Point: If It Is Important to Prevent Type 2 Diabetes, It Is Important to Consider All Proven Therapies Within a Comprehensive Approach

Type 2 diabetes is a common metabolic disease that is defined on the basis of glucose levels above specific thresholds. Individuals with type 2 diabetes are at high risk of blindness, renal failure, amputation, cardiovascular disease, premature death, dementia, and a variety of other chronic diseases and life-threatening events. However, unlike other risk factors for future events (e.g., hyperlipidemia or hypertension), type 2 diabetes is often associated with symptoms and discomfort related to elevated glucose levels that range from fatigue, nocturia, polyuria, and nonspecific aches and pains to dehydration and coma. Moreover, once diabetes is diagnosed, affected individuals incur additional cost and inconvenience related to disease labeling, dietary and lifestyle modification, glucose monitoring, eye assessments, and higher health and life insurance premiums.

Several trials have shown that aggressive management of type 2 diabetes can reduce the risk of microvascular disease (1–3), and that multifactorial risk factor interventions can reduce the risk of these and other consequences (4–6). These considerations and epidemiologic evidence that the risk of eye and kidney disease is well below the diagnostic thresholds for diabetes suggest that if glucose levels are prevented from rising past these thresholds, or the rise is delayed, these consequences will also be prevented or delayed. Moreover, evidence that the glucose level is a progressive risk factor for cardiovascular events (i.e., that the risk rises with the glucose level) (7–11) supports the hypothesis that preventing or delaying any rise within the nondiabetic range may reduce the risk of cardiovascular events. Finally, if ongoing clinical trials (12) show that therapies that lower elevated glucose levels in individuals with and without diabetes reduce the risk of cardiovascular events, then a therapy that both prevents diabetes and lowers or normalizes glucose levels may also reduce cardiovascular risk. Such a possibility has already been raised by at least one diabetes prevention trial (13).

Today, these are just hypotheses, and whether they are true may depend on the specific means by which the intervention prevents or slows the rise in glucose levels, in addition to whether it lowers nondiabetic glucose levels or just keeps them from rising any higher. For example, a hypothetical drug that dramatically lowers the renal threshold for glucose and causes glucosuria may have a very different effect on the consequences of diabetes than a drug that improves β-cell function, even though both agents could prevent or slow a rise of glucose levels past the diabetes thresholds.

Clinical trials in individuals with impaired glucose tolerance (IGT) have clearly shown that a program of diet and exercise can substantially reduce the incidence of type 2 diabetes by ~60% (14,15), and that the glucose-lowering drugs metformin and acarbose can reduce the incidence of diabetes by 25–30% (14,16). Most recently, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial showed that the addition of the thiazolidinedione rosiglitazone to healthy lifestyle advice can reduce type 2 diabetes by 60% in individuals with either impaired fasting glucose (IFG) or IGT (17), and that this metabolic benefit was accompanied by modest weight gain preferentially localized to the hip versus the abdomen. The most notable adverse effect was nonfatal congestive heart failure that occurred at a low incidence of 0.5% over 3 years.

The possibility that diabetes incidence can be reduced by agents that are not viewed as glucose-lowering agents has also been prospectively tested. One clinical trial (18) of a weight-reducing drug reported a 37% risk reduction in obese individuals. However, the fact that only 43% of the randomized participants were followed for the full study period and that benefits were most apparent in the IGT subgroup make it difficult to generalize these findings to all obese individuals. Most recently, the DREAM trial reported that ramipril did not significantly reduce diabetes incidence in individuals with IFG or IGT at low risk for cardiovascular disease (19), in contrast to a meta-analysis of previous ACE trials that suggested a modest effect on diabetes prevention in individuals at high risk for cardiovascular events (20). However, the data suggested a trend toward benefit after 3 years, and ramipril did significantly increase the secondary outcome of regression to normoglycemia (19).

Table 1 summarizes the key characteristics and results of the trials of nonpharmacologic and pharmacologic interventions that yielded a significant reduction, delay, or prevention of diabetes. It is important to note that from a clinical perspective, the words "reduction," "delay," and "prevention" are identical. For the group allocated to the interventions that yielded positive results, diabetes incidence was reduced; for the individuals within that group who did not develop diabetes, it was delayed or prevented during the trial. Moreover, if they do not develop diabetes before they die from other causes, it will have been prevented for their life. Whether either diet and exercise or the pharmacologic interventions transiently or permanently altered the underlying metabolic physiology responsible for the rise in glucose levels over time is a mechanistic or biologic question. It can be answered in part by short- and long-term follow-up of participants who did not develop diabetes during the trial and who are no longer following a diet and exercise regimen or who are no longer taking the drugs (i.e., in whom the effects of the intervention are being "washed out"). Such a question is being answered for both ramipril and rosiglitazone during a post-trial follow-up of DREAM trial par-

