurs Res. 2016
99. Kim CS, Park HS, Kawada T, et al. Circulating levels of MCP-1 and IL-8 are elevated in human obese subjects and associated with obesity-related parameters. International Journal of Obesity. 2006; 30:1347–1355. [PubMed: 16534530]
100. Li C, Ford E, Zhao G, et al. Prevalence of pre-diabetes and its association with clustering of cardiometabolic risk factors and hyperinsulinemia among U.S. adolescents: National Health and Nutrition Examination Survey 2005–2006. Diabetes Care. 2009; 32:342–347. [PubMed: 18957533]
101. Festa A, Williams K, Hanley AJ, et al. Nuclear magnetic resonance lipoprotein abnormalities in prediabetic subjects in the Insulin Resistance Atherosclerosis Study. Circulation. 2005; 111:3465–3472. [PubMed: 15983261]
102. Zheng S, Zhou H, Han T, et al. Clinical characteristics and beta cell function in Chinese patients with newly diagnosed type 2 diabetes mellitus with different levels of serum triglyceride. BMC Endocr Disord. 2015; 15:21. [PubMed: 25924608]
103. Ren X, Chen ZA, Zheng S, et al. Association between triglyceride to HDL-C ratio (TG/HDL-C) and insulinresistance in Chinese patients with newly diagnosed type 2 diabetes mellitus. PLoS One. 2016; 11:e0154345. [PubMed: 27115999]
104. Sparks JD, Sparks CE, Adeli K. Selective hepatic insulin resistance VLDL overproduction and hypertriglyceridemia. Arterioscler Thromb Vasc Biol. 2012; 32:2104–2112. [PubMed: 22796579]
105. Bosch J, Yusuf S, Gerstein HC, et al. Effect of ramipril on the incidence of diabetes. N Engl J Med. 2006; 355:1551–1562. [PubMed: 16980380]
106. Navigator Study Group. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med. 2010; 362:1477–1490. [PubMed: 20228403]
107. The Diabetes Prevention Program Research Group. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the Diabetes Prevention Program. Diabetes Care. 2005; 28:888–894. [PubMed: 15793191]
108. Moebus S, Hanisch JU, Aidelsburger P, Bramlage P, Wasem J, Jöckel K-H. Impact of four different definitions used for assessment of the prevalence of metabolic syndrome in a primary health care setting. The German Metabolic Cardiovascular Risk Project (GEMCAS). Cardiovasc Diabetol. 2007; 6:22. [PubMed: 17822558]
109. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360:1903–1913. [PubMed: 12493255]

110. Kahn R, Alperin P, Eddy D. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. Lancet. 2010; 375:1365–1374. [PubMed: 20356621]
111. Gæde P, Oellgaard J, Carstensen B, et al. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomized trial. Diabetologia. 2016; 59:2298–2307. [PubMed: 27531506]
112. Knowler WC, Barrett-Connor E, Fowler SE, et al. Diabetes Prevention Program Research Group Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002; 346:393–403. [PubMed: 11832527]
113. Urbanski P, Wolf A, Herman W. Cost-Effectiveness of Diabetes Education. J Am Diet Assoc. 2008; 108:S6–11. [PubMed: 18358259]
114. Stefan N, Staiger H, Wagner R, et al. A high-risk phenotype associates with reduced improvement in glycaemia during a lifestyle intervention in prediabetes. Diabetologia. 2015; 58:2877–2884. [PubMed: 26404062]
115. The Look AHEAD Research Group. Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes. N Engl J Med. 2013; 369:145–154. [PubMed: 23796131]
116. DPP Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002; 346:393–403. [PubMed: 11832527]
117. Sprague R, Ellsworth M. Vascular Disease in Pre-Diabetes: New Insights Derived from Systems Biology. Mo Med. 2010; 107:265–269. [PubMed: 20806839]
118. Hostalek U, Gwilt M, Hildemann S. Therapeutic Use of Metformin in Prediabetes and Diabetes Prevention. Drugs. 2015; 75:1071–1094. [PubMed: 26059289]
119. Tuomilehto J, Lindström J, Eriksson JG, et al. Finnish Diabetes Prevention Study Group. N Engl J Med. 2001; 344:1343–1350. [PubMed: 11333990]
120. Anderson J. Achievable Cost Saving and Cost-Effective Thresholds for Diabetes Prevention Lifestyle Interventions in People Aged 65 Years and Older: A Single-Payer Perspective. Journal of the Academy of Nutrition and Dietetics. 2012; 112:1747–1754. [PubMed: 23102174]
121. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT Diabetes Study. Diabetes Care. 1997; 20:537–544. [PubMed: 9096977]
122. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet. 2012; 379:2279–2290. [PubMed: 22683128]
123. DeFronzo RA, Tripathy D, Schwenke DC, et al. ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med. 2011; 364:1104–1115. [PubMed: 21428766]
124. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. STOP-NIDDM Trial Research Group: Acarbose treatment the risk of cardiovascular disease hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA. 2003; 290:486–494. [PubMed: 12876091]
125. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care. 2004; 27:155–161. [PubMed: 14693982]
126. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006; 368:1096–1105. [PubMed: 16997664]
127. Zinman B, Harris SB, Neuman J, et al. Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. Lancet. 2010; 376:103–111. [PubMed: 20605202]
128. NAVIGATOR Study Group. Effect of nateglinide on the incidence of diabetes and cardiovascular events. N Engl J Med. 2010; 362:1463–1476. [PubMed: 20228402]
129. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V, Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle

