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Introduction

As the human and economic cost of type 2 diabetes has surged, focus on its prevention has intensified. Clinical trials across the globe have demonstrated that diabetes can be prevented in high-risk populations over a wide range of cultures and ethnicities [1–12]. Further, reduction in diabetes onset is observed beyond the time of the interventions, albeit attenuated [13, 14]. Waning benefit post-intervention has been attributed to lack of long-term adherence to lifestyle changes or drug therapy. An alternate explanation, however, may be that lack of progression to diabetes rather than the restoration of normoglycemia has been our goal. All of the landmark trials for diabetes prevention to date have enrolled participants with untreated prediabetes due to their exceptionally high risk for acquiring diabetes [1–12]. Even when overt diabetes is delayed or prevented, both micro- and macrovascular diseases appear more prevalent in those with prediabetes compared to their normoglycemic peers [15–18]. Thus, there is reason to believe that true

prevention of diabetes and its complications likely reside in the reversal of prediabetes and the restoration of normoglycemia. New evidence supports this speculation [19] and guidelines are changing accordingly [20]. Nevertheless, there is much to be considered in identifying the people at highest risk for diabetes and determining when and how to institute preventive measures.

Through the combination of known and emerging risk factors, the worldwide burden of type 2 diabetes continues to rise. National statistics estimate roughly 29 million Americans – 9.3% of the population – currently have diabetes, reflecting an approximate tripling in the prevalence over the past 25 years [21]. Even more staggering are the 415 million people around the world with diabetes – a number that is expected to increase by more than 50% by 2040 [22]. And although these numbers include all diabetes, >90% have type 2. Fortunately, a number of clinical trials have demonstrated that early intervention can prevent or delay type 2 diabetes [1–12] and newer evidence has shown that prevention of diabetes can also prevent microvascular complications [13].

Diabetes Prevention: Clinical Trials

A broad array of approaches has been employed in prospective, randomized clinical trials for the prevention of diabetes. These have included a variety of glucose-lowering medications, weight

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loss medications, and intensive lifestyle modification. Collective results demonstrate that diabetes incidence can be reduced by 20–80% over 2.4–6 years in a wide range of ethnic groups. Non-randomized prospective and cross-sectional data allude to even higher rates of diabetes prevention using bariatric surgery.

Clinical Trials Using Glucose-Lowering Medication

Glucose-lowering therapy has been repeatedly shown to decrease/delay the onset of diabetes in high-risk populations. Metformin has demonstrated comparable efficacy for prevention in both the USA (−31% risk reduction with metformin 850 mg twice daily) and Indian (−26% with metformin 250 mg twice daily) Diabetes Prevention Programs (DPP) despite considerable disparity in the dosing [6, 9]. Low-dose metformin (500 mg twice daily) in combination with low-dose rosiglitazone (2 mg once daily) also proved an effective strategy in the CANOE study (−27%) [12] but paled in comparison to the robust reductions in diabetes onset seen with the full-strength thiazolidinediones (TZDs) observed in the US DPP (−75% with troglitazone 400 mg once daily), DREAM (−60% with rosiglitazone 8 mg once daily), and ACT NOW (−72% with pioglitazone 45 mg once daily) [2, 5, 23]. Similar results were generated using rosiglitazone in women at high risk due to their history of gestational diabetes in the TRIPOD study (−55%) [24]. Nevertheless, safety concerns have dampened enthusiasm for widespread dissemination. Acarbose also diminished diabetes incidence in the STOP NIDDM trial (−25%) despite participants only tolerating approximately two-thirds of the prescribed dose (192 vs. 300 mg daily) [1]. Tolerance of both metformin and acarbose was far higher, as was the reduction in diabetes incidence (−77% and 88%, respectively), in the non-randomized Chinese DPP [25]. Lastly, basal insulin lowered diabetes onset in the ORIGIN study (−20%) albeit with a threefold increase in hypoglycemia

[4]. Only the NAVIGATOR study (nateglinide 60 mg three times daily) failed to mitigate diabetes risk using glucose-lowering medication, and, in this case, diabetes risk actually increased (2.1%) [26]. Altogether, there is clear evidence that a number of glucose-lowering medications with distinct mechanisms of action can safely and effectively prevent diabetes (Fig. 2.1). Nevertheless, no prescription glucose-lowering medication to date has been approved by the Food and Drug Administration (FDA) for this indication.

