Type 2 diabetes: Where we are today: An overview of disease burden, current treatments, and treatment strategies

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Abstract

Objective: To provide an overview of the disease burden and current strategies in the treatment of patients with type 2 diabetes.

Data sources: Medline search of all relevant clinical and review articles.

Study selection: By the author.

Data extraction: By the author.

Data synthesis: The prevalence of diabetes in the United States has reached epidemic proportions with the total diagnosed and undiagnosed cases among people aged 20 years or older estimated at 12.9%, and it continues to rise at an alarming rate. This upsurge has been paralleled by an increase in rates of obesity. Type 2 diabetes accounts for up to 95% of diabetes cases and is often comorbid with hypertension and dyslipidemia.

Conclusion: Tight glycemic control is necessary for the management of type 2 diabetes, but progressive deterioration of beta-cell function can lead to a loss of glycemic control. Oral antidiabetes drugs and insulin are effective but do not always correct the associated metabolic and glucoregulatory dysfunctions, and hypoglycemia and weight gain are common adverse effects of these agents. A clear need exists for aggressive therapeutic options—particularly incretin-based agents—that can be combined with existing agents to preserve beta-cell function and halt the progression of type 2 diabetes.

Keywords: Type 2 diabetes, prevalence, beta-cell function, comorbidities, incretins, incretin-based therapies.

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The prevalence of type 2 diabetes has increased alarmingly in the United States.[1] The American Diabetes Association (ADA) estimates that more than 23 million U.S. adults aged 20 years or older have diabetes (~95% type 2 diabetes).[2] Among middle-aged Americans, for example, prevalence of type 2 diabetes has doubled during the past 3 decades.[1] Factors contributing to this increased prevalence are obesity, physical inactivity, and an increase in the number of individuals older than 65 years.[3] These factors, and corresponding prevalence of type 2 diabetes, are also in evidence worldwide. The World Health Organization (WHO) has put the number of persons with diabetes worldwide at approximately 170 million, a figure expected to rise to 366 million by 2030.[3] In 2005, WHO estimated that 1.6 billion adults worldwide were overweight and 400 million were obese.[4] Obesity, of course, is highly correlated with an increased risk of developing glycemic disorders. Diabetes is also frequently comorbid with hypertension, cardiovascular (CV) disease, and microvascular disorders (e.g., retinopathy, nephropathy, neuropathy), which may result in blindness, nontraumatic limb amputation, and renal failure.[5] Current treatments and treatment regimens include combinations of oral antidiabetes drugs (OADs), antihypertensive medications, and antidyslipidemic agents, but these have been less than successful in managing their respective disease targets with clinical goals. Measures such as screening and intensive lifestyle modification can help to delay the onset of diabetes in at-risk individuals, and stringent glycemic control with pharmacotherapy may improve outcomes. To manage the type 2 diabetes epidemic effectively, however, agents that can effectively and durably control glycemia while providing pleiotropic benefits (e.g., blood pressure [BP] reduction) are required.

At A Glance

Synopsis: Recent insight into key pathogenic and pathophysiologic mechanisms of type 2 diabetes, including incretin hormone impairments, has led to new metabolic targets, particularly defects in the action of the incretin hormones. Current agents are limited in their efficacy with respect to these targets. The primary goal in the treatment of patients with type 2 diabetes is the maintenance of beta-cell function, the decline of which is the major reason for impairment in glucose tolerance over time. Therapies that arrest progressive beta-cell deterioration while restoring and maintaining normoglycemia are required. New therapies are needed that will also minimize weight gain and correct dyslipidemia without compromising improvements in glycemic control. Incretin-based agents may better address these needs and preserve beta-cell function, halting the progression of type 2 diabetes.

