

Overcoming Obstacles to Effective Care of Type 2 Diabetes

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Introduction

Type 2 diabetes mellitus (T2DM) afflicts about 24 million people in the United States,¹ and current attempts to combat the disease have been failing. The healthcare system so far has been unable to reverse the diet and lifestyle trends that lead to the increasing prevalence, including the core contributors to diabetes and vascular disease, inadequate exercise, and overeating. Although excellent patient education and a wide variety of treatment options are available, most T2DM patients are not meeting their glycemic goals.²

Powerful environmental factors underlie poor metabolic and vascular health. Vested interests market the fat-, salt-, and sugar-laden American diet to maximize consumption, with the result of obesity. The growth of suburbs and exurbs, dependence on the automobile, and the dominance of electronic over physical pastimes contribute to the decline in exercise for children and adults.

More than in other chronic diseases, the key to preventing progression is early recognition and intervention. Appropriate screening can identify increased risk for T2DM, but too often individuals remain unscreened or results indicating diabetes remain unaddressed. Early intervention on the risk of diabetes can reduce the incidence of overt diabetes.³ Yet the American Diabetes Association (ADA) estimates that nearly one fourth of those with overt diabetes remain undiagnosed and therefore untreated.¹

When T2DM is diagnosed, treatment practices vary. Consensus on the best practices is lacking, because comparative effectiveness data resulting from head-to-head treatment trials does not yet exist. Treating physicians proceed with caution, using minimal initial therapy and slow intensification for the sake of patient safety and prevention of hypoglycemic episodes. Because of the risk of hypoglycemia and other reasons, most patients do not adhere to treatment. Lifestyle habits—poor diet and inactivity—are difficult to change.

Despite the gloomy picture, obstacles in reaching diabetes goals can be addressed and overcome. This article will discuss obstacles in T2DM care from the viewpoints of the patient, the treating healthcare professional, and the third-party payer.

Patient's Perspective on Adherence to Treatment

Adherence rates in T2DM are difficult to establish. The World Health Organization has published US adherence estimates of 52% to 70% for dietary instructions, 26% to 52% for exercise plans, and

Abstract

Type 2 diabetes mellitus affects more than 24 million people in the United States. The healthcare system up to this point has not been able to combat the diet and lifestyle trends that have led to the prevalence of this disease. Even though many excellent options exist for patients with diabetes, most are not meeting their glycemic goals. Despite all of the obstacles, with the proper attention, education, and current practice modifications, optimal patient-centered diabetes care in the United States can become a reality.

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15% to 80% for oral medications.⁴ Despite the wide ranges, adherence is clearly suboptimal.

Lifestyle. Primary care practitioners commonly treat early diabetes with diet and exercise recommendations. From the viewpoint of the patient, these are exceedingly high hurdles. Patients are often defensive about their lifestyles; overweight patients resent the term obesity as pejorative labeling and refuse to surrender lifestyle preferences. When patients receive the initial news that their tests indicate overt diabetes, they may not fully absorb important information from their doctors, in part because they do not want to have this serious disorder. Thus the doctor's explanations may be misunderstood or forgotten. Instructions will require follow-up by a healthcare professional with the presence and support of family or friends for successful adherence. The physician will likely offer access to further education from multimedia sources and appointments with nutritionists, Certified Diabetes Educators, and other professionals. However, many patients will avoid these appointments because of emotional issues resembling the classic Kübler-Ross 5 stages on death and dying (denial, anger, bargaining, depression, and acceptance).⁵ Until patients reach the fifth stage, acceptance (of the T2DM diagnosis and its consequences), they may not be able to actively participate in their disease management. Because of this, the ADA recommends individualized long-term nutritional and psychological counseling for lifestyle change.⁶ From the patient's perspective, the doctor must give that person a reason and individual motivation to attend the counseling. As with other aspects of care, patient costs associated with counseling can be an issue as well; insufficient reimbursement and higher out-of-pocket costs can disincentivize patients from seeking these services. Overall, individualizing each aspect of the treatment process is essential for success.

