Prediabetes as a toxic environment for the initiation of microvascular and macrovascular complications

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Abstract

Prediabetes is a state characterized by impaired fasting glucose or impaired glucose tolerance. Evidence is increasingly demonstrating that prediabetes is a toxic state, in addition to being a harbinger of future development of diabetes mellitus. This minireview discusses the pathophysiology and clinical significance of prediabetes, and approach to its management, in the context of the worldwide diabetes epidemic. The pathophysiologic defects underlying prediabetes include insulin resistance, β cell dysfunction, increased lipolysis, inflammation, suboptimal incretin effect, and possibly hepatic glucose overproduction. Recent studies have revealed that the long-term complications of diabetes may manifest in some people with prediabetes; these complications include classical microvascular and macrovascular disorders, and our discussion explores the role of glycemia in their development. Finally, landmark intervention studies in prediabetes, including lifestyle modification and pharmacologic treatment, are reviewed.

Keywords: Impaired fasting glucose, impaired glucose tolerance, prediabetes complications, prevention, microvascular, macrovascular

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Introduction

Nearly 415 million people worldwide are estimated to have diabetes mellitus, and over 90% of these have type 2 diabetes mellitus (T2DM). In 2014, 9% of adults 18 years and older had diabetes.[1–3] Global estimates show that diabetes accounted for 12% of health expenditures in 2010, or at least $376 billion—a figure expected to reach $490 billion by 2030.[2] The increasing prevalence affects children and adolescents as well, especially the obese pediatric population.[3]

Diabetes is the leading cause of blindness, amputation, and end-stage kidney disease, and is associated with an approximately two- to four-fold increased risk of myocardial infarction and stroke.[4–6] A number of pivotal clinical trials have demonstrated that the microvascular complications of diabetes can be prevented through optimization of glycemic control. Furthermore, glycemic control along with control of comorbid risk factors such as hypertension and dyslipidemia significantly decreases composite cardiovascular risks.[7]

The development of T2DM is usually preceded by a variable interlude of prediabetes, characterized by impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).[8–10] Studies have demonstrated that prediabetes is a toxic state in which much of the cardiovascular disease (CVD) burden associated with established diabetes is already evident.[11–13] Similarly, emerging studies indicate that the microvascular complications of diabetes (traditionally thought to develop after years of hyperglycemia) can in fact manifest during the stage of prediabetes. In this minireview, we present the epidemiology, clinical manifestations, pathophysiology, and approach to management of the microvascular and macrovascular complications associated with the toxic cardiometabolic state of prediabetes.

Scope and definition of the problem

Prediabetes is defined as an intermediate state of hyperglycemia with glycemic parameters above normal but below the diabetes threshold.[11] The diagnosis of prediabetes can be established on the basis of a fasting plasma glucose of 100–125 mg/dL (IFG), a 75-g oral glucose tolerance test showing a 2-h postload plasma glucose of 140–199 mg/dL (IGT), or an hemoglobin A_{1c} (HbA_{1c}) level of 5.7–6.4%.[14–18]

The worldwide prevalence of IGT in 2010 was estimated to be 343 million, and the International Diabetes Federation projects an increase in prevalence of prediabetes to 471 million globally by 2035.[15] In the United States, the Centers for Disease Control and Prevention National Diabetes Statistics Report from 2009 to 2012 indicated that 37% of US adults older than 20 years and 51% of those older than 65 had prediabetes, as defined by fasting glucose or HbA_{1c} levels.[6] When applied to the entire 2012 US population, these estimates suggest that there are nearly 86 million adults with prediabetes in the United States.[6]

Risk factors for prediabetes

Generally, the risk factors for prediabetes are similar to those for diabetes (Table 1). A recent Chinese study involving over 27,000 patients found that both body mass index (BMI) and waist circumference were positively associated with impaired glucose metabolism and risk of prediabetes.[19] Waist circumference had a stronger association with glucose impairment and diabetes compared with BMI, indicating that central obesity is more closely associated with risk of prediabetes.[19] These findings suggest that waist circumference should be included in assessing risk of T2DM in clinical practice.[19]