modification metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006; 49:289–297. [PubMed: 16391903]

130. Ramachandran A, Snehalatha C, Mary S, et al. Pioglitazone does not enhance the effectiveness of lifestyle modification in preventing conversion of impaired glucose tolerance to diabetes in Asian Indians: results of the Indian Diabetes Prevention Programme-2 (IDPP-2). Diabetologia. 2009; 52:1019–1026. [PubMed: 19277602]
131. The Diabetes Prevention Program Research Group. Effects of withdrawal from metformin on the development of diabetes in the diabetes prevention program. Diabetes Care. 2003; 26:977–980. [PubMed: 12663559]
132. Tripathy D, Schwenke DC, Banerji M, et al. Diabetes Incidence and Glucose Tolerance after Termination of Pioglitazone Therapy: Results from ACT NOW. J Clin Endocrinol Metab. 2016; 101:2056–2062. [PubMed: 26982008]
133. Li G, Zhang P, Wang J, et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol. 2014; 2:474–480. [PubMed: 24731674]
134. Xiang AH, Hodis HN, Kawakubo M, et al. Effect of pioglitazone on progression of subclinical atherosclerosis in non-diabetic premenopausal Hispanic women with prior gestational diabetes. Atherosclerosis. 2008; 199:207–214. [PubMed: 18054942]
135. DeFronzo RA, Tripathy D, Schwenke DC, et al. ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med. 2011; 364:1104–1115. [PubMed: 21428766]
136. Salas-Salvadó J, Guasch-Ferré M, Lee CH, Estruch R, Clish CB, Ros E. Protective Effects of the Mediterranean Diet on Type 2 Diabetes and Metabolic Syndrome. J Nutr. 2016 Mar 9.:pii. jn218487.
137. Mozaffarian D, Marfisi R, Levantesi G, Silletta MG, Tavazzi L, Tognoni G, Valagussa F, Marchioli R. Incidence of new-onset diabetes impaired fasting glucose in patients with recent myocardial infarctionthe effect of clinical lifestyle risk factors. Lancet. 2007; 370:667–75. [PubMed: 17720018]
138. Esposito K, Maiorino MI, Bellastella G, Chiodini P, Panagiotakos D, Giugliano D. A journey into a Mediterranean diet and type 2 diabetes: a systematic review with meta-analyses. BMJ Open. 2015 Aug 10.5(8):e008222.
139. Monlezun DJ, Kasprowicz E, Tosh KW, Nix J, Urday P, Tice D, Sarris L, Harlan TS. Medical school-based teaching kitchen improves HbA1c, blood pressure, and cholesterol for patients with type 2 diabetes: Results from a novel randomized controlled trial. Diabetes Res Clin Pract. 2015 Aug; 109(2):420–6. [PubMed: 26002686]
140. Salas-Salvadó J, Bulló M, Estruch R, Ros E, Covas MI, Ibarrola-Jurado N, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. Ann Intern Med. 2014 Jan 7; 160(1):1–10.
141. Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. JAMA. 2003; 289:1799–1804. [PubMed: 12684358]
142. Perreault L, Temprosa M, Mather KJ, et al. The Diabetes Prevention Program Research Group. Regression from prediabetes to normal glucose regulation is associated with reduction in cardiovascular risk: results from the Diabetes Prevention Program outcomes study. Diabetes Care. 2014; 37:2622–2631. [PubMed: 24969574]
143. Brannick B, Wynn A, Dagogo-Jack S. Prediabetes as a toxic environment for the initiation of microvascular and macrovascular complications. Exp Biol Med (Maywood). 2016; 241:1323–1331. [PubMed: 27302176]
144. Mainous AG 3rd, Tanner RJ, Scuderi CB, Porter M, Carek PJ. Prediabetes screening treatment in diabetes prevention: The impact of physician attitudes. J Am Board Fam Med. 2016; 29:663–671. [PubMed: 28076248]
145. Gopalan A, Lorincz IS, Wirtalla C, Marcus SC, Long JA. Awareness of Prediabetes Engagement in Diabetes Risk-Reducing Behaviors. Am J Prev Med. 2015; 49:512–519. [PubMed: 26091928]