Clinical Trials Using Weight Loss Medication

As glucose-lowering medications were proving their value in diabetes prevention, orlistat became the first prescription medication to show the same by virtue of its ability to induce weight loss [10]. Participants randomized to orlistat (120 mg three times daily) in the XENDOS trial demonstrated a 37% decline in diabetes incidence – an effect size commensurate with what was observed with acarbose, insulin, or metformin in their respective clinical trials (Fig. 2.1). Since this time, the reinvigorated pipeline of anti-obesity medications has performed key post hoc analyses of their pivotal trials showing the utility of these new medications not only for weight loss but for the prevention of diabetes. Pooled data from the lorcaserin (20 mg once daily) trials BLOSSOM and BLOOM boasted a 62% reduction in development of diabetes [27], whereas the combination of low-dose topiramate (92 mg once daily) with low-dose phentermine (15 mg once daily) revealed an even more impressive 79% reduction in the SEQUEL study [28]. Most recently, prospective results from the SCALE study program were released, highlighting an 80% lower rate of diabetes over 3 years in participants with prediabetes randomized to high-dose liraglutide (3 mg once daily) [29]. Not only do these emerging data rival the efficacy of the TZDs for diabetes prevention (Fig. 2.2), but they do so with the pleiotropic benefits of weight loss.

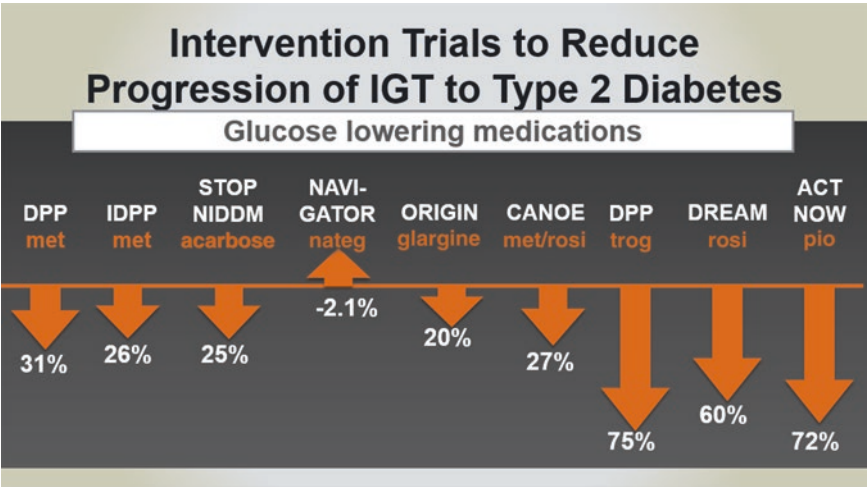


Fig. 2.1 Intervention trials to reduce progression from IGT to diabetes using glucose-lowering medication [1, 2, 4–6, 9, 12, 24, 26]

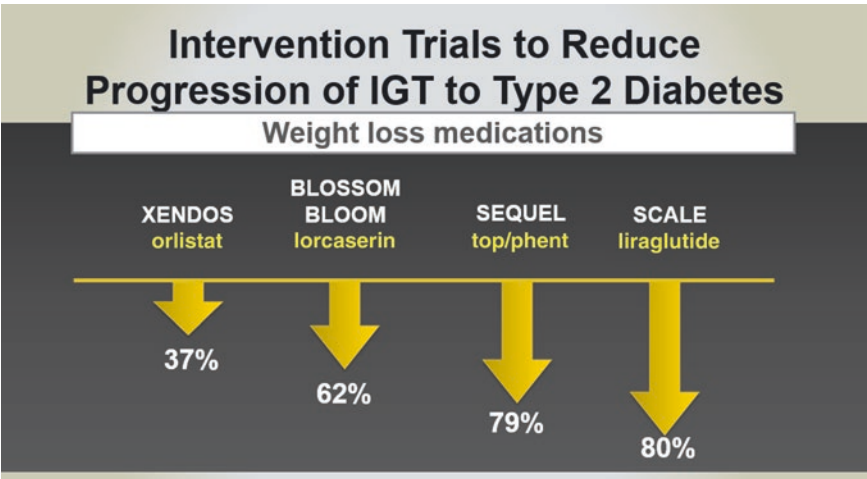


Fig. 2.2 Intervention trials to reduce progression from IGT to diabetes using weight loss medication [10, 27–29]