Pharmacotherapies. Treatment for diabetes may require blood glucose self-monitoring, insulin injections, and/or multiple medications. Glucose monitoring and insulin management are arduous daily requirements that vary in frequency and complexity according to the regimen and are beyond the scope of this article. However, even regimens based primarily on oral agents can present road-

blocks to adherence. Patients commonly require more than 1 agent to make substantial progress against hyperglycemia; the 2 or more antihyperglycemic drugs may have different dosing schedules.⁷ Furthermore, T2DM almost never stands alone. Coexisting obesity, hypertension, metabolic syndrome, cardiovascular disease (CVD), and renal disease are common. Therefore, the daily regimen is likely to include antihypertensives, lipid-lowering agents, and other medications. With so many pills to take—and often no tangible symptoms relieved by them (eg, polyuria or polydipsia)—maintaining motivation and adherence becomes difficult. Some patients have achieved improved adherence and efficacy with antidiabetic drugs that combine 2 agents in a single pill for greater convenience,^{8,9} but high cost can be a factor. Finally, adding to the patient's discomfort and resistance to therapy, some pharmacologic agents are available only as injections or cause weight gain (eg, exenatide, insulins).

The most difficult obstacle to overcome in medication adherence may be adverse events (**Table 1**). After experiencing a hypoglycemic episode of any degree, many patients will discontinue medications and some may not return to the physician. Their fear of future hypoglycemia may outweigh the opportunity to modify treatment, because they understand that all antidiabetic agents act on glyce-mic levels. The risk of hypoglycemia is even greater with more intensive treatments; therefore, often patients refuse intensive therapy.

Cost Considerations. Adverse economic conditions have caused many US residents to lose their jobs and/or health insurance, increasing the difficulty of diabetes management. Others retain health insurance but their employers, equally pressured by the economy, have negotiated less coverage or higher deductibles, copayments, and coinsurance, thus transferring more financial responsibility to members. Without insurance or with very high copayments, many individuals will not visit physicians for diagnosis and treatment. Some opt for alternatives that do not involve seeing a doctor, such as herbal supplements and inexpensive pharmaceuticals purchased in bordering countries. Without US Food and Drug Administration regulation or physician monitoring, these alternative self-treatments can present another obstacle to optimal outcomes.

■ **Table 1.** Common Adverse Effects of Antidiabetic Medications¹⁰⁻¹³

Drug Class and Route of Administration	Primary Adverse Effects
Biguanide (metformin) Oral	Gastrointestinal, lactic acidosis (rare) ¹⁰
Alpha-glucosidase inhibitors (acarbose, miglitol) Oral	Gastrointestinal ¹⁰
Sulfonylureas (glyburide, glimepiride, glipizide) Oral	Hypoglycemia, weight gain ¹⁰
Glinides (non-sulfonylurea secretagogues) (nateglinide, repaglinide) Oral	Hypoglycemia, weight gain ¹⁰
Thiazolidinediones (TZDs) (rosiglitazone, pioglitazone) Oral	Edema, weight gain, anemia, pulmonary edema, bone fractures, congestive heart failure ¹⁰
Dipeptidyl peptidase (DPP)-4 inhibitors (sitagliptin, saxagliptin) Oral	Upper respiratory infection, nasopharyngitis, headache, hypoglycemia (when combined with sulfonylureas) ¹¹
Incretin mimetic (exenatide) Injected	Gastrointestinal, pancreatitis (uncertain relationship), renal dysfunction (rare), hypoglycemia (when combined with sulfonylureas or TZDs) ¹²
Amylin analog (pramlintide) Injected; used with insulin	Hypoglycemia with meal-related insulin, gastrointestinal ¹³

Other patients, who have seen their physician, may be able to afford only 1 of the several prescriptions they were given for their diabetic, cardiovascular, and/or renal conditions. Some will refill only prescriptions for acute, symptomatic illnesses or pay for other expenses rather than buying any medications at all. A few may quit seeing the doctor because of embarrassment about not having refilled their prescriptions. Patients who do fill their prescriptions may hoard pills, taking them only when they have symptoms (eg, frequent urination). Others may not return for routine visits because of the out-of-pocket costs, and thus may receive inadequate follow-up. Ironically, leaving their diabetes untreated enables disease progression, resulting in diabetic complications, hospitalizations, and cardiovascular events, all of which incur the highest of diabetes-related costs.