Analysis: *Factors contributing to the increased prevalence of diabetes—obesity, physical inactivity, and the growing number of elderly individuals—are in evidence worldwide. Current treatments are initially successful in lowering clinical targets in patients with type 2 diabetes but are unable to restore normoglycemia over the long term. Measures such as screening and intensive lifestyle modification can help to delay the onset of diabetes in at-risk individuals, and stringent glycemic control with pharmacotherapy may improve outcomes. To manage the increase in the incidence of type 2 diabetes, however, agents that can effectively and durably control glycemia while minimizing the risk for the development of comorbid conditions are required.*

Pathophysiology of type 2 diabetes

Type 2 diabetes is characterized by a range of metabolic disorders: chronic hyperglycemia, declining beta-cell effectiveness resulting in the absence of first-phase insulin response to nutrient ingestion, insulin insensitivity in fat and muscle cells, and hepatic glucose production in the prandial state.[6,7] It is an insidious condition; disease processes may be at work years and even decades prior to diagnosis or overt clinical manifestation (e.g., neuropathy of the extremities or a wound that won't heal).[8] Type 2 diabetes is associated with a number of glycemic and insulinemic disorders such as insulin resistance, impaired fasting glucose, and impaired glucose tolerance.[8,9] Most individuals with type 2 diabetes are also insulin resistant, and insulin resistance has been designated one of the "dual defects"—along with beta-cell dysfunction—responsible for type 2 diabetes.[10,11] However, many individuals with insulin resistance will not develop type 2 diabetes.[12] In those individuals, beta cells are able to compensate for increased insulin demand consequent upon reduced peripheral tissue response to insulin signaling.[13] Impaired fasting glucose and impaired glucose tolerance—sometimes referred to as the prediabetic state—also increase the risk of developing type 2 diabetes; for example, between 30% and 40% of persons with impaired fasting glucose will develop type 2 diabetes within 5 years.[14] In these individuals, and indeed in all individuals who develop type 2 diabetes, beta-cell dysfunction, the inability of beta cells to meet metabolic demands for insulin, is the precipitating cause of type 2 diabetes. (See "Fate of the beta-cell in the pathophysiology of type 2 diabetes" by Campbell in this supplement [p. S10].[15])

Epidemiology of type 2 diabetes and of common comorbid conditions

According to data extrapolated from the 2005 to 2006 National Health and Nutrition Examination Survey (NHANES), approximately 12.9% of U.S. adults (≥20 years of age) have diabetes; nearly 30% of U.S. adults have prediabetes (defined as impaired fasting glucose, impaired glucose tolerance, or both).[16] During 2007, an estimated 1.6 million new diabetes cases were diagnosed among adults aged 20 years or older.[17] Clinically based reports and regional studies suggest that type 2 diabetes, although still rare in children and adolescents, is being diagnosed more frequently, particularly in American Indian, African American, and Hispanic and Latino American children and adolescents.[18] To consider just one example, application of an oral glucose tolerance test to a cohort (n = 167, 55 children, 112 adolescents) of obese individuals 18 years of age or younger found an impaired glucose

tolerance prevalence of approximately 23% and a 4% prevalence of diabetes.[19]

The prevalence of type 2 diabetes has been matched by steady increases in the prevalence of obesity in the United States. National Center for Health Statistics compilations indicate that in 2005 to 2006, approximately 34% of adults aged 20 years or older were obese.[20] NHANES data further indicate that 16.3% of children and adolescents were obese.[21] Hypertension is also highly prevalent in individuals with type 2 diabetes. An estimated 75% of adults with diabetes have BP levels greater than or equal to 130/80 mm Hg or use antihypertensive medication.[2] The prevalence of hypertension in the United States has also been increasing, with the latest estimates (2007) indicating that approximately 72 million Americans have elevated BP. Even more alarming are the facts that only about 50% of individuals with hypertension are being treated and only about two-thirds of those in treatment are being treated to blood pressure goal.[22,23]

Comorbidities and complications

Overweight and obesity

The U.S. Centers for Disease Control and Prevention report that approximately 55% of persons with diabetes are obese and 85% are overweight; approximately 80% of persons with type 2 diabetes are also insulin resistant, and insulin resistance is itself highly correlated with weight gain.[11,24] The lifetime risk of diabetes is greatly increased by overweight and obesity, particularly at younger ages. For example, 18-year-old men with a body mass index (BMI) greater than 35 kg/m^2 have a 70% risk of developing type 2 diabetes.[25] However, even modest weight loss has been shown to reduce this risk substantially.[26]

