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Diabetes clinical decision-making in patients at risk: Taking patient complexity into account

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The sheer numbers of patients with type 2 diabetes, a chronic illness with multifactorial pathophysiology, common comorbidities, exacerbated by an obesity epidemic and a lack of specialists to care for them may seem daunting. However, new treatment options and treatment guidelines that take a more comprehensive and holistic approach to patient care are creating new opportunities to improve glycemic control. Today's approach to the patient with type 2 diabetes is a balancing act between appropriate glucose lowering while avoiding hypoglycemia. Fortunately, the development, introduction, and integration of incretin-based therapies (GLP-1 receptor agonists and DPP-4 inhibitors) into combination treatment strategies have reduced the risks of hypoglycemia and weight gain of more traditional treatment approaches. This review article explores these topics for the osteopathic family physician.

Introduction

Currently one in ten adults in the United States (U.S.) have diabetes. If current trends continue, as many as one in three U.S. adults could have diabetes by 2050 (Fig. 1)[1,2] The increase in diabetes prevalence has been concomitant with an increase in obesity prevalence.[3,4] Despite the known benefits of weight loss on blood glucose levels, many individuals with type 2 diabetes (T2DM) continue to be overweight or obese. These worsening trends in obesity and T2DM raise a serious conundrum, namely, how to control blood glucose, blood pressure, and lipids, when many antidiabetic agents cause weight gain and thereby exacerbate other cardiovascular (CV) risk factors associated with T2DM. Obesity is a major risk factor for the development of diabetes and predisposes individuals to hypertension and dyslipidemia. Together, these pathologies increase the risk for cardiovascular disease (CVD), the major cause of morbidity and mortality in T2DM.

The Diabetes and Obesity Epidemic

While T2DM affects almost 10% of the U.S. population, it disproportionally affects minorities (Fig. 2).[1] and older Americans, both in terms of prevalence, complications, and outcomes.[1] African Americans bear the brunt of diabetes, with almost three-fourths of this adult population affected, while two in three Hispanic American adults may have diabetes.[1] Subtle distinctions can also be made within ethnic groups. For example, within the Hispanic American population, rates of diabetes are greatest in Mexican Americans and Puerto Rican Americans, and lower in Cuban Americans and those from South America.[1] Another group in which diabetes is increasingly being identified is the Asian population, especially among Southeastern Asians, who have higher rates of diabetes than waist circumference or obesity alone would predict (Fig. 3).[5]

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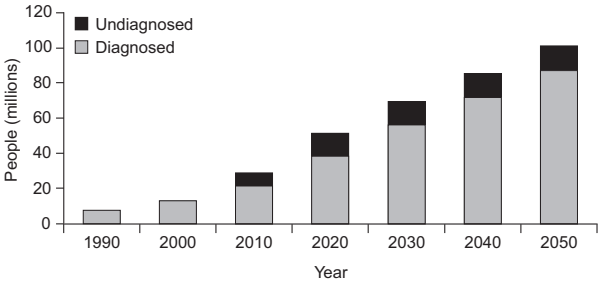


JP Boyle, et al. Popul Health Metr. 8 (2010) 29.

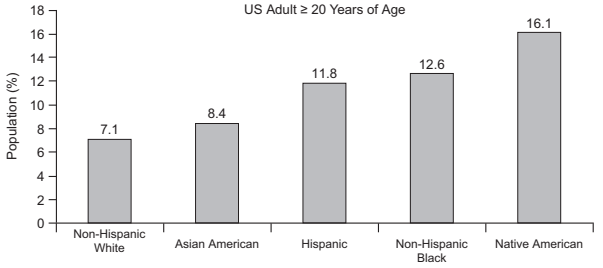
CDC, National diabetes fact sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. National Diabetes Surveillance System. http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm

Figure 1 Trends in the Number of Americans With Diabetes.

