ABSTRACT

Type 2 diabetes is both a disease of genetics and environment. This article discusses the importance of lifestyle modifications in prevention of diabetes. The potential role of pharmacologic agents in delaying disease progression is also reviewed, with an emphasis on early and aggressive intervention. Drugs currently in investigation are also discussed.


Not all obese patients develop type 2 diabetes mellitus (T2DM). This suggests in addition to obesity, there may also be important genetic factors that modulate glucose transporters and β-cell function that contribute to the ultimate development of T2DM. Undoubtedly, T2DM is a disease of genetics. But more importantly, it is a disease of environment. Historically, certain populations, such as Native Americans, experienced virtually no diabetes 100 years ago. Yet today, diabetes has reached epidemic proportions in this population. Approximately 16.5% of American Indians and Alaska Natives ages 20 years and older who are served by the Indian Health Service have diagnosed diabetes. Due to the cultural environment we live in, T2DM is in the forefront of our nation's health landscape. And it is going to remain there.

PREVENTION

The Nurse’s Health Study definitively established the important role of even modest exercise and dietary control to prevent diabetes. Simply by leading a more controlled lifestyle—limiting food intake, consuming alcohol moderately, exercising regularly, and not smoking—women without diabetes risk factors experienced a 90% lower incidence of diabetes. This study demonstrated that excess body weight was the single most important determinant of T2DM among the 84,941 participants. Remarkably, at baseline the average body mass index of study participants was 34 kg/m², indicating that this group was already at risk for metabolic dysfunction. Yet even with this risk, reasonable lifestyle choices correlated with a major reduction in the incidence of T2DM. In the Diabetes Prevention Program of 3234 patients without diabetes with elevated fasting and post-load plasma glucose concentrations, lifestyle interventions reduced the incidence of T2DM by 58% as compared to a 31% reduction with metformin. The underlying message is that metformin has some effect, but lifestyle intervention is significantly more effective in preventing T2DM.

In the absence of cultural change and behavioral modifications, one way to offset disease progression is through blockage of β-cell decompensation. The UKPDS (UK Prospective Diabetes Study) study demonstrated that in a subset of patients randomized to conventional or diet therapy for 6 years, those on diet therapy experienced a significant decline in β-cell function that was associated with a continual increase in hyperglycemia (Figure 1). The degree of β-cell
function was then extrapolated back in time to illustrate that impaired insulin secretory activity may precede the diagnosis of T2DM for up to 10 years. If we wish to attempt to slow down progression of disease, then delaying the inevitable decline in $\beta$-cell function is a likely starting point. Sulfonylureas and metformin, the traditional agents prescribed for T2DM, were not shown to play a role in preserving $\beta$-cell function.3 Studies of sitagliptin have shown improvement on several measures of $\beta$-cell function, including proinsulin:insulin ratio, HOMA-B (homeostasis model assessment of $\beta$-cell function), and HOMA-IR (homeostasis model assessment of insulin resistance). Studies of alogliptin, however, are less conclusive. The proinsulin:insulin ratio and HOMA-B were unchanged relative to placebo in 2 studies that reported indices of $\beta$-cell function.4,5 However, in a study that evaluated alogliptin 12.5 to 25 mg/day as monotherapy, proinsulin:insulin improved significantly compared to placebo.6

The potential role of pioglitazone in prevention of diabetes was examined in the ACT NOW (Actos Now for Prevention of Diabetes) study for the prevention of diabetes.7 The study enrolled 602 individuals with impaired glucose tolerance and 102 healthy controls. Subjects were randomized to receive pioglitazone or placebo over a 24-month period. Pioglitazone reduced the rate of conversion to T2DM by 81% compared to placebo. Additionally, treated subjects recovered part of their insulin production and experienced improved insulin sensitivity.

The pathophysiology of T2DM and its cardiovascular complications are associated with abnormalities in inflammatory and oxidative signaling. These abnormalities are implicated in the pathogenesis of the insulin resistance associated with not only T2DM but with the progression to T2DM from the dysmetabolic state that precedes clinical T2DM. The effect of the novel anti-inflammatory antioxidant AGI-1067 (succinobucol) on the rate of progression to new-onset T2DM was assessed in a large cardiovascular trial. The ARISE (Aggressive Reduction of Inflammation Stops Events) trial randomized 6144 patients who had an acute coronary syndrome within 1 year to AGI-1067 300 mg/day or placebo on top of standard of care. T2DM was confirmed in 37% of the subjects at baseline. AGI-1067 treatment did not differ from placebo in the primary composite end point of cardiovascular death, cardiac arrest, myocardial infarction, stroke, unstable angina, or coronary revascularization.