Evidence with Bariatric Surgery

Extrapolating diabetes prevention observed with anti-obesity medication (5–10% mean weight loss) to bariatric surgery (15–50% mean weight loss), one may imagine total obliteration of diabetes risk. And although no randomized controlled trials have specifically tested this hypothesis, increasing evidence supports this speculation. Both gastric bypass [30, 31] and laparoscopic banding [32] have revealed a con-

sistent 30-fold reduction in diabetes onset during the postsurgical follow-up. The number needed to treat (NNT) in the Swedish Obesity Study (SOS) was only 1.3 people with prediabetes to prevent one case of diabetes over 10 years [30]. Further, a recent meta-analysis compared multiple intervention strategies for diabetes prevention, highlighting the 84% risk reduction with bariatric surgery, suggesting that this may be the most effective single approach to long-term diabetes prevention [33].

Clinical Trials Employing Intensive Lifestyle Modification

Intensive lifestyle modification has been employed in Sweden, China, Finland, the USA, India, and Japan for the prevention of diabetes (Fig. 2.3) [3, 6–9, 11]. Lifestyle interventions, for the most part, have utilized a low-fat (<30% calories from fat, <10% from saturated fat) hypocaloric diet and moderate intensity exercise ~150 min per week for the purpose of 5–7% weight reduction. Interestingly, even where weight loss was not significantly achieved, diabetes incidence was still reduced. This has been largely observed in Asia where starting body mass indices were much lower than in the west [7–9, 25]. Positive results from the Asian studies implicate physical activity and dietary changes, specifically, as responsible for the reduction in diabetes risk. In contrast, the US DPP attributed the entire success of the intensive lifestyle modification group to weight loss with every 1 kg loss translating into a 16% lower risk for diabetes [34]. The Finnish DPP conducted a useful analysis to individually assess the beneficial impact of weight loss, dietary changes, and increased physical activity on the outcome. This analysis revealed an increasing reduction in diabetes for the increasing numbers of goals achieved [11]. The particular goals included >5% weight loss, dietary fat <30%

daily calories, dietary saturated fat <10% daily calories, dietary fiber intake ≥ 15 g/1000 kcal, and/or moderate exercise ≥ 30 min/day. Although weight loss appeared the most potent protective factor, the participants derived benefit from meeting each of the individual goals [35]. Importantly, the US and Finnish studies continue to demonstrate reduction in diabetes incidence well beyond the duration of the intensive intervention periods [13, 14]. These latter observations should underscore clinical messaging for patients who may cycle through periods of adherence and nonadherence to a healthy lifestyle.

Durability and Hard Outcomes

Continued observation of clinical trials' participants following the randomized intervention periods has afforded us the ability to determine durability of the interventions and their impact on hard outcomes – most notably micro- and macro-vascular disease and mortality. After 20 years of follow-up, participants randomized to the active lifestyle interventions in the Da Qing study maintained a 51% reduction in diabetes incidence compared to the control group [36]. Further, they reported a three-fold lower rate of all-cause mortality, largely attributable to fewer