A 10-year follow-up study of women aged 30 to 55 years who participated in the Nurses' Health Study[27] and of men participants aged 45 to 64 years in the Health Professionals Follow-up Study demonstrated that the risk of developing diabetes, as well as other conditions, escalates in proportion to elevated BMI.[28,29] The 10-year risk of developing diabetes was 3 times higher for overweight women (BMI 25.0–29.9 kg/m^2) and 20 times higher obese women (BMI ≥35 kg/m^2) compared with participants who had low BMIs (18.5–24.9 kg/m^2).[27] For men in the Health Professionals study, approximately 15% of the obese cohort (≥30 kg/m^2) developed type 2 diabetes versus 2% of normal-weight men (BMI 18.5–24.9 kg/m^2).[29] In the study by Bonora et al.,[30] the incidence rates for type 2 diabetes, after adjusting for sex and age, were approximately 3-fold higher in patients with a BMI of 25 or greater and approximately 10-fold higher in obese individuals. Results from another study indicated that for every unit of weight increase in BMI (2.7–3.6 kg), the risk of developing diabetes increased 12%.[31] Other research has demonstrated that overweight individuals who gained 1 kg of weight annually over 10 years had a 49% increase in risk of developing diabetes in the subsequent 10 years compared with stable-weight individuals.[26]

Macrovascular complications

Type 2 diabetes was the seventh leading cause of death on U.S. death certificates in 2006, and mortality risk is twice as high among people with diabetes than among those without the disease.[17] Diabetes mortality is linked primarily to CV disease; heart disease and stroke are responsible for 65% of deaths among individuals with diabetes.[18] An increase in macrovascular complications (e.g., coronary artery disease [CAD], peripheral arterial disease, diseases of the carotid vessels) has been observed among patients with type 2 diabetes.[32] Clinical evidence suggests that type 2 diabetes is a CAD risk equivalent to that of previous myocardial infarction (MI)/heart disease in nondiabetic individuals.[32–34] This observation was most recently supported by a Danish study published in 2009 that involved 3.3 million individuals. Participants with type 2 diabetes had an elevated risk of CV disease mortality, comparable with that of nondiabetic patients who had had a previous MI, and a significantly greater risk of all-cause mortality than nondiabetic patients with a previous MI ($P < 0.001$).[34] The risk of developing CV disease is fourfold higher, and CV events occur approximately 15 years earlier, for patients with diabetes than for nondiabetic individuals.[35] In addition, comorbid diabetes and hypertension are associated with a 7.5-fold increase in CV mortality.[33,36] As has been noted, hypertension and diabetes are highly correlated; approximately 75% of adults with diabetes have hypertension or use antihypertensive medications.[2] Results from a prospective cohort study of 12,550 nondiabetic adults (age range 45–64 years) showed that type 2 diabetes was nearly 2.5 times as likely to develop in hypertensive participants as in those with normal BP.[37] Aggressive BP control (<140/90 mm Hg) has been shown to reduce CV disease morbidity and mortality in patients with type 2 diabetes.[36]

Microvascular complications

Retinopathy and nephropathy are common in a population with diabetes. Every day in the United States, diabetes causes 33 to 66 people to lose their eyesight and 128 to begin treatment for end-stage renal disease.[38] Diabetic retinopathy is the leading cause of new cases of blindness in adults aged 20 to 74 years, responsible for 12,000 to 24,000 cases each year.[17] In 2005, nearly 50,000 people started treatment for end-stage renal disease resulting from diabetic nephropathy.[17]

Importance of glycemic control

The landmark Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study (UKPDS) have convincingly demonstrated that normalizing glycosylated hemoglobin (A1C) levels in individuals with diabetes can reduce diabetes-related CV morbidity and mortality as well as the incidence and progression of microvascular complications.[39] A1C concentration is an accurate predictor of risk for such complications, with a desirable goal of 7.0% or less. In the clinical setting, measurement of A1C assesses longer-term glycemic control among individuals with diabetes.[40]

Long-term data from the UKPDS suggest that for every 1% reduction in A1C, a corresponding decrease of 37%, 43%, 21%, and 14% occurs in microvascular complications, amputation or mortality from peripheral vascular disease, any endpoint or mortality related to diabetes, and incidence of MI, respectively.[41] However, patients frequently have difficulty achieving or maintaining glyce-