Other factors that have been examined in studies of T2DM are race, ethnicity, family background, and first-degree relatives with T2DM. The Diabetes Prevention Program enrolled approximately 3000 multiethnic individuals with IGT, diagnosed using a 75-g oral glucose tolerance test. In this landmark study, the risk of incident diabetes (approximately 11%) was the same in non-Hispanic blacks, Asian-Americans and Pacific Islanders, non-Hispanic whites, Hispanic-Americans, and Native Americans.[20] These data suggest that once individuals progress from normal glucose tolerance to IGT, the risk for further progression to diabetes is the same across ethnic groups.

Table 1 Risk factors for type 2 diabetes

- Physical inactivity
- First-degree relative with diabetes
- High-risk race/ethnicity
- Gestational diabetes or delivery of a baby weighing 9 lb or greater
- HDL cholesterol <35 mg/dL $\pm$ TG >250 mg/dL
- Hypertension ($>140/90$ mmHg or on therapy)
- A1C ≥ 5.7, impaired glucose tolerance, or impaired fasting glucose on previous testing
- Conditions associated with insulin resistance: severe obesity, acanthosis nigricans, PCOS history
- History of cardiovascular disease

Source: American Diabetes Association.[14]

Pathophysiology of prediabetes

Similar to the findings in established T2DM, prediabetes is associated with demonstrable alterations in insulin sensitivity, pancreatic β-cell function, inflammatory cytokines, incretin response, and hepatic glucose production (HGP) (Figure 1).[21–39] Insulin resistance precedes the development of diabetes by several years and is evident in individuals with IFG or IGT.[21–23] Using hyperinsulinemic euglycemic

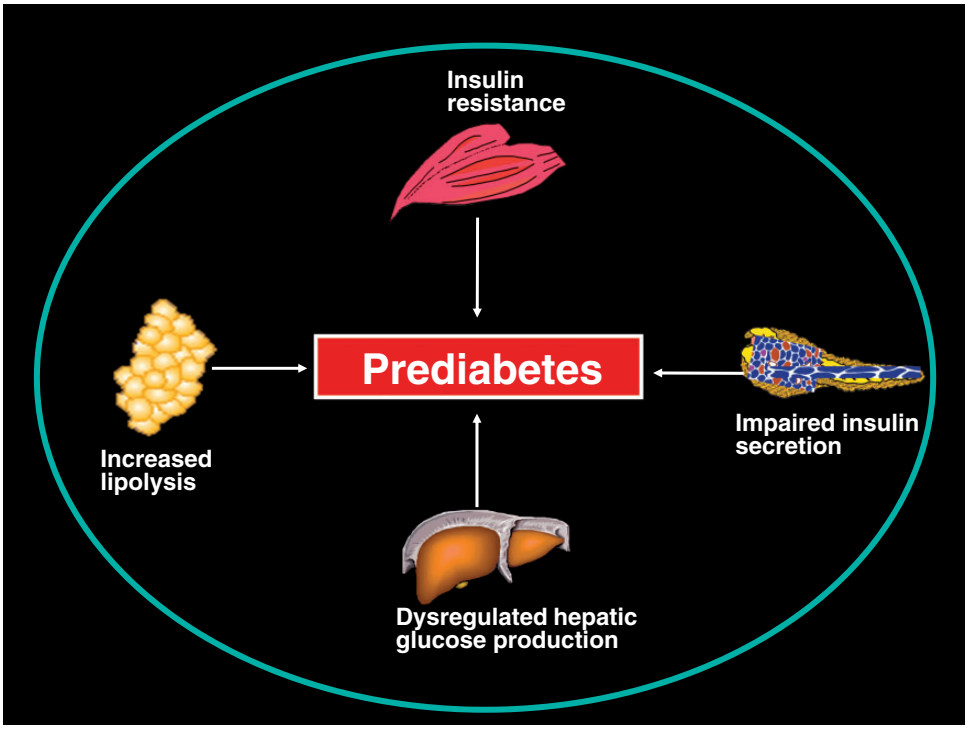

Figure 1 Pathophysiology of prediabetes: skeletal muscle insulin resistance, impaired insulin secretion by the pancreatic β-cells, dysregulated hepatic glucose production and increased lipolysis are among the documented defects underlying the development of prediabetes. (A color version of this figure is available in the online journal.)