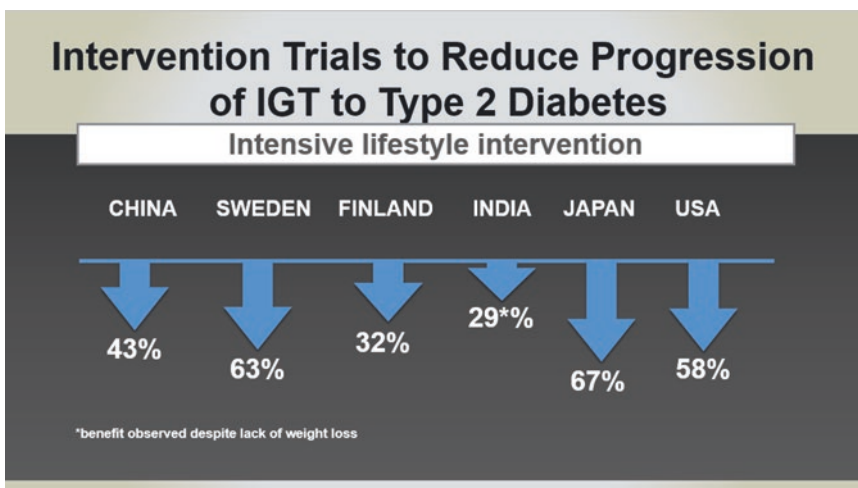


Fig. 2.3 Intervention trials to reduce progression from IGT to diabetes using intensive lifestyle modification [3, 6–9, 11]

cardiovascular and cerebrovascular events, in participants who regressed to normoglycemia compared to those who had progressed from impaired glucose tolerance (IGT) to diabetes in the 23-year follow-up [37]. It should be noted that results remained significant after adjustment for age and traditional cardiovascular risk factors implicating diabetes status, specifically, on the mortality outcome. Both Finnish and US DPPs also continue to follow their participants. The 58% reduction in diabetes onset observed in the active lifestyle participants of the Finnish study has declined to 33% during the 13-year post-intervention observational period [14], but remains highly statistically significant with a high level of residual adherence to the lifestyle curriculum. Similar results were reported from the US DPP where the intervention-mediated reduction in diabetes incidence of 58% and 31% in the lifestyle and metformin groups, respectively, has since declined to 27% and 18%, respectively, over the 15-year observational follow-up [13]. Although no treatment-specific effects on the composite microvascular outcome (retinopathy, nephropathy, and/or neuropathy) have yet to be observed, where diabetes can be prevented, risk of microvascular disease is reduced 28% [13].

Diabetes Prevention: Translation of Clinical Trials to the Real World

Widespread success of clinical trials aimed at diabetes prevention has led to cautious optimism that their recapitulation in a real-world setting is possible. Hence is the charge of the National Diabetes Prevention Program (NDPP). With support from the Centers for Disease Control (CDC), the NDPP provides a free online curriculum for lifestyle coaches and organizations dedicated to lifestyle change programs, as well as training and resources for delivering the curriculum (www.cdc.gov/diabetes/prevention/). The NDPP has been most widely disseminated through the YMCA (<http://www.ymca.net/diabetes-prevention/about.html>) [38]. The 12-month group-based program consists of 16 1-h, weekly sessions, followed by monthly ses-

sions led by a trained lifestyle coach who facilitates a small group of people with similar goals. Education around healthy eating, increasing physical activity, reducing stress, and problem solving is coupled with strategies to maintain motivation. Success of the YMCA's translation of the NDPP is the subject of great anticipation [38–43].

Much ado has been made about the cost-effectiveness of the DPP lifestyle intervention and whether its translation to the real world would be hindered because of the associated expense. Analyses conducted within the DPP have demonstrated its cost-effectiveness within the confines of a clinical trial [44, 45]. The use of the “community health-care worker” for the translation of the DPP lifestyle intervention has also demonstrated consistent positive results and cost-effectiveness in a variety of non-trial settings [46, 47]. These efforts appear particularly efficacious when delivered in a culturally appropriate manner [48] and are achievable regardless of socioeconomic status [49]. Lastly, there is evidence to support the use of the DPP lifestyle model in routine clinical care. A recent study demonstrated that 7% weight loss was achieved in ~36% of intensively treated patients (vs. 14% in the usual care group) 1 year after a 3-month intervention delivered in a primary care setting [50].

Diabetes Prevention: In Clinical Practice

As we ponder the notion of early intervention to prevent diabetes, strategic allocation of resources to do so is critical. Obesity has long been touted as the number one risk factor for diabetes, and although roughly two-thirds of people with diabetes are overweight or obese, only 2–13% of people who are simply obese will acquire diabetes [51]. Likewise, the 50 or so known genes associated with type 2 diabetes explain only a small fraction of the risk and are dwarfed by modifiable risk factors [52]. To reconcile our seeming inability to readily identify the highest-risk people – the people most likely to benefit from early preventive therapy – the American Diabetes Association

(ADA) publishes a list of risk factors [53], and a number of groups have developed diabetes risk calculators based on these risk factors [54, 55]. Collectively, these tools lend guidance for who should be screened for diabetes.