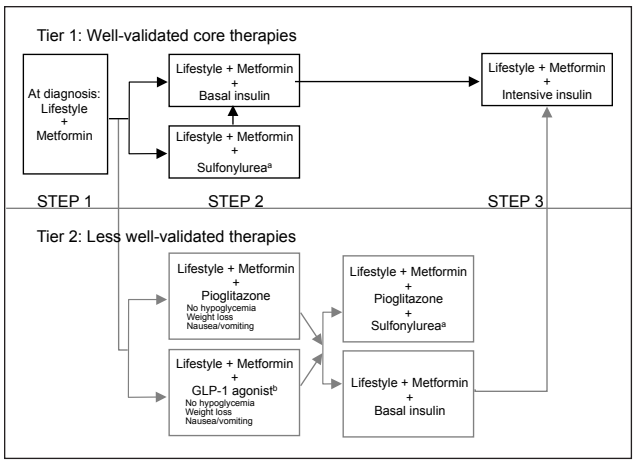

Figure 1. American Diabetes Association/European Association for the Study of Diabetes algorithm

Abbreviation used: GLP-1, glucagon-like peptide-1.

[a]Sulfonylureas other than glibenclamide (glyburide) or chlorpropamide.

[b]Insufficient clinical use to be confident regarding safety.

mic control with current therapeutic options. Terminal levels of A1C have been found to increase substantially as patients progress from nonpharmacologic therapy through combination therapy.[42] The progressive worsening of diabetes, often accompanied by weight gain and characterized by continual loss of pancreatic beta-cell function (physiologically, a progressive decline in insulin secretory response to plasma glucose; clinically, a progressively worsening of glycemia and loss of therapeutic control of A1C), necessitates continual treatment adjustment or culminates in treatment failure.[42,43] A recent study indicated that although a trend toward improved glycemic control was found among people with diabetes in the United States, approximately 40% remain poorly controlled (not consistently at glycemic goal, A1C <7%).[40] The accumulating evidence from large clinical trials supporting aggressive therapeutic interventions to manage hyperglycemia, as well as dyslipidemia and hypertension, is reflected in current treatment guidelines.[5,44]

The National Committee for Quality Assurance reported in 2007 that poor glycemic control (A1C >9.0%) was found in 30% of patients with diabetes enrolled in managed care organizations, 29% of those in Medicare, and 48% of patients in Medicaid.[45] Glycemic control ultimately deteriorates, even in treated patients who are adherent to therapy, owing to the continuation of beta-cell dysfunction. In UKPDS 16, patients who were assigned to conventional therapy and followed during a 6-year period demonstrated increased fasting plasma glucose levels, decreased fasting plasma insulin levels, and progressive, significant deterioration in beta-cell function from 53% at 1 year to 28% at 6 years.[9] Those who were treated intensively initially demonstrated about a 46% to 78% improvement in beta-cell function; however, this improvement was followed by significant functional decline after 1 year that paralleled the decline observed in patients on conventional diet therapy. The progressive loss of beta-cell function over the course of 6 years occurred irrespective of therapy used.[9] Deterioration in glycemic control and progressive beta-cell dysfunction have been observed in more recent trials, for example, A Diabetes Outcome Progression Trial.[46] (See "Fate of the beta-cell in the pathophysiology of type 2 diabetes" by Campbell in this supplement [p. S10].[15])

Therapeutic options for the treatment of type 2 diabetes

A range of therapeutic classes of oral agents as well as insulin, targeting different metabolic pathologies, exist for the treatment of type 2 diabetes (Figure 1). Metformin, a biguanide, is a commonly prescribed OAD agent; ADA/European Association for the Study of Diabetes (EASD) guidelines recommend metformin as initial pharmacotherapy for type 2 diabetes, with an expected reduction in A1C of between 1.0% and 2.0%.[47] Metformin therapy has also been associated with small reductions in systolic and diastolic BP; DeFronzo et al.[48] also found small improvements in lipid profiles to be associated with metformin therapy in patients with type 2 diabetes—a 5% reduction in low-density lipoprotein cholesterol, an 8% reduction in triglycerides, and a 5% increase in high-density lipoprotein cholesterol (HDL-C) concentrations. In addition, studies have shown that metformin effectively reduces microvascular and macrovascular complications and may be weight neutral.[49,50] In their recommendations, both the ADA and the International Diabetes Foundation support metformin as initial pharmacotherapy for type 2 diabetes.[51] However, metformin is associated with increased CV risk and lactic acidosis, and it is contraindicated in patients with heart failure or impaired renal function.[50–52] Metformin monotherapy has also been associated with diarrhea in approximately 50% of patients and nausea or vomiting in 25% of patients.[53]