Data from the Healthy People 2010 database (Fig. 4)[6] show that diabetes-related death rates in the U.S. also disproportionally affect many minority groups.[6] Some of these differences relate to educational and income levels (and access to medical care) and some to genetic predisposition.[6] These data suggest that more educated patients suffer less from diabetes complications and consequences, and point to an opportunity for osteopathic physicians to address educational needs of their patients, at least as it relates to their patients' understanding of diabetes care. Specific regions of the United States are also disproportionally affected, giving rise to a recent appellation, the "Diabetes Belt," which consists primarily of the southern states as well as areas of Appalachia.[7] These areas are, not coincidently, also areas with higher than average rates of obesity[8] (Fig. 5).[7,8]

Identifying Patients at Risk

Diabetes risk screening is important for all clinicians to consider within their patient populations for several reasons. The onset of T2DM is estimated to occur several years before the clinical diagnosis is usually made and epidemiologic evidence suggests that complications may occur several years before diagnosis.[9] Furthermore, at least one-third of patients with diabetes are not aware of their condition.[10] Another 54 million patients have pre-diabetes,[1] or to use the American Diabetes Association's (ADA) terminology, are "at-risk" patients.[10] Patients who should be considered for diabetes risk screening are identified in Table 1.[9] The ADA has recently made available a patient screening



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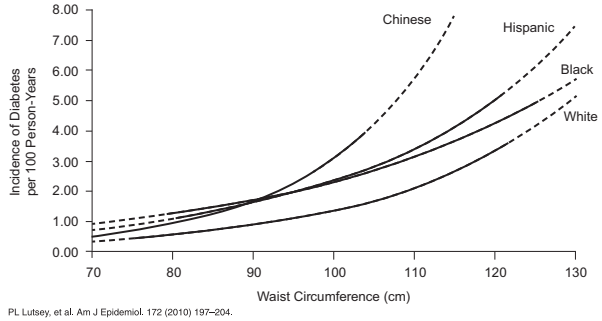
Note: Data for Native Americans from 2009 only.
CDC. National diabetes fact sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed January 28, 2011.

Figure 2 Percent of Adults With Diabetes, by Ethnicity.



PL Lutsey, et al. Am J Epidemiol. 172 (2010) 197–204.

Solid lines pertain to values between the race-specific 5th and 95th percentiles of waist circumference. Dotted lines are extrapolated values outside the aforementioned race-specific ranges. Lines are curved because Poisson regression calculates incidence on the log scale. Adjusted for age, sex, education, and income.

Figure 3 Absolute Incidence Rates of Diabetes by Waist Circumference, Stratified by Race/Ethnicity. The Multi-Ethnic Study of Atherosclerosis, United States, 2000–2007.

tool, which is available both in English and in Spanish (http://www.diabetes.org/diabetes-basics/prevention/diabetes-risk-test/) (Fig. 6). Criteria for the diagnosis of diabetes by various methods are summarized in Table 2.[10] Fortunately, the use of laboratory evaluation of hemoglobin (Hb) A1C (though not point-of-care HbA1C testing) can now be used to identify patients who should be further evaluated.[11] A1C levels $\geq$ 6.5% are associated with an increased risk of blood vessel damage (detected in the eye as retinopathy) and patients with A1C levels confirmed with repeat testing are considered to have diabetes.[12] A1C levels $<$ 5.7% are considered normal (ie, no diabetes) while patients with A1C results between 5.7% and 6.4% should be considered "at risk" and counseled on nutrition and physical activity, and should be followed more closely over the years.[9] Patients with uncontrolled T2DM (A1C levels persistently above 7%) are at risk for serious diabetes-related complications which include both macrovascular disease (CVD being the primary cause of death for patients with T2DM) and severe, and life-altering microvascular complications including diabetic retinopathy (which can result in blindness), painful diabetic neuropathy (which may culminate in the need for amputation of an extremity) and diabetic nephropathy (which may ultimately lead to end-stage renal disease and a need for dialysis).[1] Good glycemic control (to A1C levels $<$ 7%) has been shown to substantially reduce microvascular complications,[13,14] and good long-term glycemic control can reduce macrovascular complications.[15] Along with good glycemic control, which often requires the use of multiple therapeutic agents, the control of CV risk factors such as hypertension and dyslipidemia are essential components of a comprehensive care approach for patients with T2DM.[16,17] Table 3[10,16] summarizes the A, B, C's of diabetes care – attention to **A**1C, **B**lood pressure, and **C**holesterol. Thus, polypharmacy is a de-facto reality for the majority of patients with T2DM.