146. Dagogo-Jack S. Preventing diabetes-related morbidity and mortality in the primary care setting. J Natl Med Assoc. 2002; 94:549–560. [PubMed: 12126280]

147. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health: recommendation from the Centers for Disease Control Prevention and the American College of Sports Medicine. JAMA. 1995; 273:402–407. [PubMed: 7823386]

148. Kimm SY, Glynn NW, Kriska AM, et al. Decline in physical activity in black and white girls during adolescence. N Engl J Med. 2002; 347:709–715. [PubMed: 12213941]

149. Dagogo-Jack S. Primary prevention of cardiovascular disease: the glass is half full and half empty. Diabetes Care. 2005; 28:971–972. [PubMed: 15793208]

Key Points

- Prediabetes carries an increased risk in cardiovascular disease
- Significant physiological, metabolic, and biochemical features are dysregulated in prediabetes
- Extensive Randomized Controlled Trials have demonstrated that lifestyle modification can decrease the rate of progression from prediabetes to diabetes.
- Early detection and intervention is vitally important for prevention of prediabetes progression to diabetes

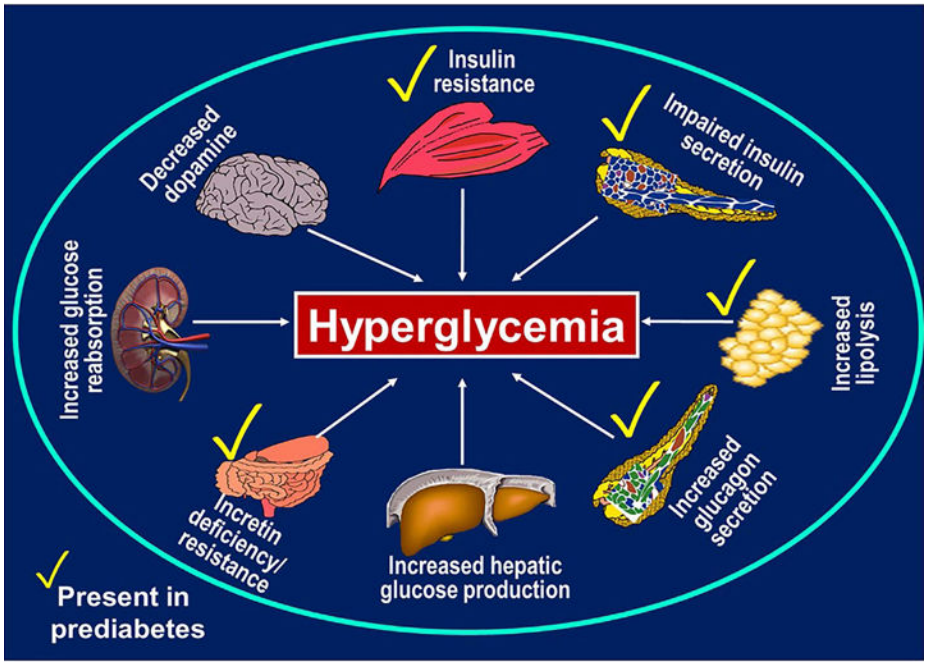

Figure 1.

Recognized pathophysiological defects in type 2 diabetes mellitus and prediabetes. From Dagogo-Jack, S. Diabetes risks from prescription and nonprescription drugs. ADA press, Alexandria VA, 2016, with permission.

