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Clin Chem. Author manuscript; available in PMC 2015 April 13.

Published in final edited form as:

Clin Chem. 2011 February ; 57(2): 215–220. doi:10.1373/clinchem.2010.149096.

Prediabetes as a Therapeutic Target

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Abstract

BACKGROUND—The term “prediabetes” is used to describe a condition that involves impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). IGT is defined by a 2-h oral glucose tolerance test plasma glucose concentration >140 mg/dL (7.8 mmol/L) but <200 mg/dL (11.1 mmol/L), and IFG is defined by a fasting plasma glucose concentration ≥100 mg/dL (5.6 mmol/L), but <126 mg/dL (7.0 mmol/L). Studies have shown that people with prediabetes tend to develop type 2 diabetes within 10 years and are at increased risk for cardiovascular disease and death even before the development of diabetes.

CONTENT—In this minireview we discusses the epidemiology, pathophysiology, and clinical implications of prediabetes. The rationale for therapeutic intervention in people with prediabetes, the goals of intervention, and the specific tools for intervention are presented. Emphasis is placed on data from randomized controlled clinical trials, whenever such data are available.

SUMMARY—Approximately 57 million Americans have prediabetes and are consequently at risk for cardiometabolic complications. Lifestyle modifications (dietary restriction and exercise) and certain medications can prevent the development of diabetes in persons with prediabetes. Lifestyle intervention also has been demonstrated to decrease cardiovascular disease risk markers, although data on clinical events are lacking.

The term “prediabetes” refers to an intermediate stage between glucose concentrations within reference intervals and hyperglycemia that meets current criteria for diagnosis of diabetes. Prediabetes can be diagnosed on the basis of either impaired fasting glucose (IFG)[2] or impaired glucose tolerance (IGT), according to the revised 2003 American Diabetes Association (ADA) criteria (1). IFG is defined as a fasting plasma glucose concentration of 100 mg/dL (5.6 mmol/L) but <126 mg/dL (7.0 mmol/L). IGT is defined as a 2-h response to

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Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

[2]Nonstandard abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ADA, American Diabetes Association; OGTT, oral glucose tolerance test; DPP, Diabetes Prevention Program; CVD, cardiovascular disease; BMI, body mass index; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; PPAR-a, peroxisome proliferator-activated receptor subtype *a*.

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a 75-g oral glucose tolerance test (OGTT) of 140 mg/dL (7.8 mmol/L) and <200 mg/dL (11.1 mmol/L) (1). The pathophysiology of prediabetes includes alterations in insulin sensitivity and pancreatic β-cell function, usually on a background of increased adiposity (2–5). Insulin sensitivity is inversely related to glycemia, even within the normal fasting glucose range; increases in fasting plasma glucose concentrations from 70 to 125 mg/dL (3.9–6.9 mmol/L) are associated with a >3-fold decrease in insulin sensitivity (2). Persons with isolated IFG show an approximately 25% decrease in insulin sensitivity, and individuals with combined IFG and IGT show a decrease of approximately 80% in insulin sensitivity compared with persons with fasting glucose concentrations within reference intervals (2). With regard to β-cell function, defects in acute insulin response to intravenous and oral glucose have been reported in patients with IGT. Moreover, the disposition index (i.e., insulin secretion corrected for ambient insulin resistance) is markedly decreased in patients with combined IFG and IGT (2–5).

Scope of the Problem

Approximately 24 million Americans have diabetes, and >90% of them have type 2 diabetes. The prevalence of type 2 diabetes continues to increase, and is expected to exceed 366 million persons worldwide by 2030 (6). Approximately 1.5 million persons in the US are newly diagnosed with diabetes each year, and are at risk for diabetic complications (7). The CDC estimated that, in 1988–1994, among US adults 40–74 years old, 33.8% had IFG, 15.4% had IGT, and 40.1% had prediabetes (IGT or IFG or both) (7). More recent data indicated that, in 2003–2006, 25.9% of US adults 20 years old or older and 35.4% of adults 60 years old or older had IFG (7). Considering the entire US population in 2007, the CDC estimated that there were approximately 57 million American adults aged 20 years or older with IFG.