clamp and the homeostasis model assessment of insulin resistance (HOMA-IR), Dagogo-Jack et al.[23] determined that subjects with IFG or combined IFG+IGT have up to a three-fold difference in insulin sensitivity compared with normoglycemic subjects. In the Pathobiology of Prediabetes in a Biracial Cohort study, it was found that, with regard to insulin sensitivity, both clamp-derived insulin sensitivity (predominantly muscle action) and HOMA-IR (a reflection of hepatic insulin sensitivity) were predictive of progression to prediabetes (Figure 1).[24] Similarly, early development of insulin resistance was associated with progression from normoglycemia to prediabetes, and from prediabetes to T2DM, among Pima Indians.[25]

Along with insulin resistance, β-cell dysfunction (characterized by impaired insulin secretory response to glucose administration) occurs in prediabetes and worsens with subsequent progression to T2DM.[28–31] Insulin secretory dysfunction has also been demonstrated during transition from normoglycemia to prediabetes in African-American and Caucasian offspring of T2DM parents.[24] The incretin effect refers to the greater increase in plasma insulin response to glucose ingestion when compared with intravenous glucose infusion in amounts that match plasma glucose levels generated by ingested glucose (isoglycemic). The incretin effect is thought to be responsible for 70–80% of total insulin release to the oral glucose load and is mediated by glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide.[33–35] The intestinal secretion of GLP-1 following oral glucose ingestion has been reported to be attenuated in people with IGT compared with normoglycemic subjects.[34]

Other pathophysiological processes associated with T2DM that may be initiated during the prediabetes phase include adiposopathy, increased lipolysis, chronic low-grade inflammation, and dysregulated HGP.[36–44] As the magnitude of insulin secretion or insulin action declines during progression to T2DM, there is tendency to increased lipolysis; the resultant increase in circulating free fatty acids (FFAs) further worsens insulin resistance in muscle and liver tissue.[36–38] Moreover, in non-diabetic individuals, FFAs stimulate insulin secretion, whereas in people predisposed to diabetes elevated FFAs may fail to augment insulin secretion, while continuing to impair peripheral glucose uptake and promote hepatic glucose overproduction.[38] Several studies have reported that elevated levels inflammatory cytokines, such as high-sensitivity C-reactive protein (hsCRP)and tumor necrosis factor-alpha are associated with an increased risk of progression from normoglycemia to prediabetes.[24,41,42] In contrast, adiponectin, a cytokine with favorable cardiometabolic and anti-inflammatory effects, is less abundant in subjects with prediabetes compared with healthy control, and its levels decrease further during progression to T2DM.[40,43] Finally, although measurement of HGP can be challenging, hyperinsulinemic clamp studies coupled with stable isotope techniques in healthy subjects, subjects with isolated IFG, and those with combined IFG + IGT have led to the conclusion that HGP is indeed increased in prediabetes (IFG with or without IGT).[44,45] Taken together, these data lend additional support to the concept that hepatic insulin resistance occurs early in the evolution of T2DM.[45]

Complications of prediabetes

The most obvious sequela of prediabetes is the risk of development of T2DM. The estimated annual conversion rate from prediabetes to diabetes is approximately 10%, making it a high-risk state for development of diabetes.[20] In the China Da Qing Diabetes Prevention Study, the cumulative incidence of progression to diabetes from IGT over a 20-year period was reported to be higher than 90%.[16] The predictors of progression from prediabetes to T2DM include weight gain, insulin resistance, decreased insulin secretion and unfavorable adipocytokine profile, among others.[20,21,25,31,32,43] In addition to the risk of progression to T2DM, the prediabetes state itself is associated with a spectrum of microvascular and macrovascular complications.