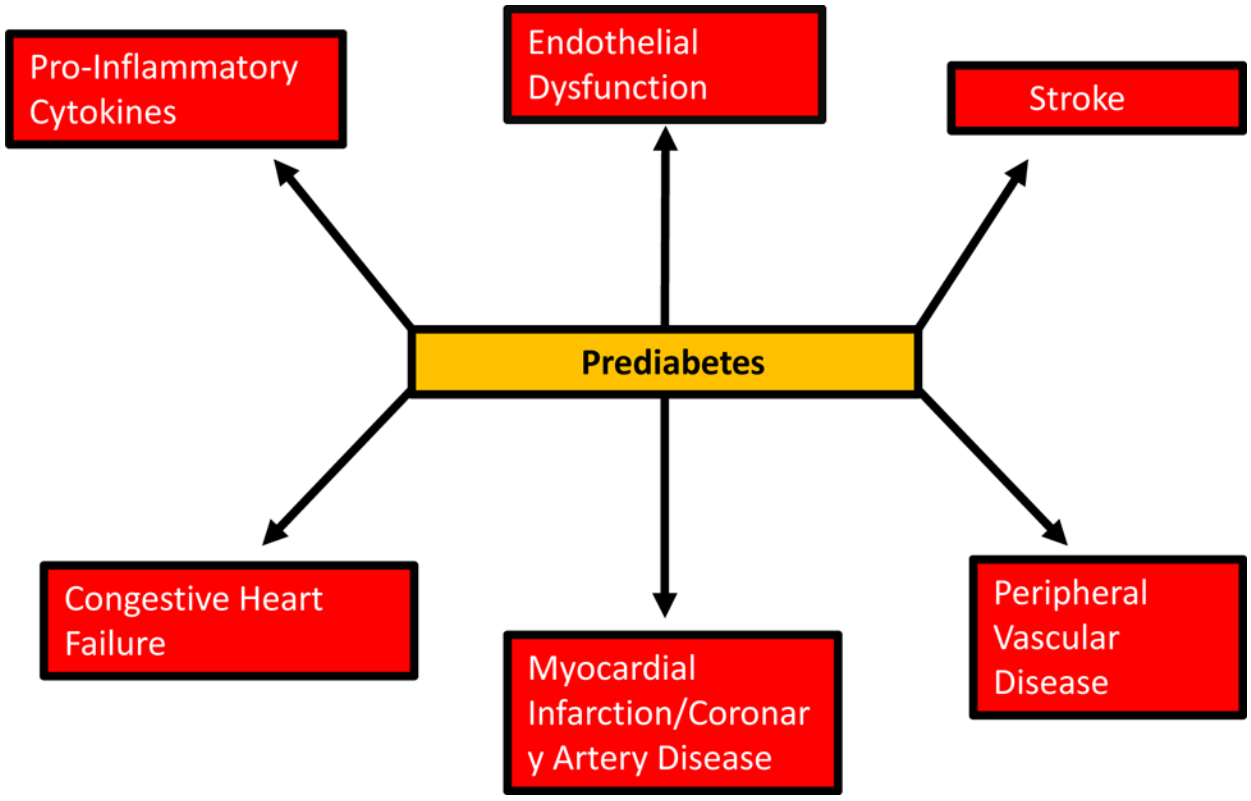

Figure 2.
Recognized macrovascular complications associated with prediabetes.
Data from references[57–74].

Table 1

Pathophysiological Defects in Prediabetes

Defect	References
Loss of beta-cell volume	35
Defects in insulin action and secretion	24,26,29–31,33,51,52
Endothelial dysfunction	26,52
Arterial Stiffness	72–74
Increased lipolysis	25,36
Reduced incretin levels	36,38
Increased hepatic glucose production	26, 32,33
Impaired glucagon levels	33
Dysregulated cytokines	41,42,99

Table 2

Pertinent Prediabetes Intervention Studies

Study	Intervention	Number of subjects	Study population	Risk reduction	Years
Da Qing[121]	Diet and exercise	577	Chinese IGT adults, mean age 46, BMI 26	31–46% after 6 years	1986–1992
Finnish DPS[119]	Diet and exercise	522	IGT adults, mean age 55, BMI 31	58% after 3.2 years	1993–1998
STOP-NIDDM[124]	Acarbose	1428	IGT adults, mean age 55, BMI 31	25% after 3.3 years	1995–1998
DPP[120]	Diet and exercise	3234	IGT adults, mean age 54 years, BMI 34	Metformin 31%, lifestyle 58% after 2 years	1996–1999
Xendos[125]	Orlistat and diet and exercise	3305	Swedish, BMI >30, mean age 43, 21% with IGT	Entire group 37%, IGT 45% after 4 years	1997–2002
DREAM[126]	Rosiglitazone	5269	IGT and/or IGF subjects mean age 54.7 years, BMI 30.9	62% after approximately 3 years	2001–2003
IDDP-1[129]	Lifestyle modifications and metformin or lifestyle modifications	531	Indian, IGT mean age 46 years, BMI 25.8	Diet and exercise 28.5%, Metformin 26.4%, Diet and exercise and metformin 28.2% after 30 months	2001–2004
ACT-NOW[132]	Pioglitazone	602	IGT, mean age 53, BMI 33	72% with pioglitazone over 2.4 years	2004–2006
CANOE[127]	Combination rosiglitazone and metformin vs placebo	207	IGT, mean age 50, BMI 31.3	26% in the combination group after 3.9 years	2004–2006
IDDP-2[130]	Lifestyle modifications or pioglitazone and lifestyle modifications	407	Indian IGT, mean age 45.3, BMI 25.9	28% though pioglitazone not additive to lifestyle modification	2006–2009
Navigator[128]	Nataglinide and lifestyle modifications or Valsartan and lifestyle modifications	9306	IGT, mean age 63.7, BMI 30.5	Nataglinide none, Valsartan 14%	2005–2010