Rationale for Prevention

The natural history of prediabetes predicts that the majority of persons with the condition progress to diabetes in the long run (8). In addition to the risk of progression to diabetes, IGT has been reported to increase the risk for certain microvascular complications that are typically associated with diabetes (9, 10). Data from the Diabetes Prevention Program (DPP) research group showed that 7.9% of individuals with impaired glucose tolerance and 12.6% with newly diagnosed diabetes had retinopathy (10). Multiple prospective studies have demonstrated the increased risk of cardiovascular disease (CVD) in patients with IGT. For example, the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe study showed a significant association between the magnitude of the 2-h postchallenge plasma glucose concentration and CVD mortality, and a J-shaped relation between fasting plasma glucose and CVD mortality (11). A meta-analysis of 38 prospective studies showed a linear relationship between increased CVD risk and fasting and postchallenge blood glucose concentration within the nondiabetic range (12), which is consistent with the findings of the Norfolk cohort of the European Prospective Investigation of Cancer and Nutrition (13). Thus, it is clear that prediabetes is not a benign condition. The data showing increased risks for glycemic progression and microvascular and macrovascular complications strengthen the rationale for intervention in prediabetic individuals. There is

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now abundant evidence that progression to type 2 diabetes can be delayed or prevented through lifestyle and pharmacologic interventions (14–19).

Lifestyle Intervention

Several studies have demonstrated beneficial effects of lifestyle intervention in preventing the development of type 2 diabetes in prediabetes populations. The lifestyle intervention applied in these studies generally resulted in 5%–10% weight reduction through dietary modification and increased physical activity. The dietary modification included decrease in caloric intake, reduction in saturated fat calories, and increase in intake of complex carbohydrates. The physical activity part involved 150–240 min per week of moderate-intensity exercise (15–18). The Malmö study (15), one of the earliest lifestyle intervention studies to be reported, enrolled men with IGT or early-stage type 2 diabetes. Approximately 50% of study participants with initial IGT showed normalization of glucose tolerance with lifestyle modification after a mean follow-up of 6 years. Moreover, lifestyle intervention improved glucose tolerance in the majority of patients with early-stage type 2 diabetes (15). Similar findings have been reported from the Da Qing study, which examined the effects of diet and/or exercise in 577 Chinese adults with IGT over a 6-year follow-up period (16). All interventions were associated with a significant reduction in the risk of diabetes, ranging from 36% in the diet-only group to 39% in the combined diet-plus-exercise group and 47% in the exercise-only group (16). Surprisingly, the Da Quing study failed to show an additive effect of diet plus exercise. The results of these early studies were subsequently confirmed by the DPP and the Finnish Diabetes Prevention Study (17, 18). Each of these studies followed the study participants for approximately 3 years and showed a consistent 58% relative risk reduction in the incidence of type 2 diabetes in the lifestyle intervention group compared with controls.

EFFECTS OF LIFESTYLE INTERVENTION ON CVD

The DPP investigators assessed the effects of lifestyle intervention, metformin, and placebo on CVD risk factors among patients with IGT (19). Compared with the placebo and metformin groups, the lifestyle group showed decreased blood pressure, a 33% decrease in incident hypertension, increased HDL cholesterol concentrations, and lower triglyceride concentrations. Furthermore, lifestyle intervention resulted in decreased concentrations of the atherogenic small, dense LDL particles (19). Overall, there was a reduced need for antihypertensive and lipid-lowering medications among individuals assigned to the intensive lifestyle arm compared to the placebo and metformin arms of the DPP. These improvements in CVD risk markers suggest that long-term follow-up of the DPP cohort may show reduction in clinical events in the lifestyle intervention arm (19, 20).

LIMITATIONS OF LIFESTYLE INTERVENTION

The impressive results of the lifestyle intervention to prevent incident diabetes have been obtained predominantly from clinical trials conducted at academic centers. These trials involved frequent clinic visits, multi-disciplinary teams (including physicians, nurses, dietitians, psychologists, exercise physiologists, and others), and substantial resources and support from study sponsors. Most importantly, the services were offered at no cost to the

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study participants, who were often reimbursed for their expenses and also given stipends for their participation. Thus, it remains to be shown whether similar success rates with lifestyle modification could be achieved in routine clinical practice in the community.