Macrovascular complications

Prediabetic dysglycemia increases the risk of adverse CVD events, such as myocardial infarction, stroke, or cardiovascular death.[9,46] In the EPIC-Norfolk study, a 1% increase in HbA_{1c} within the normal range was associated with increased 10-year cardiovascular mortality.[47] An analysis of the 44–55-year-old men from the Paris Prospective Study cohort showed that, compared with normoglycemic subjects, the presence of IGT was associated with a doubling of CVD mortality.[48] Furthermore, patients who progress to T2DM manifest an additional risk for atherosclerotic disorders, resulting in an increased burden of CVD, stroke and peripheral vascular diseases, compared with non-diabetic subjects.[49,50] Most patients with prediabetes have features of the 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 T2DM (Figure 2).[49,50]

Microvascular complications

The three classical microvascular complications—retinopathy, neuropathy, and nephropathy—have all been documented in people with prediabetes (Figure 2).[50–57] The occurrence of these "long-term" complications of hyperglycemia in people with prediabetes indicates susceptibility of certain individuals to the development of microvascular complications following exposure to subdiabetic glycemic burden. The exact basis for such increased susceptibility has not been unraveled. In the Diabetes Prevention Program (DPP), ~8% of subjects with IGT had retinopathy,[51] similar to the 8.1% prevalence of retinopathy observed among individuals with prediabetes in the Gutenberg Health Study in Germany.[53] In another study, the estimated prevalence of microalbuminuria among prediabetic subjects at15.5%.[13] Individuals with prediabetes also have altered retinal hemodynamics and microvascular function.[54] Thus, retinal vasoreactivity measurements may be a sensitive tool to assess early vascular risk.[54]

Remarkably, symptoms and signs of classical diabetic peripheral polyneuropathy can occur in people with

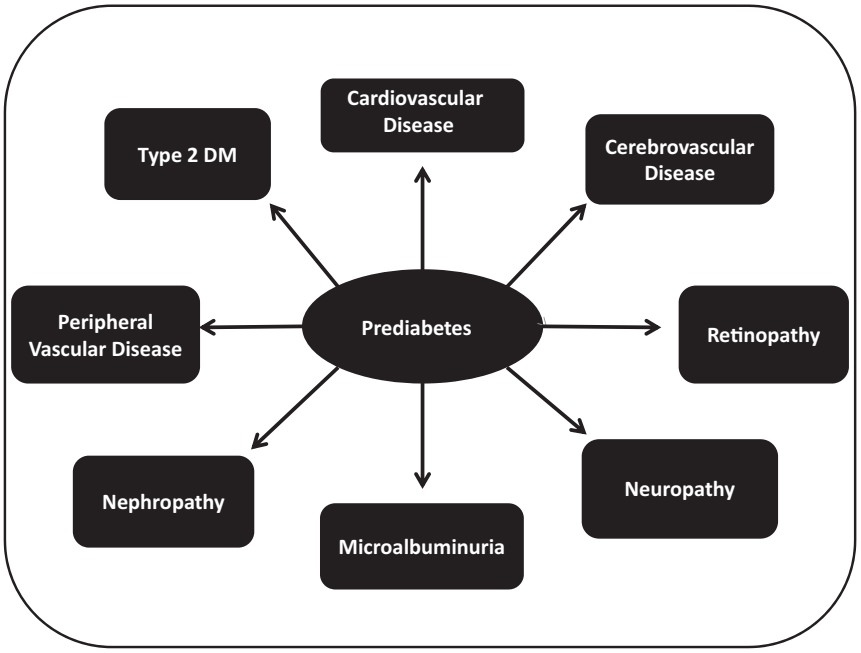

Figure 2 The toxic environment of prediabetes increases the risks for macrovascular and microvascular complications

prediabetes.[11,55,56] Approximately 11–25% of individuals with prediabetes show evidence of peripheral neuropathy.[55] Furthermore, prediabetes is associated with autonomic dysfunction, manifesting as reduced heart rate variability and increased prevalence of erectile dysfunction.[11]