Type 2 Diabetes: Complex Pathophysiology Creates Treatment Challenges

T2DM is a disease with a multifactorial pathophysiology, which also drives the need for combination therapy strategies,

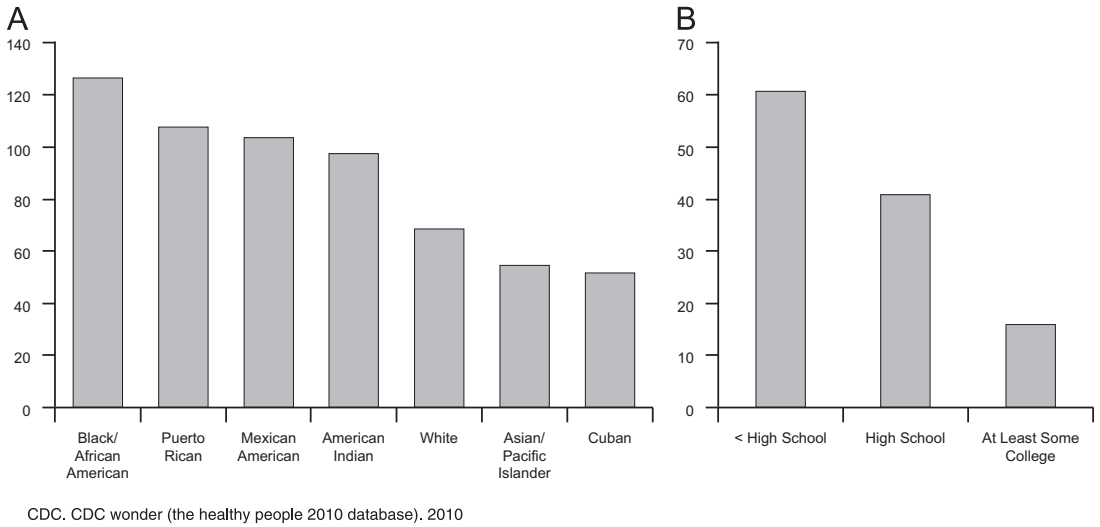


Figure 4 Diabetes-related Death Rates in the US; Deaths per 100,000. Panel A by Racial/Ethnic Group; Panel B by Education Level.

as no single agent addresses each of the core defects of T2DM. Until recently, and in large part as a result of a limited number of mechanisms of action (MOAs) with which to address hyperglycemia, the primary defects of T2DM were considered to be only insulin resistance and insulin deficiency. Now as a result of a better understanding of the complex pathophysiology and the availability of new drugs with additional MOAs, the concept of numerous pathophysiologic defects have been identified[18], the main ones being summarized in Fig. 7.

Therapeutic options have increased dramatically from insulin in the 1920's, sulfonylureas in the 1950's, metformin in the 1980's, thiazolidinediones (TZDs) in the late 1990's, to today's options of agents from at least 11 different drug classes.

Goal Setting for Patients With Type 2 Diabetes: Balancing Glucose Lowering While Avoiding Hypoglycemia

Before delving into a discussion of treatment options and treatment strategies, it is important to be aware that a first step is the appropriate and individualized setting of treatment goals. Both the ADA[19] and the American Association of Clinical Endocrinologists (AACE)[20] suggest that A1C goals be as close to normal as can safely be achieved in a given individual, although they vary slightly in their cut-points. However, both groups strongly support that treatment goals be individualized, with tighter goals advocated for patients with shorter duration of diabetes and less evidence of