Table 1—*Therapies proven effective in diabetes prevention trials*

Study (reference)	*n*	Population	Age (years)	Duration (years)	Follow up	Intervention (daily dose)	Control subjects (%/year)	Relative risk
Finnish DPS (15)	522	IGT, BMI ≥25 kg/m^2	55	3.2	92	Individual diet/exercise	6	0.42 (0.30–070)
DPP (14)	2,161*	IGT, BMI ≥24 kg/m^2, FPG >5.3 (95)	51	3	93	Individual diet/exercise	10	0.42 (0.34–0.52)
Pan et al. (22)	259*	IGT (randomized groups)	45	6	92	Group diet/ exercise	16	0.62 (0.44–0.86)
Kosaka et al. (23)	458	IGT (men), BMI = 24 kg/m^2	~55	4	92	Individual diet/exercise	2	0.33 (0.10–1.0)†
Indian DPP (24)	269*	IGT	46	2.5	95	Individual diet/exercise	22	0.71 (0.63–0.79)
DPP (14)	2,155*	IGT, BMI >24 kg/m^2, FPG >5.3	51	2.8	93	Metformin (1,700 mg)	10	0.69 (0.57–0.83)
Indian DPP (24)	269*	IGT	46	2.5	95	Metformin (500 mg)	22	0.74 (0.65–0.81)
STOP NIDDM (16)	1,419	IGT, FPG >5.6	54	3.2	96	Acarbose (300 mg)	13	0.75 (0.63–0.90)
XENDOS (18)	3,277	BMI >30 kg/m^2	43	4	43	Orlistat (360 mg)	2	0.63 (0.46–0.86)
DPP (25)	1,067*	IGT, BMI >24 kg/m^2, FPG >5.3	51	0.9	93	Troglitazone (400 mg)	12	0.25 (0.14–0.43)†
TRIPOD (26)	266	Previous GDM	35	2.5	67	Troglitazone (400 mg)	12	0.45 (0.25–0.83)
DREAM (17)	5,269	IGT or IFG	55	3.0	94	Rosiglitazone (8 mg)	9	0.40 (0.35–0.46)

*Number of participants in the indicated comparisons and not the total randomized; †calculated from information in the article. DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; GDM, gestational diabetes mellitus; STOP, Study to Prevent Non-Insulin Dependent Diabetes; TRIPOD, Troglitazone in Prevention of Diabetes; XENDOS, Xenical in the prevention of Diabetes in Obese Subjects.

ticipants who are taking single-blind placebo.

Thus, strong evidence from randomized clinical trials shows that diabetes can be prevented by dietary modification, increased physical activity, and a growing list of drugs. Moreover, it is likely that the list of drugs will continue to grow with time and that their benefits will magnify the benefits of diet and exercise. If this is true, the impact of combination therapy would indeed be impressive. For example, if the effects of rosiglitazone and a diet and exercise program similar to that offered by the Diabetes Prevention Program (both with a hazard ratio of ~0.4) are completely independent, the combination could theoretically yield a hazard ratio as low as 0.16 or a relative risk reduction of 84%. This would reduce the 3-year risk of diabetes from 26 to 4% in an individual similar to a DREAM participant; the addition of metformin would reduce it even further.

These considerations suggest that we are quickly acquiring the tools to mount a comprehensive approach to diabetes prevention, which will include both nonpharmacologic and pharmacologic approaches. Indeed, as learned from other epidemics, even this will be insufficient to stem the diabetes epidemic without broader perspective. The response to the diabetes epidemic needs to include societal changes to urban planning, food, education, and social and public health policies so they more effectively promote metabolically healthy behaviors. Public health initiatives that facilitate self assessment of the risk of diabetes with simple tools (21) and routine glucose testing of high-risk patients by health care providers need to be tested and promoted. For high-risk individuals, healthy lifestyle approaches should be recommended first and as background therapy. After subsequent evaluation of the risks and benefits for a particular individual, the addition of pharmacologic therapy should be considered when nonpharmacologic approaches are insufficient or inappropriate, and both the response to therapy and adverse effects should be monitored and reevaluated periodically. It is only if we use all of the tools at our disposal that we will be able to reverse the growing threat that diabetes poses to both the length and quality of our lives.

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