Provider's Perspective

A 2006 study of patients being treated for diabetes by primary care clinicians found that only 40% were achieving target glycosylated hemoglobin (A1C) levels of less than 7%; additionally research from the National Health and Nutrition Examination Survey has reported that more than half (52%) of treated diabetics are not reaching glycemic goals.^{2,14}

Patients who present for other reasons are routinely screened for diabetes via fasting plasma glucose measurement. However, T2DM is still underdiagnosed because individuals will not present for screening. Persons at high risk (eg, obese and sedentary) usually know they are at risk. They dislike the concept of getting a diagnosis for diabetes and do not want to learn that they have it. They may see a physician only when symptoms begin to interfere with their lives (eg, frequent urination). By then T2DM may have been progressing for years. In the United Kingdom Prospective Diabetes Study, patients had lost 50% of pancreatic beta-cell function by diagnosis.^{7,15} Many patients already have macrovascular complications at diagnosis,¹⁶ and a small percentage even have early retinopathy,¹⁷ which are situations that compound the difficulty of initial management. At a minimum, providers should educate all newly diagnosed patients about their diabetes or risk of diabetes, discuss lifestyle factors, offer nutritional education, and schedule a follow-up appointment to ensure that possible disease progression is not overlooked. Physicians should personalize treatment regimens and inform patients that all aspects are tailored to their individual needs. However, almost all problems of cooperation and adherence derive from lifestyle issues and emotional resistance.

■ **Table 2. Actions of Antidiabetic Agents**^{7,10-13,26-28}

Drug Class	Action
Biguanide	Decrease glucose production in liver, increase glucose uptake by skeletal muscle ^{10,26}
Alpha-glucosidase inhibitors	Delay glucose absorption by inhibiting enzymatic carbohydrate breakdown ^{10,27,28}
Sulfonylureas	Stimulate insulin secretion by pancreatic beta cells ^{10,25}
Glinides	Stimulate insulin secretion by pancreatic beta cells ^{10,25}
Thiazolidinediones	Increase insulin sensitivity, may reduce hepatic glucose production ^{10,26}
Dipeptidyl peptidase (DPP)-4 inhibitors	Slow DPP-4–induced inactivation of incretin hormones, thereby increasing glucose-dependent insulin release and decreasing circulatory glucagon levels, slow gastric emptying, promote satiety for weight loss ^{7,11}
Incretin mimetic	Stimulate glucose-dependent insulin secretion, decrease hepatic glucose output, slow gastric emptying, promote satiety for weight loss ^{7,12}
Amylin analog	Slow gastric emptying, prevent postprandial rise in glucagon, promote satiety for weight loss ^{7,13}

Successful Approaches to Initial and Ongoing Treatment. According to the ADA, medical treatment of diabetes without patient training in self-management, delivered by an interdisciplinary team, is inadequate.¹⁸ Team treatment is widespread but logistically challenging. Schedules and responsibilities may be difficult to coordinate and comprehensive patient education is complex. Ongoing professional follow-up and family support are required for effective, patient-centered treatment. In one study, automated biweekly telephone calls and self-care training reduced the proportion of patients with poor adherence by 21%.¹⁹

Adverse effects are a major obstacle. Providers should remember that tolerance varies among individuals and ethnic groups. For many patients, hypoglycemia is the worst adverse effect and the greatest cause of nonadherence. Studies have demonstrated patient safety and improved efficacy with early treatment intensification and combination therapies including newer drugs.^{8,9,20-25} However, their use by physicians has been limited by reasonable caution and patient concerns about hypoglycemic and weight gain potential. Regardless of the medications prescribed, providers must remind patients to contact them in case of adverse effects and reassure them that many treatment alternatives are available to minimize these effects.

For other chronic diseases (eg, hypertension, CVD) there has been movement to more aggressive, earlier treatment. Blood pressure and lipid levels outside the normal range are routinely treated to reduce risk factors earlier in the atherosclerotic process, thus delaying or preventing cardiovascular and cerebrovascular events. First-line treatment for hypertension may include several medications (angiotensin-converting enzyme inhibitors, beta-blockers, and others). Dyslipidemia is commonly treated with statins before cardiovascular events occur. As physicians treat early vascular risk factors aggressively, they can treat early diabetes to lower overall risk. All risk factors should be considered and monitored; for example, patients with diabetes should have routine screening for microalbuminuria indicating early renal dysfunction.

Pharmacotherapy Choices. Several drug classes are available for diabetes treatment. Regimens commonly include more than 1 agent, partly because different classes affect different aspects of glycemic-related pathophysiology (Table 2).