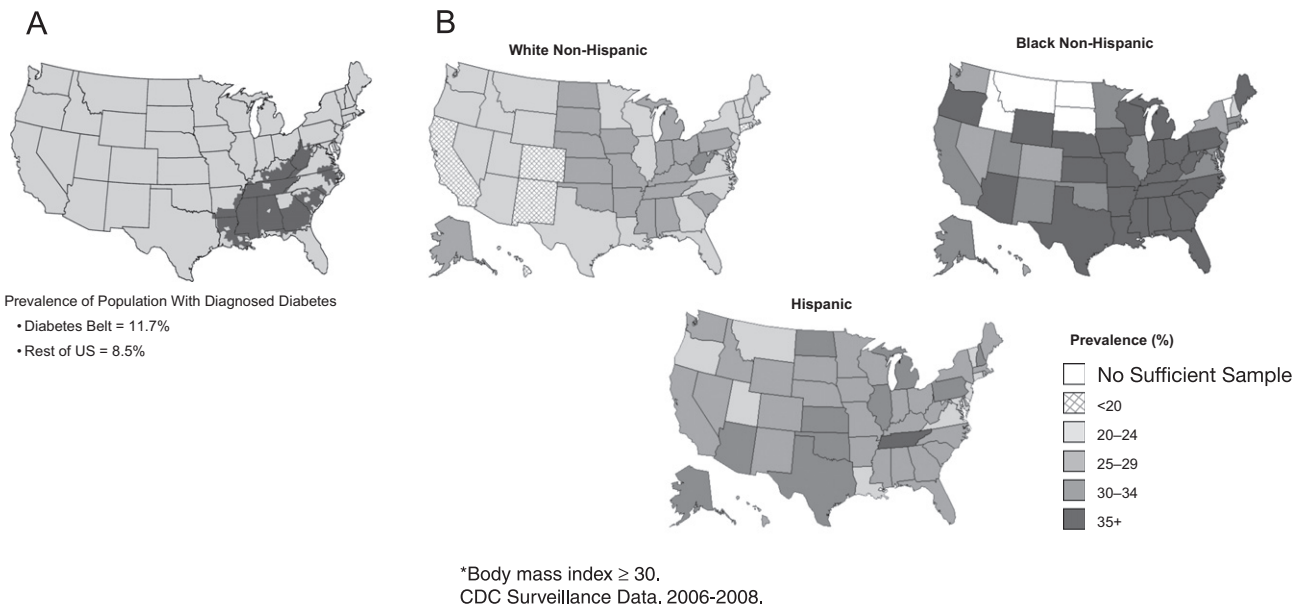


Figure 5 The Diabetes Belt Correlates With Regions of Greater Obesity Prevalence.

Table 1 Characteristics of populations at high risk for the development of diabetes who should be considered for targeted screening for diabetes

- Family history of diabetes
- Non-white ancestry
- Previously identified IGT, IFG, and/or metabolic syndrome
- Cardiovascular disease
- Hypertension
- Increased levels of triglycerides, low concentrations of high-density lipoprotein cholesterol, or both
- Being overweight or obese
- Sedentary lifestyle
- History of gestational diabetes
- Delivery of a baby weighing more than 9 lb (4 kg)
- Polycystic ovary syndrome
- Receiving antipsychotic therapy for schizophrenia and severe bipolar disease

IFG, impaired fasting glucose; IGT, impaired glucose tolerance
Prediabetes Consensus Statement, Endocr Pract. 14 (2008) 937.

Table 2 Criteria for diagnosis of diabetes

A1C $\geq$ 6.5%
OR
Fasting plasma glucose (FPG) $\geq$ 126 mg/dL (7.0 mmol/L)
OR
Two-hour plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L) during an OGTT
OR
A random plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L)

OGTT, oral glucose tolerance test.
ADA. Standards of Medical Care in Diabetes–2012. Diabetes Care. 35 (2012) S11–S63.

complications (in whom good glycemic control can prevent complications) vs more liberal goals in those with longer duration diabetes, shorter life expectancies, or evidence of more advanced complications, in whom the risks of hypoglycemia may be more serious. An algorithm for individualizing treatment targets is shown in Fig. 8.[21]

Treatment of Type 2 Diabetes and the Use of Combination Therapy

A clear need exists for family physicians to be at the forefront of data about the benefits and limitations of different