Mechanisms of prediabetic complications

The pathogenesis of microvascular complications in patients with established diabetes is not fully understood. Besides genetic predisposition, some proposed mechanisms include hyperglycemia-induced alterations in the polyol, hexosamine, and protein kinase C (PKC) pathways; advanced glycosylation; glomerular hyperfiltration; induction of transforming growth factor-β and other deleterious growth factors; and oxidative stress, among others.[50,57]

Among these various contenders, those involving blood glucose elevation are particularly pertinent when considering potential mechanisms to explain the occurrence of diabetic complications in people with prediabetes. Intracellular hyperglycemia has been linked to the activation of four toxic pathways that can lead to tissue damage: increased flux through the polyol pathway, formation of advanced glycosylation end products, increased hexosamine pathway activity, and PKC activation (Figure 3).[50,57] The operation of these toxic pathways has been documented in experimental models and humans with diabetes; however, clinical experience indicates that actual tissue damage leading to diabetes complications requires several years of exposure to uncontrolled hyperglycemia. What is unclear, therefore, is why some individuals with subdiabetic levels of glycemia become susceptible to the ''premature'' development of complications typically seen in patients with long-standing diabetes. It is possible that individuals vary in their responses to varying levels of glycemia with regard to the threshold for triggering the aforementioned toxic pathways.[50,57] Equally plausible is a multiplier effect, wherein the simultaneous activation of multiple pathways might render certain individuals particularly vulnerable to the development of premature microvascular and macrovascular complications. Indeed one toxic pathway, involving activation of PKC, links elevated blood glucose to downstream mechanisms that induce tandem alterations in the expression of nitric oxide synthase, vascular endothelial growth factor, plasminogen activator inhibitor-1, TGF-β, reactive oxygen species, and nuclear factor-kappa B, a master regulator of inflammation (Figure 3).[50,57] These downstream effects of glycemic activation of PKC, especially those involving vascular and inflammatory pathways, can account for the worsening β-cell function, insulin resistance, microvascular and macrovascular complications in susceptible persons. Thus, current understanding suggests that the modest elevation of blood glucose levels in the prediabetic state may have profound deleterious effects in susceptible individuals.[50,57–59] Despite emerging contributions from the application of metabolomics, the current lack of precise tools for predicting which persons with prediabetes would develop microvascular and macrovascular complications argues in favor of a comprehensive prevention approach broadly targeted at individuals with prediabetes.[60–62]

Intervention studies

The U.S. Food and Drug Administration have not approved any drug specifically for the treatment of prediabetes. Several landmark clinical trials have established the efficacy and primacy of lifestyle modification in preventing