Assessment of glycemic control and development of new-onset T2DM were prespecified end points. For patients without diabetes, AGI-1067 was associated with a 63% reduction in the incidence of new-onset T2DM: 82/1950 (4.2%) placebo subjects and 30/1923 (1.6%) AGI-1067 subjects developed new-onset T2DM (hazard ratio = 0.37; 95% confidence interval, 0.32–0.42; $P<.0001$). A post hoc analysis of subjects with impaired fasting plasma glucose (FPG; $>100 \text{mg/dL} \leq 125 \text{mg/dL}$) pooled with subjects having abnormal FPG ($>125 \text{mg/dL}$) but not diagnosed with T2DM at baseline revealed that 63/567 placebo-treated and 27/557 AGI-1067-treated subjects developed new-onset T2DM (hazard ratio = 0.40; 95% confidence interval, 0.26–0.63; $P<.0001$). AGI-1067 reduced glycosylated hemoglobin ($A_1c$) by 0.5% (baseline $A_1c$ 7.2%, $P<.0001$) at 1 year in patients with diabetes with no increases in edema, weight gain, or hypoglycemia. Serious adverse events occurred with similar frequency between groups (31% with AGI-1067 vs 29% with placebo). Although some end points, such as the new-onset diabetes and the composite of cardiovascular death, cardiac arrest, myocardial infarction, and stroke, were in favor of AGI-1067, others such as heart failure and unstable angina showed higher event rates with AGI-1067. This is the first clinical demonstration that an antioxidant/anti-
inflammatory agent can reduce the rate of progression to T2DM, further supporting the important role of oxidative/inflammatory signaling in the pathogenesis of T2DM. Notably, this trial was a cardiovascular trial, which is fitting because the majority of undiagnosed patients seen initially present with cardiovascular symptoms.

TREATING MORE AGGRESSIVELY EARLIER

Clinical inertia in the management of T2DM, despite therapeutic failure, is a well-documented phenomenon. Researchers at the Kaiser Permanente Center for Health Research conducted a prospective, population-based study using retrospective observational data to identify 7208 courses of treatment with nondrug therapy, sulfonylurea monotherapy, metformin monotherapy, and combination oral antihyperglycemic therapy among plan members. This study essentially asked a simple question: When patients reach an A1c of more than 8%, does the provider change therapy? The study found that for patients on diet therapy, nearly 70% had therapy advanced promptly to either metformin or a sulfonylurea. However, once patients were managed with combination therapy, there was a virtual therapeutic standstill. The average patient experienced 5 years of A1c levels of more than 8% before therapy was advanced, and 10 years at more than 7% (Figure 2). Although there is often a need to advance therapy in T2DM, therapeutic considerations surrounding treatment decisions are quite complex. For example, what A1c delta is needed? If the patient has an A1c of 9.5%, acarbose would not be the agent of choice. Will the patient accept the therapy? How complex is the overall medication regimen? Cost is often a serious issue for people. What are the side effects and secondary effects, and can the patient tolerate them? The complexity of the treatment decision explains why clinicians are often reluctant to advance therapy.

NOVEL APPROACHES TO MITIGATING HYPERGLYCEMIA

Many novel medications are in development for treatment of T2DM or have been recently approved. These medications are discussed in the following sections.

DPP-4 INHIBITORS

Four dipeptidyl peptidase-4 (DPP-4) inhibitors are either in development or undergoing US Food and Drug Administration (FDA) review. Sitagliptin is a pyrazine derivative. Saxagliptin is a pyrrolidine-carbonitrile compound, vildagliptin a pyrrolidine-carbonitrile compound, and alogliptin a dioxo-dihydropyrimidine compound. What distinguishes these agents from each other is the degree of affinity for different DPP-4 enzymes that impact a variety of physiologic functions, in addition to glucose metabolism. On average, these agents achieve A1c reductions of approximately 0.7% to 0.8% when compared to placebo, but it is important to recognize that in individuals, reductions may vary considerably from this average. Saxagliptin has passed the FDA cardiovascular safety review and was recently approved for treatment of T2DM and released in both a monotherapy formulation and in combination with metformin. Vildagliptin is already available in Europe in combination with metformin. Some concerns have been expressed that sitagliptin may have unintended effects on the pancreas that could lead to a form of low-grade pancreatitis in some patients and a greater risk of pancreatic cancer in long-term users.

SELECTIVE SODIUM-GLUCOSE TRANSPORTERS

In the kidney, glucose is reabsorbed via active transport in the proximal convoluted tubule. Two sodium-glucose cotransporters are responsible for glucose reabsorption. Sodium-dependent glucose cotransporter (SGLT) 1, which is also found in the gut and

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Figure 2. Clinical Inertia: Failure to Advance Therapy When Required

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Percentage of Subjects Advancing when A1c &gt; 8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>66.6%</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>35.3%</td>
</tr>
<tr>
<td>Metformin</td>
<td>44.6%</td>
</tr>
<tr>
<td>Combination</td>
<td>18.6%</td>
</tr>
</tbody>
</table>

At insulin initiation, the average patient had:
- 5 years with A1c > 8%
- 10 years with A1c > 7%