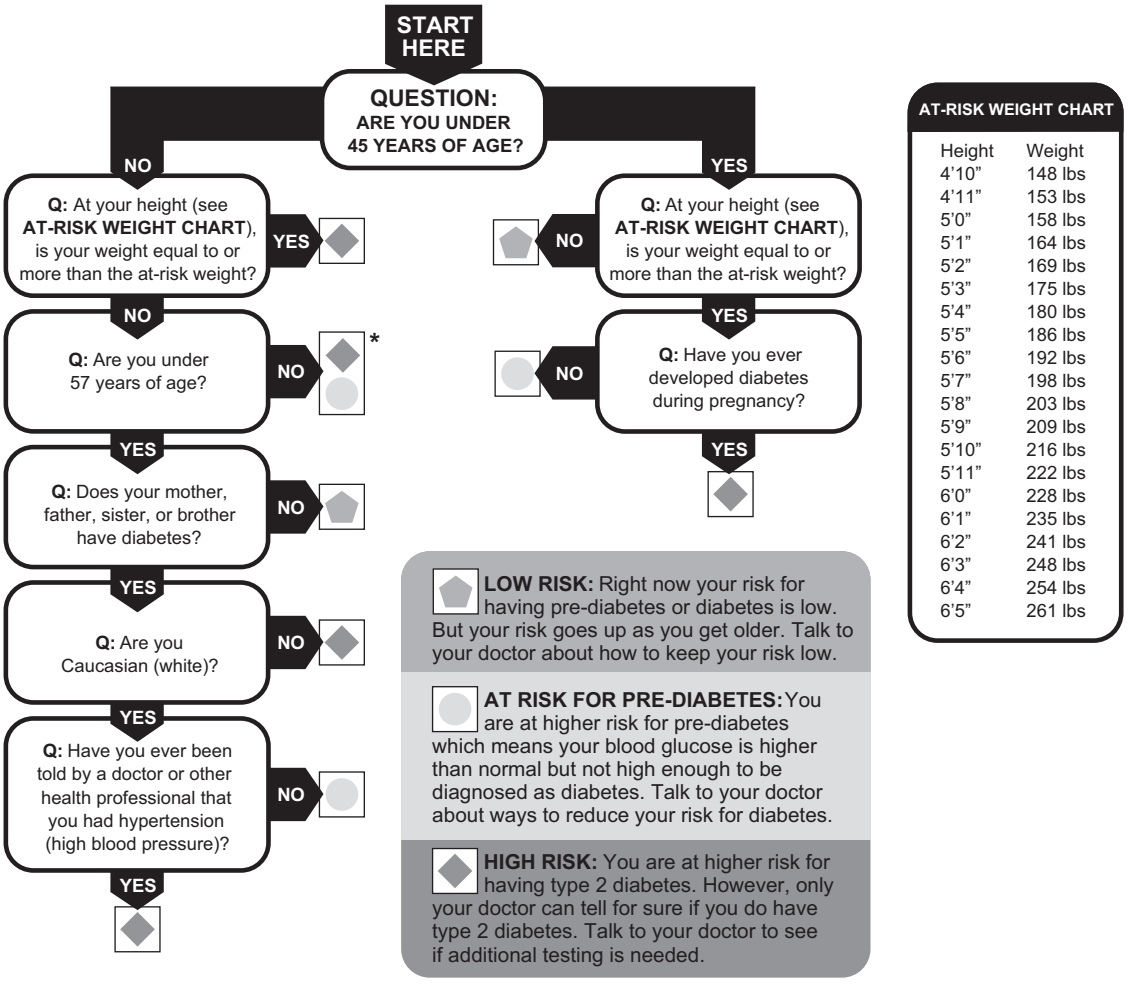


Figure 6 Diabetes Risk Test.

Table 3 The ABCs of diabetes care: Attention to more than glucose

Target Treatment Goals	AACE/ACE 2011	ADA 2012
A1C (Glucose)	A1C $\leq$ 6.5% (FPG $<$ 110 mg/dL; PPG $<$ 140 mg/dL)	A1C $<$ 7.0% (FPG $<$ 70-130; PPG $<$ 180)
Blood pressure	$<$ 130/80 mmHg	$<$ 130/80 mmHg
Cholesterol (lipids)		LDL-C $<$ 100 mg/dL ($<$ 70 mg/dL for patients with diabetes and coronary artery disease) HDL-C $>$ 40 mg/dL in men, $>$ 50 mg/dL in women Triglycerides $<$ 150 mg/dL

Y Handelsman, et al. Endocr Pract. 17 (2011) 1–53.
ADA. Standards of Medical Care in Diabetes–2012. Diabetes Care. 35 (2012) S11–S63.

pharmacologic options so as to maximize patient adherence and treatment outcomes. Current treatment algorithms recommend consistent application of lifestyle modification (appropriate nutrition and physical activity) and early use of pharmacotherapy as well as recommending the use of combination therapy strategies if treatment goals are not achieved or are not maintained. Generally, advancement of therapy is indicated if patients are not at goal for two to three months;[16,19,22] patients should not be allowed to languish at unacceptable levels of hyperglycemia for prolonged periods. This is an area of opportunity to improve healthcare performance gaps as recent data show that patients may in fact have persistently elevated glucose levels and yet no changes in their therapeutic regimen have been made.[23,24]