Approximately 50% of people with diabetes remain undiagnosed, in part, because they have never been screened. According to ADA, all adults ≥ 45 years old without additional risk factors or adults of any age who are overweight ($\text{BMI} > 25 \text{ kg/m}^2$) and have at least one other risk factor should receive a screening test for diabetes [53]. The screening test should be HbA_{1c} , fasting glucose, or 2-h glucose and repeated at least at 3-year intervals, once yearly in those diagnosed with prediabetes [53]. The European Society of Cardiology and the European Association for the Study of Diabetes (EASD) stated in 2007 that stepwise screening for type 2 diabetes using a noninvasive risk score [54] as first step and then an oral glucose tolerance test (OGTT) for those with high score values is more efficient than performing invasive testing in all people [56]. However, the efficiency of a stepwise screening strategy may be counterbalanced by the observation that many high-risk individuals fail to complete first step of the screening program unless they are in contact with a doctor for other reasons [57]. Therefore, *opportunistic*, stepwise screening for diabetes and prediabetes may be the most cost-effective approach for identifying individuals at risk [58].

Opportunities to Improve Diabetes Prevention

A Closer Look at Prediabetes

Adoption of any of the proposed approaches to screening people for diabetes may result in a diagnosis of normoglycemia, diabetes, or an intermediate dysglycemic state termed “prediabetes.” Diagnostic criteria for “impaired glucose tolerance” (IGT, one subtype of pre-diabetes) were introduced by the National Diabetes Data Group in 1979, concurrent with the first ever proposed criteria for diabetes itself [59]. Interestingly, criteria for IGT have remained steadfast over the

past three decades, whereas the introduction and refinement of criteria for impaired fasting glucose (IFG, a second subtype of prediabetes that can be seen in isolation or in combination with IGT) have been far more moveable [60, 61]. The latter observation stems from the explicit expectation that people with IFG would also have IGT, a notion repeatedly debunked over the past decade [62, 63]. IFG and IGT are indeed discreet prediabetic states (Table 2.1).

Unlike diagnostic criteria for diabetes that are based on their predictive value for retinopathy [60], diagnostic thresholds for prediabetes are based on the likelihood of developing overt diabetes [62–66]. However, discussion regarding the existing cut points is ongoing. Longitudinal data from a cohort of Israeli soldiers suggest that a fasting glucose above 87 mg/dl ($\sim 4.8 \text{ mmol/L}$) is associated with an increased risk of future diabetes [67]. Further, misclassification is common given the day-to-day variability in the fasting

Table 2.1 Overview of the metabolic defects in IFG and IGT

	Isolated IFG	Isolated IGT	Combined IFG+IGT
<i>Insulin resistance</i>			
Reduced peripheral glucose disposal	–	+	++
Increased hepatic glucose production	+	–	+
<i>Beta cell dysfunction</i>			
Defective absolute insulin secretion	+	–	++
Defective relative insulin secretion	+	++	++
<i>Ectopic fat accumulation</i>			
Increased fat content in liver	+	++	+++
Increased fat content in skeletal muscle	+	+	+

The symbols (+ and –) illustrate whether the condition is present in the different prediabetic subtypes seen in relation to individuals with NGR. The number of symbols illustrates the severity of the conditions

References: [81–87]

IFG impaired fasting glucose, IGT impaired glucose tolerance

(15%) and 2-h (46%) glucose concentrations [68]. The use of the 1-h glucose value (post-OGTT), fructosamine, 5-androhydroglucitol, and others has also been proposed [69]. With the standardization and widespread use of the HbA_{1c}, in 2010, the American Diabetes Association (ADA) advocated its use in the screening and diagnosis of prediabetes (e.g., 5.7–6.4%) [70]. It should be noted, however, the HbA_{1c} does not discriminate between IFG and IGT. Furthermore, the World Health Organization (WHO) only supports the use of HbA_{1c} for diagnostic use if stringent quality assurance tests are in place, assays are standardized to criteria aligned to the international reference values, and no clinical conditions are present which preclude its accurate measurement [71].