Pharmacologic Intervention

Some randomized controlled studies that have tested the effects of lifestyle intervention and different medications on the progression from prediabetes to type 2 diabetes are summarized in Table 1. The drugs that have been investigated in clinical trials for the prevention of diabetes include metformin, acarbose, orlistat, rosiglitazone, and pioglitazone. The DPP demonstrated that intervention with metformin decreased the development of diabetes in adults with impaired glucose tolerance by 31% (17). However, the effect of metformin was more pronounced in younger, obese [body mass index (BMI) >35 kg/m^2] individuals than in older or leaner individuals (17).

In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus, intervention with the α glucosidase–inhibitor drug acarbose decreased the rate of progression to diabetes by approximately 25% after 3.3 years (21). In the Xenical in the Prevention of Diabetes in Obese Subjects study, the weight-reducing agent orlistat (a gastrointestinal lipase inhibitor) in combination with lifestyle modification resulted in greater weight loss and a 37% reduction in the incidence of type 2 diabetes compared with lifestyle intervention alone (22). A reduction in the incidence of diabetes was seen only in individuals with IGT. In the Pioglitazone in the Prevention of Diabetes study, treatment with pioglitazone resulted in relatively low rates of diabetes, which the same authors had previously observed with troglitazone (23). The results of the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study underscore the protective effect of thiazolidinediones on diabetes risk: rosiglita-zone treatment resulted in a 60% reduction in the risk of diabetes or death compared to placebo in patients with prediabetes (24).

FIBRATES

Many patients with diabetic dyslipidemia (characterized by hypertriglyceridemia and low HDL-cholesterol concentrations) receive treatment with fibrates (gemfibrozil, fenofibrate, bezafibrate). These drugs decrease serum triglycerides and increase HDL-cholesterol concentrations through their agonistic interaction with the peroxisome proliferator-activated receptor subtype α (PPAR-a). A retrospective analysis of a large database showed that exposure to the PPAR-a agonist bezafibrate was associated with a reduced risk of incident diabetes (25). The database comprised information from 12 161 patients treated with bezafibrate and 4191 patients treated with other fibrates. The baseline characteristics were similar between the 2 groups, but the hazard ratio for incident diabetes was 0.66 (95% CI 0.53–0.81) among bezafibrate users compared to users of other fibrates. The protective effect of bezafibrate became stronger with increasing duration of therapy. The exact mechanism(s) underlying the apparent diabetes prevention effect of bezafibrate is unknown, but the specificity of the report to bezafibrate over other fibrates indicates that the effect is not mediated by PPAR-a receptors per se. Thus, amelioration of insulin resistance (26) through dual activation of PPAR-a and PPAR-γ receptors (27) by bezafibrate could be a putative mechanism for the reported diabetes prevention effect. Clearly, randomized

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controlled trials are needed before bezafibrate or other fibrates can be recommended specifically for diabetes prevention.

LIMITATIONS OF PHARMACOLOGIC INTERVENTION

The drawbacks to pharmacologic prevention of diabetes include the risks from adverse effects of the specific drugs, the costs of medication, the need for long-term medication, and problems with patient adherence. Furthermore, current experience has indicated a high likelihood of glycemic rebound following cessation of these medications, so these medications may need to be administered for an indefinite period (28). The occur-rence of glycemic rebound following withdrawal of medications (observed in both the DPP and DREAM trials) indicated that available medications have not essentially changed the underlying pathophysiology of prediabetes. In addition, medication cost is a significant concern, particularly in developing countries (29). Because of these limitations, pharmacologic intervention cannot be considered a first-line approach for diabetes prevention in the general population.

Nonetheless, for practical reasons, there is a societal need for safe, effective, and durable medications that could serve as alternatives or adjuncts to lifestyle intervention for diabetes prevention. This need is underscored by the poor human record of long-term adherence to dietary and exercise recommendations. Ideally such a drug (Table 2) should be well tolerated and nontoxic, match or surpass the beneficial effects of lifestyle intervention, and correct the pathophysiologic defects that underlie prediabetes (30). Importantly, a durable effect that outlasts the period of medication exposure would be desirable for such a drug, to permit withdrawal of the medication after a defined period of intervention without the risk of relapse. Finally, the cost of such a drug must not be prohibitive, given the large number of people with prediabetes (57 million in the US alone).