Guidelines and Optimal Treatment. The ADA has set glycemic goals for diabetes treatment of A1C less than 7%, fasting plasma glucose 70 to 130 mg/dL, and postprandial glucose of less than 180 mg/dL.^{29,30}

A treatment algorithm in the 2007 ADA Standards of Medical Care recommended metformin as the first-line agent for all cases in which lifestyle changes are insufficient.³¹ Of other antihyperglycemic agents, only sulfonylureas and thiazolidinediones (TZDs) (“glitazone”) are included.³¹ Not mentioned are alpha-glucosidase inhibitors, glinides, dipeptidyl peptidase (DPP)-4 inhibitors, incretin mimetics, or amylin analogs. Updated standards and algorithms published in 2008 and 2009 have added antihyperglycemic pharmaceutical recommendations including use of metformin at diagnosis (along with lifestyle modifications), glucagon-like peptide-1 agonists (exenatide) for use in “step two,” and advising greater caution in TZD use.^{29,30,32,33} In addition to the use of oral agents, the 2007 ADA guidelines specifically recommend early initiation of injected insulin: “Although 3 oral agents can be used, initiation and intensification of insulin therapy is preferred...”³¹

Conversely, guidelines of the American Association of Clinical Endocrinologists (AACE) set lower glycemic goals and embrace a wider variety of agents as first-line treatment.⁷ AACE recommends adding a third medication if targets are not met.⁷ Insulin initiation is recommended for A1C levels of 6.5% to 7.5% only *after maximum combination therapy*.⁷

Endocrinologists encounter the most severe and complex diabetes cases and typically have a different perspective from primary care physicians, who constitute the front line of T2DM care. The American Academy of Family Physicians (AAFP) has not officially endorsed other organizations’ guidelines.³⁴ Inconsistencies between the ADA and AACE guidelines and a lack of specific treatment guidelines from the AAFP suggest the potential for a treatment practice gap between primary care and specialists.³⁴

The lack of consensus on best practices was reflected in a recent commentary in the *New England Journal of Medicine*, which stated, “The care of patients with diabetes whose glycated hemoglobin remains above target levels, despite dual oral hypoglycemic therapy, remains controversial.”³⁵ Readers were polled regarding a case vignette of a patient who had not achieved glycemic targets with metformin and glipizide.³⁵ Whereas most North American diabetologist respondents preferred add-

ing exenatide, most other North American physicians preferred advancing to bedtime neutral protamine Hagedorn insulin.³⁵ Without expert consensus, physicians, especially “front-line” primary care physicians, may hesitate to try newer treatments.

Intensive diabetes management, defined as treatment with the goal of euglycemia or near-normal glycemia,⁶ has been shown to reduce hospitalizations and delay or minimize microvascular and macrovascular complications.^{6,36-40} Intensive management has delayed the progression of retinal, renal, and neurologic complications and lowered macrovascular risk factors including plasminogen activator inhibitor-1 levels, platelet aggregation, and small dense low-density lipoprotein particles.⁶ However, the risks of hypoglycemia remain a concern, and intensive regimens should not be tried in all patients who are not attaining their goals. Physicians should become familiar with the many therapeutic options and their effects to individualize and optimize treatment. Ideally, research will someday identify the subpopulations that would benefit most from employing multiple mechanisms of action.

Additive therapy of more than one agent offers the ability to attack different aspects of T2DM pathophysiology through complementary mechanisms of action. For example, prescribing both a sulfonylurea and metformin increases insulin release, decreases hepatic glucose production, and increases muscular glucose uptake (Table 2). Combining a DPP-4 inhibitor with metformin increases insulin release from pancreatic beta cells, reduces hepatic glucose production, delays intestinal glucose absorption, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.²⁵ As a result of the complementary actions, combination regimens can provide greater improvements in several outcomes measures when compared with monotherapy.^{8,9,21-25}

A more important advantage of combination therapy is the ability to increase efficacy without increasing a single drug’s dosage to the point of adverse effects. For example, the use of TZDs plus lower-dose metformin has been associated with fewer gastrointestinal adverse effects than monotherapy with maximal-dose metformin.^{8,21} The same approach is applied in the treatment of dyslipidemia and hypertension, with the result that T2DM

patients may have many pills to take each day. To address this problem, fixed-dose combinations of 2 antihyperglycemic agents (also seen in other therapeutic areas such as hypertension and dyslipidemia) have been developed, and some studies have shown better adherence with this type of single-pill medication than with 2 separate pills.^{41,42} However, the studies were not long term enough to predict adherence over years of chronic diabetes.