Much discussion remains over the term “prediabetes” because not all people with prediabetes will develop diabetes, but many will. A recent meta-analysis showed that the yearly progression rate to diabetes in individuals with prediabetes is 3.5–7.0% (vs. 2%/year in their normoglycemic counterparts [64]), with highest rates in those with combined IFG and IGT and the lowest in those with IFG by ADA (vs. WHO) definition [72]. Increasing HbA_{1c} is also associated with increased risk of diabetes with yearly incidence rates approximating 5% for those with an HbA_{1c} of 5.7–6.0% and up to 10% for those with an HbA_{1c} of 6.1–6.4% [73]. Adding non-glycemic risk factors (e.g., obesity, hypertension, and family history of diabetes) to the diagnosis of prediabetes markedly increases risk for diabetes, approaching 30% per year [74]. Large clinical trials for diabetes prevention around the globe have universally enrolled participants with untreated prediabetes due to their high risk for acquiring overt diabetes [1–12]. Altogether, the prediabetic state, especially when enriched with other risk factors, should be our target population for diabetes prevention.

Altogether, strong evidence supports the notion that we can prevent or delay the onset of diabetes in people with prediabetes using lifestyle modification or drug therapy. Not uncommonly, however, the question is posed as to whether these trials prevented diabetes or simply treated prediabetes. Although seemingly rhetorical, the answer has implications that could change treatment goals and guidelines for people with prediabetes.

Targeting Defects Specific to the Subtypes of Prediabetes

Elegant human clinical research has delineated the pathophysiology of IFG vs. IGT (Table 2.1). Liver insulin resistance, as measured using stable isotopes, has been reported to be 8–25% higher in people with IFG vs. normoglycemic controls in some studies [75, 76], or “inappropriately” comparable to people with normoglycemia (given the higher circulating glucose and insulin levels in IFG) in others [77, 78]. In contrast, skeletal muscle, not liver, has been implicated in the insulin resistance of IGT. Muscle insulin sensitivity has been shown to be 42–48% lower in IGT vs. normoglycemic controls [77, 78] with only minimal impairments seen in IFG [76]. Because of the larger contribution of muscle (vs. liver) to whole body insulin sensitivity, people with isolated IGT demonstrate on average 15–30% greater whole body insulin resistance compared to those with isolated IFG [79–81]. Additionally, aspects of beta cell dysfunction are discrepant in isolated IFG vs. isolated IGT with impaired first-phase insulin release noted in the former and diminished second phase in the latter [78, 80]. To date, no intervention aimed at diabetes prevention has considered the clear physiologic differences in IFG vs. IGT, a matter not likely to be resolved as we move increasingly to the use of A1c or the diagnosis of both diabetes and prediabetes.

Restoration of Normoglycemia in People with Prediabetes

Despite the various strategies employed, only intensive lifestyle modification has been universally advocated (whereas metformin can be considered) for the treatment of prediabetes [82]. The rationale for this decision has included the questionable risk/benefit ratio, cost-effectiveness, and reduction in complications, such as cardiovascular disease, in people with prediabetes using medications for glucose lowering or weight reduction. Nevertheless, any intervention appears to diminish in effectiveness over the long-term [13, 14]. Waning benefit post-intervention has been attributed to lack of long-term adherence to lifestyle changes or drug

therapy. An alternate explanation, however, may be that lack of progression to diabetes rather than the restoration of normoglycemia has been our goal.

In clinical trials to date, interventions were deemed successful if diabetes was prevented or delayed, yet many participants remained with prediabetes. Arguably, prevention of diabetes and its complications lies in the restoration of normoglycemia rather than in the maintenance of prediabetes. This was confirmed by a recent post hoc analysis from the Diabetes Prevention Program Outcomes Study (DPPOS) [19]. This analysis demonstrated a 56% lower risk of diabetes 10 years from randomization among those who were able to achieve normoglycemia during DPP vs. those who remained with prediabetes. The concept that diabetes risk can be significantly reduced over the long term through the pursuit of normoglycemia represents a major shift in our current thinking and has quickly gained consensus as the goal for people with prediabetes [20, 83]. Exactly how normoglycemia should be