This brings us to a discussion of treatment combinations that take into account not only complex pathophysiology, but the needs of the patient (both from a patient co-morbidity perspective, as well as a tolerability profile appropriate for the individual). The presence and/or severity of diabetes-related complications also alter the risk:benefit consideration for the choice of agents used for glycemic control. Metformin is considered the cornerstone of pharmacotherapy for patients with T2DM.[16,19,22] This is for many reasons including its efficacy, durability, low risk of hypoglycemia, generic availability, long-term outcome data, availability of long-term safety data, and its weight-neutral profile or in some cases, associated effect of weight loss when used to treat diabetes. In some patients, gastrointestinal tolerability limits the utility of metformin; in others, severe renal impairment may contraindicate its use. Metformin works as an insulin sensitizer and thus, over the long-term, as insulin deficiency due to progressive beta cell failure becomes more evident, it may not be adequate alone to maintain glucose control. Clinical trial data suggest that 75% of patients are no longer maintained at glycemic goals at nine years (and only 50% are at goal at three years) of metformin monotherapy.[25] Data from A Diabetes Outcome Progression Trial (ADOPT) trial suggest that the durability of glucose control is even less with sulfonylureas;[26,27] sulfonylureas are also associated with hypoglycemia and weight gain.[16] While the TZDs appear to have a more durable glucose lowering effect than either metformin or the sulfonylureas, recent safety concerns such as the risk for osteoporosis[28] and the possibility of an increased risk of bladder cancer,[29] may not make them ideal choices for long-term therapy. As most physicians are aware, TZDs should be prescribed with both caution and warnings to the patient about the potential for water retention/weight gain, especially in patients with decreased ventricular function (New York Heart Association [NYHA] grade III or IV heart failure). To maintain glycemic control, many patients will ultimately need insulin monotherapy or in combination with other medications. Insulin remains our most potent agent with which to reduce hyperglycemia, with hypoglycemia being the dose-limiting side effect to

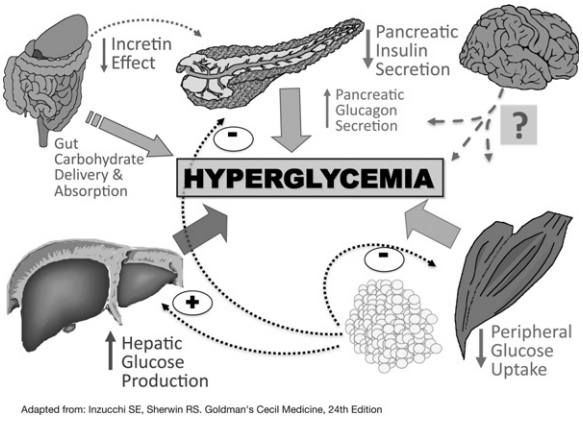
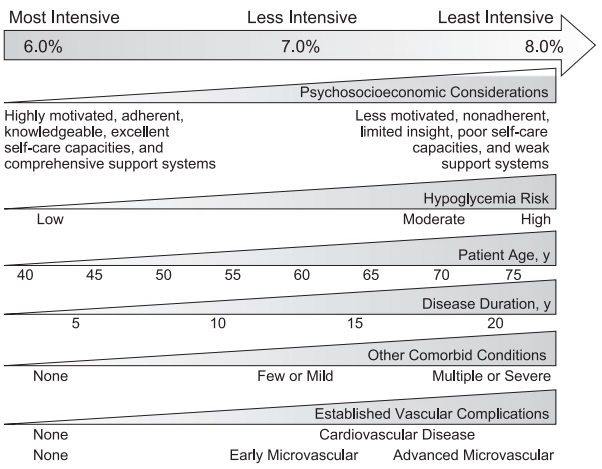


Figure 7 Main Pathophysiological Defects in T2DM.



F Ismail-Beigi, et al. Ann Intern Med. 154 (2011) 554-559.

Figure 8 Algorithm for Individualizing Glycemic Targets.