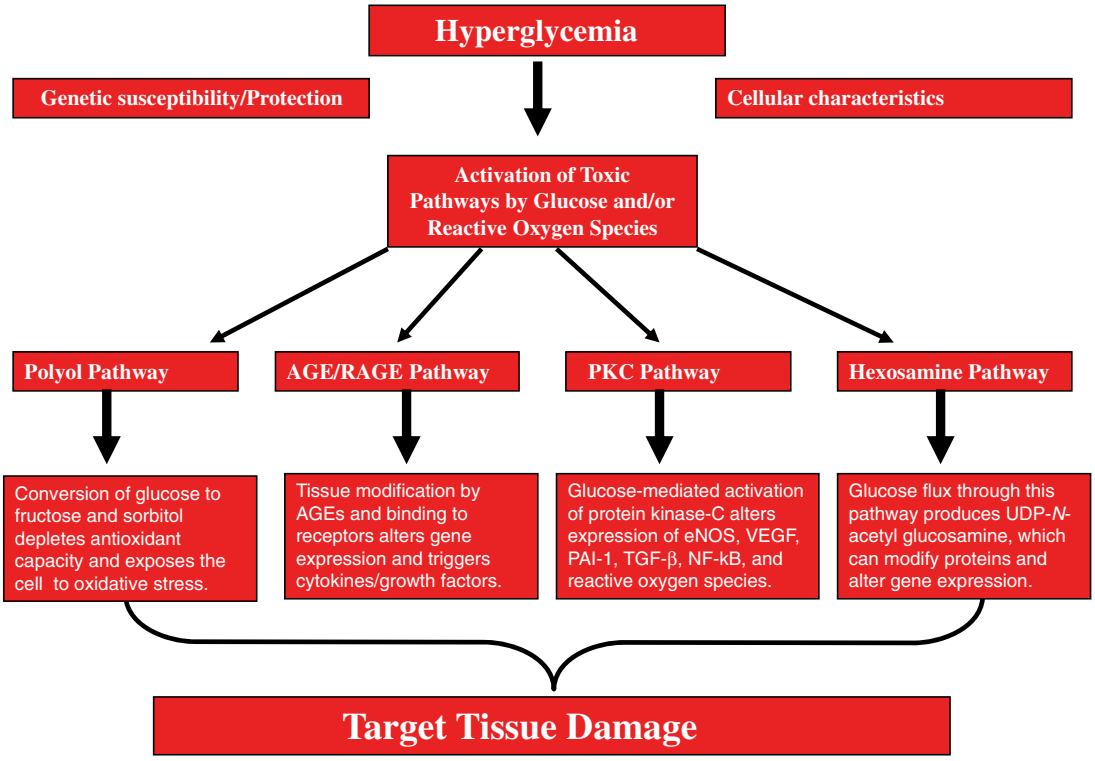

Figure 3 Toxic pathways linking blood glucose levels to tissue damage in susceptible persons. Intracellular hyperglycemia activates the aldose reductase (polyol) pathway as well as other pathways involving advanced glycosylation, PKC activation and increased flux through nutrient-sensing the hexosamine pathway. These activated pathways further lead to induction of downstream processes that mediate fibrosis, vascular dysfunction, inflammation, free radical generation, and tissue damage.
AGE: advanced glycosylation end products; eNOS: endothelial nitric oxide synthase; NF-kB: nuclear factor-kB; PAI-1: plasminogen activator inhibitor-1; PKC: protein kinase C; RAGE: receptor for AGE; TGF-b: transforming growth factor-b; UDP: uridine diphosphate; VEGF: vascular endothelial growth factor. (A color version of this figure is available in the online journal.)

progression from prediabetes to T2DM.[20,63,64] The Finnish Diabetes Prevention Study showed that for every 1 kg decrease in weight, the risk of developing diabetes in the future was reduced by 16%.[63] The DPP demonstrated that approximately 10% of subjects with IGT and high-normal FPG progressed to clinical diabetes each year over an average of 2.8 years of follow-up in the study.[20] The Da Qing study showed a 42% decrease in the incidence of diabetes in participants in the lifestyle intervention groups compared with those in the control group over 6 years.[64] The Da Qing study cohort also showed reduction in cardiovascular and all-cause mortality and diabetes complications in the lifestyle intervention arm during a 20-year follow-up period.[64,65] Clearly, lifestyle intervention is a cost-effective approach to diabetes prevention, with evidence of a 40–70% relative risk reduction for future development of T2DM.[20,63,64–66]

In addition to lifestyle modification, several medications have been tested for their efficacy in preventing diabetes among people with prediabetes (Table 2).[67–79] Some pharmacologic agents approved for obesity treatment (e.g. orlistat) and drugs used for the treatment of T2DM (metformin, thiazolidinediones, alpha-glucosidase inhibitors) have been shown to delay or prevent the conversion from prediabetes to T2DM.[67–79] The medications that have been tested have had variable efficacy on diabetes prevention (~25–% risk reduction vs. placebo) and are often associated with adverse effects. In the studies that attempted drug withdrawal, a rapid increase in blood glucose ensued, indicating that the drugs were masking rather than preventing diabetes.[71,73] Notably, the effect of metformin (31% risk reduction vs.placebo) was weaker than the 58% risk reduction observed in the lifestyle arm in the DPP.[20] In the Indian Diabetes Prevention Program, neither metformin nor pioglitazone showed additive effect on diabetes prevention when combined with lifestyle modification.[78,79] Besides pharmaceutical agents, nutraceuticals have been proposed as an alternative remedy for mitigating diabetes risk; however, there is insufficient evidence to support that approach.[75]