The currently available drugs do not meet all the desirable criteria, but it may be possible to design a drug or combination of agents that can meet most of the desired criteria. A medication that improves insulin sensitivity through induction of significant weight loss, along with improving β-cell function through cellular growth or regeneration, could have a durable effect in reversing the history of prediabetes. Incretins, incretin analogs, and incretin mimetics offer some promise in this direction. Future diabetes prevention studies should evaluate the efficacy of these agents alone and in combination with lifestyle interventions and other proven medications for diabetes prevention.

Current Guidelines

Published guidelines on the approach to the patient with prediabetes consist of a consensus statement from the ADA, the Indian Health Services guidelines for care of adults with prediabetes and/or metabolic syndrome, and a position statement from the Australian Diabetes Society and Australian Diabetes Educators Association (Table 3). The ADA consensus statement (31) recommended lifestyle modification with a weight loss goal of 5%–10% along with moderate physical activity of about 30 min daily for patients with IFG or IGT. The option of prescribing metformin is included in the ADA recommendations. However, it is unclear exactly who should receive metformin as a first-line agent for

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diabetes prevention. Notably, lifestyle modification was nearly twice as potent as metformin in preventing diabetes in the DPP (17). The results of the subgroup analysis of the efficacy of metformin in the DPP suggest that metformin treatment should be considered in high-risk prediabetic patients younger than 60 years who are massively obese (BMI >35 kg/m^2) (17). Additional selection criteria for metformin use include a family history of diabetes in first-degree relatives, increased triglycerides, reduced HDL-cholesterol concentrations, hypertension, and HbA1c more than 6.0% (31). Even for persons in whom all of these risk factors are aggregated, and who thus seem eligible for metformin prophylaxis, the primary recommendation should focus on lifestyle modification. The Indian Health Services guidelines also encourage lifestyle changes with consideration for metformin on an individualized basis (32). The Australian guidelines recommend lifestyle intervention as first-line therapy for a minimum of 6 months before consideration of pharmacotherapy (33). A recent study in the US demonstrated that more than 96% of individuals with both IFG and IGT would be eligible for metformin therapy according to the ADA consensus criteria (34). Because approximately 30% of persons with IFG seem to meet the criteria for metformin treatment, it is recommended that oral glucose tolerance tests be performed to identify those with coexisting IGT (34).

In conclusion, lifestyle interventions (modest caloric restriction and moderate-intensity physical activity) in prediabetic individuals have shown remarkable efficacy in preventing the development of type 2 diabetes. Favorable effects on glycemia in conjunction with other metabolic and cardiovascular benefits make the implementation of lifestyle interventions a public health imperative. Several medications have also been reported to decrease the rate of progression from prediabetes to diabetes. However, a drug-based diabetes prevention approach is fraught with inherent drawbacks, including toxicity, tolerability, cost, and lower efficacy than lifestyle intervention, among others. For the millions of people with prediabetes, lifestyle modification is the ideal initial option because of its minimal toxicity and excellent efficacy compared with medications. Therefore, pharmacologic interventions for diabetes prevention should be individualized as a second-line adjunct to lifestyle modification.

With regard to specific drugs, the choice of metformin is supported by its proven efficacy, relative safety, and cost-effectiveness, and the availability of long-term data from the DPP. Metformin is recommended for those individuals at high risk for diabetes who may have greater benefit from this drug, as was seen in the DPP (17, 30). The thiazolidinediones have efficacy profiles for diabetes prevention that exceed that of metformin. However, the lack of long-term safety data and higher cost argue against their adoption for primary prevention of diabetes. It is important for both patient and provider to realize that any pharmacotherapy for prediabetes will require a long-term commitment. The ideal pharmacological intervention must demonstrate long-term safety, sustained efficacy, ancillary health benefits (reduced risks of macrovascular and microvascular complications), cost-effectiveness, and the ability to alter the underlying pathophysiology of prediabetes (34). The current lack of such an agent provides a compelling rationale for continued research to discover novel drugs.

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Acknowledgments

Employment or Leadership: None declared.

Consultant or Advisory Role: None declared.

Stock Ownership: None declared.

Honoraria: None declared.

Research Funding: S. Dagogo-Jack, NIH grants R01 DK067269 and MO1 RR00211.