Table 4 Properties of currently available glucose-lowering agents that may guide treatment choice in individual patients with type 2 diabetes

Class	Compound(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost
Alpha glucosidase inhibitors	Acarbose Miglitol	Slows intestinal carbohydrate digestion/absorption	No hypoglycemia Reduces postprandial hyperglycemia May decrease CVD (STOP-NIDDM) Non systemic	Modest A1C reductions Gastrointestinal side effects (flatulence, diarrhea) Frequent dosing schedule	Moderate
Amylin mimetics	Pramlintide	Decreases glucagon secretion Slows gastric emptying Increases satiety	Reduces postprandial hyperglycemia Weight reduction	Modest A1C reductions Gastrointestinal side effects (nausea/vomiting) Hypoglycemia unless insulin dose is simultaneously reduced Frequent dosing schedule Injectable	High
Biguanides	Metformin	Decreases hepatic glucose production	No hypoglycemia No weight gain Likely decrease in CVD events (UKPDS) Extensive experience	Gastrointestinal side effects (diarrhea, abdominal cramping) lactic acidosis risk (rare) Vitamin B12 deficiency Multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc	Low
Bile acid sequestrants	Colesevelam	Unknown; possibly decreases hepatic glucose production, increases incretin levels	No hypoglycemia Lowers LDL-C No weight gain	Modest A1C reductions Constipation Increases triglycerides May decrease absorption of other drugs	High
Dopamine-2 agonists	Bromocriptine quick-release	Modulates hypothalamic regulation of metabolism Increases insulin sensitivity	No hypoglycemia Decreases CVD events (Cycloset safety trial)	Modest A1C reductions Dizziness/syncope Nausea Fatigue Rhinitis	High
DPP-4 inhibitors	Linagliptin Saxagliptiin Sitagliptin	Glucose dependent increases in insulin secretion, glucose dependent decreases in glucagon secretion	No hypoglycemia Weight neutral Well tolerated	Modest A1C reductions	High
Glinides	Nateglinide Repaglinide	Increases insulin secretion	Decreases postprandial hyperglycemia Dosing flexibility	Hypoglycemia Weight gain Frequent dosing Blunts myocardial ischemic preconditioning	High

Continued on page 43

Table 4 Continued from page 42

Class	Compound(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost
GLP-1 receptor agonists	Exenatide Exenatide extended release Liraglutide	Glucose dependent increases in insulin secretion, glucose dependent decreases in glucagon secretion, slows gastric emptying, increases satiety	No hypoglycemia Weight reduction Potential for improved beta cell function Potential for CV protective actions	Gastrointestinal side effects (nausea/vomiting) Injectable C-hyperplasia/medullary thyroid tumors in animals	High
Insulins	Human: NPH, Regular, Premixed rapid acting analogs: aspart, glulisine, lispro Long-acting analogs: detemir, glargine Premixed analogs: several	Increases glucose disposal Decreases hepatic glucose production	Corrects a primary defect of diabetes Universally effective Efficacy limited only by hypoglycemia Decreased microvascular risk (UKPDS)	Hypoglycemia Weight gain Injectable Education requirements Mitogenic effects	Variable
Sulfonylureas	Glyburide Glipizide Glimepiride	Increases insulin secretion	Extensive experience Decreased microvascular risk (UKPDS)	Hypoglycemia Weight gain Lack of durable effects Blunts myocardial ischemic preconditioning	Low
Thiazolidinediones	Pioglitazone Rosiglitazone (prescribing highly limited in US)	Increases insulin sensitivity	No hypoglycemia Durable glucose-lowering effects Experience in patients with renal impairment Increases in HDL Decreases in triglycerides (pioglitazone) Decreases in CVD events (pioglitazone: ProACTIVE)	Weight gain Edema/heart failure Bone fractures Risk of bladder cancer (pioglitazone) Increases in MI (rosiglitazone) Increases in LDL-C (rosiglitazone)	High

DPP-4=dipeptidyl teptidase-4; GLP-1=glucagon-like pertide1; NPH=neutral protamine Hagedorn.
Adapted from SE Inzucchi, et al. Diabetes Care. (2012) 1-16.