Indeed, the desirable characteristics of an acceptable drug for the primary prevention of T2DM set a high bar that has so far been elusive (Table 3).

Restoration of normal glucose regulation

In the DPP, intensive lifestyle modification, but not metformin therapy, was significantly associated with the restoration of normal glucose regulation (NGR).[80,81] A recent analysis of the Diabetes Prevention Program Outcome Study revealed a 56% long-term reduction in diabetes incidence in people with prediabetes who were able to return to NGR, even if transiently. Thus, regression from prediabetes to NGR, even if transient, appears to predict long-term

Table 2 Randomized controlled diabetes prevention trials in subjects with prediabetes

Study acronym	Intervention	Number of subjects	Study population	Risk reduction	Years
DPP[20]	Diet and exercise or metformin	3234	IGT adults, mean age 54 years, BMI 34	Metformin 31%, lifestyle 58% after 2.8 years	1996–1999
Finnish DPS[60]	Diet and exercise	522	IGT adults, mean age 55, BMI 31	58% after 3.2 years	1993–1998
Da Qing[61]	Diet and exercise	577	Chinese IGT adults mean age 46, BMI 26	31–46% after six years	1986–1992
ACT-NOW[66]	Pioglitazone	602	IGT, mean age 53, BMI 33.0	72% with pioglitazone over 2.4 years.	2004–2006
STOP-NIDDM[73]	Acarbose	1429	IGT Adults, mean age 55, BMI 31	25% after 3.3 years	1995–1998
Xendos[74]	Orlistat + diet + exercise	3305	Swedish, BMI >30, mean age 43 years, 21% with IGT	Entire Group 37%, IGT subgroup 45% after 4 years	1997–2002
DREAM[70]	Rosiglitazone	5269	IGT and/or IFG subjects, mean age 54.7 years, BMI 30.9	62% after approximately 3 years	2001–2003
IDDP-1[75]	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, exercise and metformin 28.2%, after 30 months	2001–2004
CANOE[76]	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

IGT: impaired glucose tolerance; BMI: body mass index.

Table 3 Characteristics of an ideal prediabetes drug

- Efficacy should equal or exceed that of lifestyle intervention (>60% diabetes risk reduction).
- Mechanism(s) of action should address pathophysiologic defects underlying prediabetes.
- The effects of drug should normalize glucose metabolism.
- The drug should have a durable effect that outlasts the period of exposure.
- The drug should not cause weight gain, but should induce weight loss or be weight neutral.
- The drug should have minimal toxicity and its use should require no safety monitoring.
- The drug should be well tolerated, without significant adverse effects.
- The retail cost of the drug should be less than that of the least expensive drug for diabetes treatment.
- The drug should be widely available to all patient populations regardless of socioeconomic status.

decrease in the risk of glycemic progression to T2DM.[81] Logically, subjects who remain free from dysglycemia and experience NGR would be protected from diabetes complications. These considerations argue strongly in favor of having reversal of prediabetes and restoration of NGR as a primary goal for intervention in people with prediabetes.

Conclusions

In conclusion, prediabetes, far from being benign, is a toxic environment that is associated with the development of microvascular and macrovascular complications. Given the increasing global burden of diabetes, it is imperative for public health planners to promote screening and early recognition of people with prediabetes, so that timely lifestyle counseling can be offered. Also, advances are needed in the science of prediction, so as to better identify and target individuals with prediabetes at high risk for the premature development of classical diabetes complications.

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DECLARATION OF CONFLICTING INTERESTS

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