achieved is far less clear. Data from the DPP would contend that only lifestyle modification (OR = 2.05), not metformin, is useful in achieving normoglycemia in people with prediabetes [84]. Nevertheless, the use of low-dose metformin in combination with low-dose rosiglitazone in the CANOE trial (OR = 1.50) was able to attain normoglycemia [12]. Full-strength TZDs have also been shown to do the same in both the DREAM and ACT NOW studies (OR = 1.71 for both) [2, 5]. High-dose liraglutide boasted a robust and sustained ability to restore normoglycemia in the SCALE studies (OR = 4.9) [29], an effect that rapidly declined off treatment in the 12 weeks that followed the 160-week active treatment period (Table 2.2). Collectively, there is mounting interest in learning if normoglycemia should be the goal for people with prediabetes and, further, if they should be monitored for relapse to prediabetes with escalating and earlier intervention instituted as needed to maintain normoglycemia [85].

Table 2.2 Regression to normoglycemia in people with prediabetes

	N = Population		Follow-up (years)	Regression in controls	Treatment	Regression
US DPP	1990	IGT+IFG	10	37	Lifestyle	2.05 (1.66–2.53)
					Metformin	1.25 (0.99–1.58)
Indian DPP	531	IGT	2.5	24.1	Lifestyle	1.48 (0.99–2.22)
					Metformin	1.27 (0.85–1.89)
					Both	1.31 (0.87–1.95)
ACT NOW	602	IGT	2.4	28	Pioglitazone	1.71 (1.33–2.19)
DREAM	5269	IGT+/-IFG	3.0	30.3	Rosiglitazone	1.71 (1.57–1.87)
					Ramipril	1.16 (1.07–1.27)
CANOE	207	IGT	3.9	53.1	Rosi+Met	1.50 (1.21–1.86)
STOP NIDDM	1429	IGT+IFG	3.3	31	Acarbose	1.14 (0.98–1.33)
SCALE	2254	IGT+/-IFG	3.1	36	Liraglutide	3.60 (3.40–4.40)

References: [1, 2, 5, 6, 9, 12, 30]

IFG impaired fasting glucose, IGT impaired glucose tolerance

This shift in our clinical approach may be justified considering the higher incidence of diabetic complications seen in people with prediabetes, independent of their conversion to overt diabetes [15–18]. Nevertheless, enthusiasm for the medical treatment of prediabetes is currently tempered by cost and risk/benefit ratio, especially in light of the many clinical trials failing to demonstrate CVD risk reduction from glucose lowering in frank diabetes [86–89]. Most surprising, however, are data to the contrary in prediabetes. The rate of progression of carotid intima media thickening has been slowed in women with a history of gestational diabetes [90], as well as people with prediabetes [2], using glucose-lowering therapy for ≤ 3 years. More convincing still was the 49% CVD event reduction in prediabetic participants of the STOP NIDDM trial who underwent glucose-lowering medical therapy [91]. Together, these data suggest that glucose lowering has a disproportionate benefit in CVD risk reduction in prediabetes vs. diabetes – possibly because CVD is less established – providing some of the most vital support for the pursuit of normoglycemia.

Conclusions

As the human and economic cost of type 2 diabetes has surged, focus on its prevention has intensified. Clinical trials across the globe have demonstrated that diabetes can be prevented in high-risk populations over a wide range of cultures and ethnicities [1–12]. Further, reduction in diabetes onset is observed beyond the time of the interventions, albeit attenuated [13, 14]. Waning benefit post-intervention has been attributed to lack of long-term adherence to lifestyle changes or drug therapy. An alternate explanation, however, may be that lack of progression to diabetes rather than the restoration of normoglycemia has been our goal. All of the landmark trials for diabetes prevention to date have enrolled participants with untreated prediabetes due to their exceptionally high risk for acquiring diabetes [1–12]. Even when overt diabetes is delayed or prevented, both micro- and macrovascular diseases appear more prevalent in those with

prediabetes compared to their normoglycemic peers [15–18]. Thus, there is reason to believe that true prevention of diabetes and its complications likely reside in the reversal of prediabetes and the restoration of normoglycemia. New evidence supports this speculation [19], and the American Association of Clinical Endocrinologists (AACE) has changed its guidelines accordingly [20]. Nevertheless, there is much to be considered in identifying the people at highest risk for diabetes and determining when and how to institute preventive measures.

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