Table 5 Cardiovascular Treatment Goals/Recommndations for Patients with Diabetes, As Recommended by the American Association of Clinical Endocrinologists (Adapted from Handelsman, 2011)

Parameter	Treatment Goal
Lipids	
Low density lipoprotein cholesterol, mg/dL	≤70 highest risk; <100 his risk
Non-high density lipoprotein cholesterol, mg/dL	< 100 highest risk; <130 high risk
Apolipoprotein B, mg/dL	<80 highest risk; <90 high risk
High-density lipoprotein cholesterol, mg/dL	>40 in m en; >50 in women
Triglycerides, mg/dL	<150
Blood pressure	
Systolic, mm Hg	<130
Diastolic, mm Hg	<80
Weight	
Weight loss	Reduce weight by at least 5%-10%; avoid weight gain
Anticoagulant therapy	
Aspirin	For secondary CVD prevention or primary prevention for patients at very high risk

High risk = diabetes mellitus without CVD; highest risk = diabetes mellitus plus CVD

consider.[19] Newer analog insulins provide more physiologic profiles, with lower risks of nocturnal hypoglycemia than (for example) neutral protamine Hagedorn (NPH) insulin, with greater dosing convenience than older insulin agents.[30] The use of insulin remains limited by risks of hypoglycemia and patient acceptance of injectable therapy. Newer insulin agents are currently in development with what appear to be lower rates of hypoglycemia then even current analog insulins,[31–38] which may further enhance therapeutic options.

New Treatment Options Create New Opportunities to Improve Glycemic Control

There have been several recent additions to therapeutic choices for glycemic control in patients with T2DM. These include incretin-based therapies (Dipeptidyl peptidase-4 [DPP-4] inhibitors and glucagon-like peptide1 receptor agonists [GLP-1 RAs]) (which will be discussed in much greater detail later in this supplement), glinides, alpha glucosidase inhibitors, the injectable form of the amylin hormone (pramlintide), colesevelam, as well as a quick release form of bromocriptine. These agents vary in their ability to lower blood glucose levels (dose-response effects), which blood glucose level they primarily affect (bearing in mind that A1 consists of both fasting- [FPG] and postprandial-glucose [PPG] components), their MOAs (which aspect of diabetes pathophysiology they target, and therefore what makes for logical combination therapy), their safety profiles (which may preclude use in some patients) and their tolerability profiles (which may affect patient adherence and ultimately treatment success). The broad profiles of all the major classes are presented in Table 4.[19]

Current treatment algorithm places an emphasis on agents that carry lower risks of hypoglycemia, as well as considering the weight effects of treatment.[39,40] Incretin-based therapies (both DPP-4 inhibitors and GLP-1 RAs) feature prominently in the algorithm because they work on multiple defects of diabetes' pathophysiology, work in a glucose-dependent manner (and so are associated with a low risk of hypoglycemia unless used with insulin or insulin secretagogues), and are not associated with weight gain.[39,40]

Cardiovascular disease (CVD)

Cardiovascular disease (CVD) is the primary cause of death for most persons with T2DM; therefore a comprehensive care plan for patients with T2DM should include modification of CVD risk factors such as blood pressure and lipids. Incretin-based therapies do not adversely affect CV risk factors and in fact appear to have some positive effects,[41] are being explored in prospective trials.[42]

Although outside the scope of this supplement, cardiovascular risk reduction targets are summarized in Table 5.[16] Readers also are referred to the 2011 American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan, which provides further guidance on lifestyle modification and prevention and treatment of diabetes-related complications, among other important issues.[16]

Summary

Screening patients at risk and diagnosing patients with T2DM early in the disease process is important. The mainstays of any treatment program for T2DM are nutrition, physical activity, and patient education. Early treatment, emphasizing both lifestyle modification, pharmacotherapy for hyperglycemia, and management of CV risk factors, is effective in reducing the risks of diabetes-related complications. Glycemic targets and treatments to lower glucose should be individualized according to the specific characteristics of the individual patient. In the absence of contraindications, metformin is the preferred first-line drug. The pathophysiology of T2DM is multifactorial. Most patients will require combination therapy to achieve or maintain glycemic control. A reasonable approach is combination therapy with one to two additional oral or injectable agents, with the goal of minimizing side effects and maximizing patient adherence. Whenever possible, the patient should participate in all treatment decisions, focusing on their preferences, needs, and values. Because T2DM is a progressive disease, characterized by progressive beta cell failure, to maintain glycemic control many patients will ultimately need insulin monotherapy or in combination with other medications. Newer treatment options including the incretin-based therapies, which are not associated with

either weight gain or hypoglycemia, may be very helpful to achieve treatment goals as part of combination therapy strategies.

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