A1c = glycosylated hemoglobin.
Data from Brown et al.
other tissues, accounts for approximately 10% of reabsorption. SGLT2, expressed only in the proximal tubule, accounts for most glucose reabsorption and is therefore the most promising target for drug development. Inhibition of SGLT2 promotes glucose loss in the urine, while minimizing the gastrointestinal side effects associated with SGLT1 inhibition with nonselective agents. This creates the unique potential to cause negative energy balance with no effect on insulin secretion. Agents in development in this class include dapagliflozin (C-aryl glucoside) and sergliflozin (O-glucoside). Dapagliflozin is very selective for SGLT2, and therefore its action is localized to the kidney. Study results for these agents have not been published.\textsuperscript{11-13}

Liraglutide, a once-daily injectable, is a long-acting form of GLP-1 that triggers insulin release. The FDA has indicated that cardiovascular events in clinical studies of liraglutide were minimal, but raised concerns about a small number of patients who developed thyroid cancer during clinical studies and observations of thyroid tumors in animal studies.\textsuperscript{14}

**Antisense Molecules**

These molecules interact with complementary strands of nucleic acids, modifying expression of genes. Four antisense drugs are in the pipeline to treat T2DM, each of which acts upon targets in the liver, fat tissue, or the kidney through mechanisms designed to improve insulin sensitivity, reduce glucose production, or affect other T2DM metabolic aspects. An agent that targets glutamate transporter 2 is in phase I clinical study.\textsuperscript{15}

**Other Agents**

D-tagatose is a hexose approved by the FDA in 2001. It has been found to reduce postprandial glucose levels, but it is unclear how. One possibility is that the molecule may bind to a receptor in the mouth or gut, potentially changing incretin patterns. Phase III trials are in progress.

Bromocriptine, a dopamine agonist once used to restrain lactation, was approved for treatment of T2DM on May 6, 2009. In animal models of insulin resistance and type 2 diabetes bromocriptine acts centrally to reduce resistance to insulin-mediated suppression of hepatic glucose output and tissue glucose disposal.\textsuperscript{16} Although its exact mechanism of action is unknown, the assumption is that by augmenting central nervous system levels of dopamine, the drug upregulates glucose metabolism. A 24-week placebo-controlled study of bromocriptine as monotherapy for patients with T2DM demonstrated a -0.1 reduction in A1c from baseline and no change in FPG. In separate studies, bromocriptine combined with a sulfonylurea achieved reductions of A1c of -0.1 and -0.4. Nausea was the most frequently reported side effect, occurring in 33% of patients when used as monotherapy.\textsuperscript{17}

**Conclusions**

The more we learn about the underlying pathophysiology of T2DM, the more difficult it is to interpret. Many new agents are in development targeting varied pathways, receptors, and even molecules. Lifestyle modification is central to prevention, although if that fails, there is some evidence to support a preventive role for some treatments. Early and aggressive treatment can help to preserve β-cell function and delay disease progression.

**Discussion**

**Dr Rich:** I am glad that you brought up the issue of costs, because from a managed care perspective cost is a critical issue. It has been said in regard to health-care reform, the issue is not that there is not enough money. The fact is that we do not use the money that we have appropriately. We have to look at the agents and determine what the appropriate therapies are for our patients.

**Dr Elasy:** Another important outcome as we consider cost benefit is the common, untoward events associated with attempting to improve glucose control. Although traditional therapies remain effective, some of the newer agents are better not so much from a glucose-lowering perspective but from a safety perspective. As we think about costs we also need to consider quality. And quality probably has more definitions beyond A1c. It is important to balance the gains in A1c control with a drug’s side-effect profile.

**Dr Rich:** I think we have to treat the individual patients. Do we want to give the 78-year-old frail female a nice inexpensive sulfonylurea and have her become hypoglycemic, fall down, break her hip, and end up in the emergency department? Definitely not.

**Dr Rodgers:** The problem is, of course, that A1c correlates most poorly with the most important outcome in diabetes, which is cardiovascular disease. It works very well for renal and retinal disease, of course, but ACCORD (Action to Control Cardiovascular Risk in Diabetes) and ADVANCE (Action in Diabetes
and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) showed us that lower A1c does not necessarily result in lower cardiovascular disease.14

Finally, The Veterans Affairs Diabetes study reported not only that the effect of better glucose control on cardiovascular complications diminished with duration of the disease, but that the risk of cardiovascular events actually increased in patients with severe hypoglycemic episodes.15 Of course, this continues to be an area of controversy, with some evidence suggesting a relationship such as the recent meta-analysis19 and even older UKPDS data.20

**Dr Alvarez:** Many patients have had multiple myocardial infarctions, and have had coronary artery bypass graft prior to diagnosis. Maybe we have missed the boat on cardiovascular disease in a lot of these patients. Pushing them to tighter glycemic control and causing more hypoglycemia may not be in their best interests. Perhaps setting a target goal of approximately 7% A1c would be good enough for these patients.

**Dr White:** We should not lose sight of the fact, however, that A1c control is very important for preventing microvascular disease and neuropathy in T2DM. Most patients with end-stage renal disease have T2DM. I think we can probably all agree that achieving an A1c of 7% or slightly lower is reasonable in patients with T2DM, even if there is no cardiovascular benefit.

**Dr Kane:** I think we really need to consider the full spectrum of health concerns with the individual patient, and customize therapeutic goals and treatments accordingly.

**REFERENCES**