Payer's Perspective

The estimated \$190-billion annual healthcare expenditure of patients with T2DM covers all medical costs including both conservative treatment and aggressive treatment with "a large share of the spending on complications and a smaller share of the remainder."⁴³ Poorly controlled diabetes contributes to the cost of hospitalizations, wounds and amputations, and emergency department visits, and greatly increases the risk of cardiovascular and cerebrovascular events. Treatments that optimize glycemic control and reduce complications decrease costs significantly.¹⁸ Because combination therapies provide better glucose control than monotherapies,^{8,9,21-25} effective treatment will ordinarily include at least 2 antidiabetic agents and maybe more. Other prescriptions will likely be necessary for control of dyslipidemia and hypertension. Health organizations encourage early diabetes treatment to prevent progression to the more impairing, more expensive stages, but obstacles persist among patients, providers, and employers.

As a result of the economic recession, more employers are mandating higher copayments and coinsurance or limiting benefits to catastrophic coverage only. More members, also affected by the recession, are limiting or discontinuing their prescription drugs. Employer-mandated cost-sharing strategies can lead to lower rates of drug treatment, poorer adherence, and more frequent therapy discontinuation.⁴⁴ For example, patients prescribed combination therapy may fill only the least expensive prescription(s), thereby receiving treatment that does not fulfill the treatment plan designed by their provider.

In a 2007 analysis of 132 studies that examined associations between prescription cost-saving measures and outcomes, while pharmacy spending for diabetes decreased with higher cost sharing,

hospitalizations and emergency department visits increased.⁴⁴ In another study, a large US company that shifted all diabetes drugs and devices from tier 2-3 to tier 1 achieved greater adherence, decreased total pharmacy costs, and decreased rise in overall healthcare costs for plan participants with diabetes.⁴⁵ Net per-participant costs increased slower than national industry benchmarks (annual costs \$4000 vs \$6500).⁴⁵

With rapid change in medical advances for diabetes, prescription policies might delay introduction of new drugs to formularies. Payers commonly withhold recommendation of newly approved drugs for a year to ensure safety. From the viewpoint of the payer, prescription policies are necessarily based on placebo-controlled studies, which offer incomplete data on comparative effectiveness of the many available drugs. An evidence base of head-to-head comparison studies is urgently needed to formulate the best policies and encourage the most effective treatments.

However, changes in policies can do only so much to improve patient care, increase attainment of glycemic goals, and control the costs of diabetes. Persistent nonadherence remains a huge problem. Studies of diabetic patients with CVD or CVD risk factors have found associations between poor medication adherence and higher mortality.^{29,46} Compared with highly adherent diabetes patients, those with low adherence had higher 1-year risk of hospitalization (30% vs 13%, $P < .05$) and higher total annual healthcare costs (\$16,498 vs \$8886, $P < .05$).^{19,47}

Continued poor diet and lack of exercise are the biggest roadblocks to cost control in diabetes. If diet and exercise recommendations were followed, the need for prescriptions might decline and medication adherence issues might recede in importance. Managed care organizations are in a unique position to help providers educate their patients. Member-targeted education tailored according to cultural competency and medical literacy can successfully inform patients about diabetes and risks for diabetes, promote healthy lifestyles, and encourage adherence. Disease management programs offer varied and valuable assistance, but finding ways to make voluntary participation attractive remains a challenge.

Employers can help combat diabetes and CVD by making changes in the workplace that encourage

healthier lifestyles. Onsite fitness centers or nearby health club memberships, walking tracks or paths, elimination of junk-food vending machines, and educational programs to raise awareness can all benefit employee health while offering the potential to reduce absenteeism and lower healthcare costs.

Conclusion

Diabetes is an individual and national problem that is worsening despite current efforts to contain it. Obstacles including lifestyle habits, lack of comparative effectiveness data, poor adherence, and economic pressures contribute to increased incidence of T2DM and nonattainment of treatment goals for patients afflicted with it. However, with proper attention, education, and well-considered modification of current practices, obstacles to optimal patient-centered diabetes care in the United States can be overcome.

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