Expert Testimony: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

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Table 1

Randomized controlled trials on diabetes prevention.

Study	No. of participants	Study population	Type of intervention	Risk reduction	Duration
Da Quing [Pan et al. (16)]	577	Chinese, mean age 45 years, BMI 26 kg/m^2	Diet, exercise	31%–46%	6 years
STOP-NIDDM[a] [Chiasson etal. (21)]	1429	IGT adults, mean age 55 years, mean BMI 31 kg/m^2	Acarbose	25%	3.3 years
Finnish DPS [Tuomilento et al. (18)]	522	IGT adults, mean age 55 years, mean BMI 31 kg/m^2	Diet and exercise	58%	3.2 years
DPP [Knowler et al. (17)]	3234	IGT adults, mean age 51 years, mean BMI 34 kg/m^2	Diet and exercise, or Metformin	Metformin 31% Lifestyle 58%	2.8 years
XENDOS [Orgerson et al. (22)]	3305	Swedish, BMI >30 kg/m^2, mean age 43 years, 21% with IGT	Orlistat + diet + exercise	Entire group 37% IGT subgroup 45%	4 years
DREAM [Hanley et al. (24)]	5269	IGT and/or IFG patients, mean age 54 years, BMI 30.9 kg/m^2	Rosiglitazone	62%	3 years

[a]STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; DPS, Diabetes Prevention Study; XENDOS, XENical in the Prevention of Diabetes in Obese Subjects.

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Table 2

Desirable characteristics of the ideal drug for diabetes prevention.[a]

• Efficacy: should equal or exceed the efficacy of lifestyle intervention.
• Mechanism(s): should repair the pathophysiologic defects that underlie prediabetes.
• Glucoregulation: should normalize glucose metabolism.
• Durability: effects should outlast the period of medication exposure.
• Adiposity: should induce weight loss or be weight neutral.
• Safety: should have minimal toxicity and require no safety monitoring.
• Tolerability: should be well tolerated, without GI or other adverse effects.
• NCost: should cost less than the least expensive drug for diabetes treatment.

[a]Modified with permission from Edeoga and Dagogo-Jack (30).

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Table 3

Published guidelines on the approach to the patient with prediabetes.

	ADA consensus statement [Nathan et al. (2007) (31)]	Indian Health Service guidelines for prediabetes [Indian Health Services (2006) (32)]	Australian Diabetes Society statement [Twigg et al. (2007) (33)]
IFG	100 ≤ FPG[a] < 126 mg/dL	100 ≤FPG < 126 mg/dL	110 ≤ FPG < 126 mg/dL
	5.6 ≤ FPG < 7.0 mmol/L	5.6 ≤ FPG < 7.0 mmol/L	6.1 ≤ FPG < 7.0 mmol/L
IGT	140 ≤ 2 hPG < 200 mg/dL	140 ≤ 2 hPG < 200 mg/dL	140 ≤ 2 hPG < 200 mg/dL
	7.8 ≤ 2 hPG < 11.1 mmol/L	7.8 ≤ 2 hPG < 11.1 mmol/L	7.8 ≤ 2 hPG < 11.1 mmol/L
Who should be screened for prediabetes	Individual with risk factors for diabetes	Annual testing for individuals with risk factors for diabetes	Incidental detection when screening for diabetes
Method of screening	1) FPG	1) FPG	Incidental detection when screening for diabetes
	2) 2-h OGTT if metformin is considered	2) Optional 2-h OGTT	
Recommended treatment	Lifestyle modification for IFG or IGT. Lifestyle modification and/or metformin for IFG and IGT and at least 1 of the following: age <60y, BMI >35 kg/m^2, family history of diabetes mellitus in first degree relative, high triglycerides, low HDL, hypertension, hemoglobin A1c >6%	Lifestyle modification	Lifestyle modification for a minimum of 6 months before pharmacotherapy
		Metformin treatment on an individualized basis	
Follow-up	Metformin group: hemoglobin A1c every 6 months	Monitor glucose every 6 months	OGTT initially performed annually then retesting every 1–3 years
	Lifestyle: annual follow-up		

[a] FPG, fasting plasma glucose; 2 hPG, plasma glucose 2 h after a meal.