Sulfonylureas (SUs; e.g., glimepiride) have long been an effective and low-cost mainstay of type 2 diabetes therapy; as with metformin, SU monotherapy can be expected to reduce A1C by 1.0% to 2.0%.[47] SUs are a common alternative or add-on to metformin and act by stimulating pancreatic beta-cell insulin secretion in a glucose-independent manner.[54] Weight gain is a common adverse effect of SU therapy, as is an increased risk of hypoglycemia, particularly in the elderly and in patients with worsening renal function.[39,51] As with metformin, SU therapy has been associated with minimal effects on BP (<5 mm Hg).[51] SU effects on lipids have not been extensively studied.

Alpha-glucosidase inhibitors, such as acarbose, act as competitive inhibitors of the alpha glucosidases, thereby delaying glucose absorption. This effect on glucose uptake decreases glucose peak and insulin response postprandially and moderately lowers fasting plasma glucose levels and A1C, but gastrointestinal adverse effects and the requirement for three times daily dosing may inhibit adherence to therapy.[13,47] Monotherapy with alpha-glucosidase inhibitors have been associated with A1C reductions of between 0.5% and 0.8%, with no weight gain. Effects on BP are minimal (<3 mm Hg)[55]; one study reported a small benefit (–10%) on triglycerides.[56]

Thiazolidinedione (TZD) monotherapy has been associated with A1C reductions of between 0.5% and 1.4%.[47] TZDs have beneficial effects on CV markers, including lipid levels (particularly triglycerides and HDL-C),[57] BP, inflammatory mediators, endo-

thelial function, and fibrinolytic status. However, weight gain and increased risk of edema and heart failure are frequent adverse effects, particularly when TZDs are used in combination with insulin.[13,49] Rosiglitazone is currently under some degree of clinical suspicion after a recent meta-analysis of 42 trials by Nissen and Wolski[58] found the drug to be associated with a significantly increased risk of MI ($P = 0.03$) as well as an increased risk of CV-related mortality ($P = 0.06$).

Glinide (i.e., repaglinide, nateglinide) monotherapy has been reported to reduce A1C by between 0.5% and 1.5%. The rapid onset of action of glinides necessitates three times daily dosing, and they have been associated with hypoglycemia.[47] Weight gain has been reported with glinide therapy (between 0.7 and 1.8 kg).[59]

Insulin, either alone or in combination with other agents, most commonly metformin, is an effective option for restoring normoglycemia, especially when administered early in the disease course. The disadvantages of insulin therapy are weight gain and an increased risk of hypoglycemia.[39] Insulin has not been observed to have clinically relevant effects on either blood pressure or lipids.[39,60] Effects on blood pressure and lipids have not been extensively studied.

In addition to devising the most appropriate pharmacotherapeutic regimen for the patient with type 2 diabetes, patient management is also of critical importance and is best handled by a medical care team including the physician, the pharmacist, the dietitian, and a diabetes education specialist. Ideally, a diabetes care plan should be developed with input from all medical care team practitioners and the patient. Assessments should occur at least twice yearly, and may be scheduled more often in patients who have undergone a change in therapy or who have a history of not attaining glycemic goals.[5] For more information about the role of the pharmacist in the management of the patients with type 2 diabetes, see the article by Sisson and Kuhn (p. S41) in this supplement.[61]

Shortcomings of current diabetes pharmacology

The OADs are able, for a time, to reduce A1C but do not correct all the metabolic and glucoregulatory dysfunctions involved in type 2 diabetes pathophysiology. As a result, A1C goals become more difficult to maintain and a significant glycemic burden accumulates, increasing the risk of CV diseases. The treatment of comorbid conditions, particularly hypertension, may also impede achieving and maintaining glycemic goals. For example, beta-blocker therapy has been shown to increase body weight, particularly visceral adiposity, which may have a deleterious effect on insulin resistance or interfere with glycemic control.[62] An association also has been demonstrated between thiazide diuretics and glucose intolerance, including elevated levels of fasting plasma glucose.[63]

Difficulties in maintaining long-term glycemic control with currently available antidiabetes therapies have led to the need for additional treatments that can be used as monotherapy or combined safely with existing agents and that may target more of the underlying pathologies of type 2 diabetes.

Incretin effect and a new class of antidiabetes therapy

Significant differences in the insulin responses to oral versus intravenous glucose—the so-called "incretin effect"—led to the discovery of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, hormones secreted in the gut in response to a meal. These incretin hormones play pivotal roles in the stimulation of glucose-dependent insulin secretion.[64] The recognition that impairments in the incretin response, and particularly in GLP-1 activity, may contribute to dysregulation of insulin and glucagon secretion has resulted in the development of an incretin family of therapeutic agents. Because native GLP-1 is rapidly deactivated (within minutes of secretion) by dipeptidyl peptidase 4 (DPP-4), a ubiquitous enzyme, two types of incretin-based agents have been developed: GLP-1 receptor agonists, which mimic the physiologic actions of native GLP-1 but with considerably longer half-lives due to resistance to DPP-4, and DPP-4 inhibitors, which block the effect of the enzyme on the native hormone.[65,66] See the articles by Neumiller (p. S16)[67] and White (p. S30)[68] in this supplement.

Incretin-based therapies, which include the GLP-1 receptor agonists exenatide and exenatide LAR (in development), and liraglutide (awaiting approval) and the DPP-4 inhibitors sitagliptin, vildagliptin, and saxagliptin (the former awaiting approval in the United States, the latter recently approved), represent a new class of antidiabetes drugs. Data suggest an equal or potentially greater efficacy of incretin-based therapies to lower A1C compared with other antidiabetes therapies, with a low risk of hypoglycemia.[69,70] Other benefits include weight reduction (GLP-1 receptor agonists) or weight neutrality (DPP-4 inhibitors).[70,71] Preliminary data suggest that incretin agents may decrease blood pressure and improve triglyceride levels.[70,72] GLP-1 receptor agonists have recently been added to the ADA/EASD treatment algorithm as a tier 2 alternative to the addition of SUs or basal insulin in patients inadequately controlled on metformin plus lifestyle modification.[47]

DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin) have a good safety profile in general, and have demonstrated modest reductions in A1C in a weight neutral environment with some positive effects on beta-cell function. GLP-1 receptor agonists (exenatide, liraglutide) have shown more robust reductions in A1C while promoting weight loss and reductions in systolic BP. They have also demonstrated improvements in markers of beta-cell function, which offer some promise toward delaying or even halting disease progression.[67] Preclinical evidence indicates that GLP-1 receptor agonists may also exert cardioprotective effects.[73]

Conclusion

Although traditional treatments and treatment combinations are initially successful at lowering A1C, they are unable to restore normoglycemia over the long term. Recent data that suggest the mean time to secondary failure on OADs (a therapeutic event necessitating the addition of another agent or insulin) may be as short as 1.3 years.[74] Recent insight into key pathogenic and pathophysiologic mechanisms of type 2 diabetes, including incretin hormone impairments, has led to new metabolic targets, particularly defects in the action of the incretin hormones. Current

agents, however, are limited in their efficacy with respect to these targets.[75] The primary goal in the treatment of patients with type 2 diabetes is the maintenance of beta-cell function, the decline of which is the major reason for impairment in glucose tolerance over time. Consequently, therapies that arrest progressive beta-cell deterioration while restoring and maintaining normoglycemia will be required.[75] New therapies are needed that will also minimize weight gain and correct dyslipidemia without compromising improvements in glycemic control.[76] Incretin-based agents, in particular, may better address these needs and preserve beta-cell function, potentially halting the progression of type 2 diabetes.

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