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The Early Treatment of Type 2 Diabetes

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ABSTRACT

The growing epidemic of type 2 diabetes is one of the leading causes of premature morbidity and mortality worldwide, mainly due to the micro- and macrovascular complications associated with the disease. A growing body of evidence suggests that although the risk of developing complications is greater with glucose levels beyond the established threshold for diagnosis − increasing in parallel with rising hyperglycemia—individuals with glucose levels in the prediabetic range are already at increased risk. Early intervention, ideally as soon as abnormalities in glucose homeostasis are detected, is of great importance to minimize the burden of the disease. However, as the early stages of the disease are asymptomatic, diagnosing prediabetes and early overt type 2 diabetes is challenging. The aim of this article is to discuss these challenges, the benefits of early intervention—with emphasis on the prevention trials showing that progression to type 2 diabetes can be delayed by addressing prediabetes—and the existing evidence-based guidelines that have been drawn to optimize the standards of care at the prediabetes and overt type 2 diabetes stages.

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KEYWORDS: Complications; Diabetes prevention trials; Diagnosis; Early intervention; Prediabetes

THE INCREASING BURDEN OF TYPE 2 DIABETES

Diabetes—A Growing Epidemic

The global prevalence of diabetes is rising to epidemic proportions due to population growth, aging, urbanization, and the increasing prevalence of obesity and a sedentary lifestyle. In 2012, diabetes affected more than 371 million adults worldwide (prevalence of 8.3%), with more than 90% of diabetes cases diagnosed as type 2 diabetes.[1,2] This number is estimated to increase to approximately 552 million adults by 2030 (prevalence of 9.9%), mostly due to the growing burden of diabetes in developing countries.[1] The prevalence of diabetes is increasing, not only due to an increase in incidence, but also as a result of better health care improving life expectancy of patients with diabetes.[1] Despite advances in health care, diabetes is still a major cause of premature mortality, mainly due to associated cardiovascular disease (CVD), with an estimated 4.8 million deaths worldwide attributable to diabetes in 2012.[3]

In the US alone, the number of Americans suffering from diabetes has increased from 23.6 million in 2007 to 25.8 million at the start of 2011.[4] The increasing prevalence of diabetes follows an epidemic of overweight and obesity, the prevalence of which has increased dramatically over the past 20 years. The latest National Health and Nutrition Examination Survey performed in 2007-2008 estimated that approximately 33.8% of the adult US population are obese, up from 22.9% in the period between 1988 and 1994.[5] Indeed, 85% of type 2 diabetes patients are overweight or obese.[6] As obesity is the strongest acquired risk factor for developing type 2 diabetes,[7,8] the prevalence of obesity and diabetes will likely continue to increase unless preventive measures are taken.

Pathophysiology of Type 2 Diabetes

Type 2 diabetes is a complex and progressive disease characterized by various metabolic defects and affecting multiple organs (**Figure**).[9-11] The main defects contributing to the

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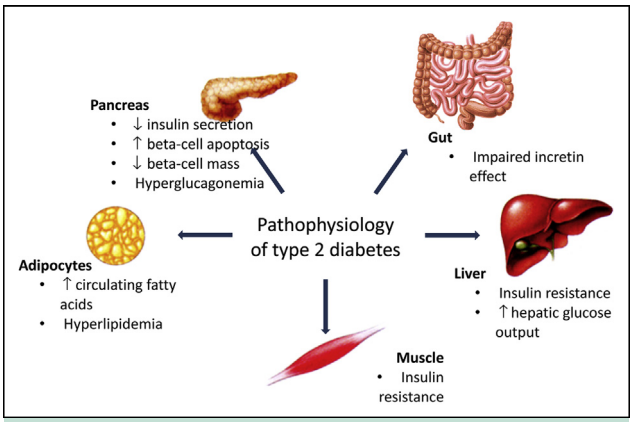

Figure Pathophysiology of type 2 diabetes.

development of type 2 diabetes are impaired insulin secretion and insulin resistance in peripheral tissues, such as adipose and muscle, and the liver. The decrease in insulin secretion is due to the gradual decline in pancreatic beta-cell function and also is linked to reduced beta-cell mass, which is evident before the onset of frank type 2 diabetes.[9-12] Indeed, some data suggest that, at the time of diagnosis, a mere 20% of beta-cell function remains.[13] The development of chronic hyperglycemia further impairs beta-cell function and insulin secretion. In addition, increased hepatic glucose production, due to both impaired insulin action on the liver and excessive glucagon secretion and an impaired incretin effect, play a major role in the pathophysiology of type 2 diabetes.[9,14,15]

The hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are responsible for the incretin effect, a phenomenon whereby insulin secretion increases more in response to an oral compared with an intravenous glucose challenge.[15,16] GLP-1 has been shown to regulate beta-cell mass by inhibiting beta-cell apoptosis in vitro and in animal models,[17,18] and improve beta-cell function in patients with type 2 diabetes.[19] However, the incretin effect is impaired in patients with type 2 diabetes, mainly due to loss of the insulinotropic effect of GIP and GLP-1 in some, but not all, patients.[20]

The Long-term Burden of Type 2 Diabetes

Type 2 diabetes is one of the leading causes of premature morbidity and mortality worldwide as a result of the long-term microvascular and macrovascular complications associated with this disease.[21] For instance, diabetic retinopathy is the leading cause of blindness among adults aged 20-74 years[22]; diabetic nephropathy, which affects approximately 40% of type 2 diabetes patients, is the leading cause of chronic kidney disease in patients starting replacement therapy; and diabetic neuropathy, which affects up to 50% of individuals with diabetes, increases the risk of foot ulcers and limb amputation.[2] In fact, more than 80% of nontraumatic limb amputations follow a foot ulcer or injury, and the risk of amputation in individuals with diabetes is up to 25 times greater compared with patients without diabetes.[23]

Although microvascular complications increase morbidity and lead to premature mortality, the major cause of death in individuals with diabetes is CVD, accounting for approximately 65% of all diabetes-related deaths.[24] For example, transient ischemic attacks are 2-6 times more common in patients with type 2 diabetes,[24] while the risk of developing heart failure is a startling 2- to 8-fold higher.[25]

POSSIBLE INTERVENTIONS TO REDUCE BURDEN OF DIABETES

Hyperglycemia is strongly and independently associated with the complications of type 2 diabetes, including diabetes-related and all-cause mortality, even after adjusting for other metabolic abnormalities often present in this population, such as hypertension and hyperlipidemia.[26]

Results from randomized controlled trials have unequivocally shown that the risk of microvascular complications is reduced with intensive glycemic control.[27,28] By contrast, evidence that intensive glycemic control reduces the risk of macrovascular complications is less clear. In the UK Prospective Diabetes Study (UKPDS) and its long-term observational component, early (upon diagnosis) intensive therapy with either metformin or insulin and a sulfonylurea (SU) was associated with a reduced risk of myocardial infarction or all-cause mortality compared with conventional therapy.[28-30] However, results from 3 recent interventional trials suggest that short-term intensive glycemic control to near normoglycemia in high-risk patients with established type 2 diabetes does not improve CVD outcomes and may even have a detrimental effect.[31-33] Nevertheless, the results of subset analyses of these trials, together with the results of the observational follow-up of the UKPDS, suggest that patients with shorter duration of diabetes, lower glycated hemoglobin (A1c) at entry, and who do not have CVD may derive a cardiovascular benefit from intensive glycemic control.[34] In addition, intensive multifactorial intervention to address not only hyperglycemia, but also other cardiovascular risk factors often associated with type 2 diabetes, such as hypertension, dyslipidemia, and microalbuminuria, has proven to be highly beneficial to prevent micro- and macrovascular complications.[35,36]

Based on this evidence, the American Diabetes Association (ADA), the American Heart Association, and the American College of Cardiology Foundation, in a joint statement, recommended a general A1c goal of <7% to prevent the micro- and macrovascular complications of diabetes, except in patients with long-term diabetes, a history of severe hypoglycemia, or long-term micro- or macrovascular complications for whom a higher target may be more appropriate. Controlling nonglycemic risk factors was also recommended as the primary strategy to reduce the risk of CVD in type 2 diabetes patients.[34] Unfortunately, despite the considerable burden associated with type 2 diabetes, A1c, blood pressure, and low density lipoprotein-cholesterol targets were achieved, respectively, by only 52.5%, 51.1%, and 56.2% of participants surveyed

in the US between 2007 and 2010, and a very small minority (18.8%) achieved all 3 targets.[37]

Benefits of Early Intervention: Addressing Prediabetes

Prediabetes is a condition in which normal glucose homeostasis is compromised. It is characterized by impaired fasting glucose (ie, fasting plasma glucose of 100-125 mg/dL [5.6-6.9 mmol/L]), impaired glucose tolerance (IGT; ie, 2-hour postglucose load of 140-199 mg/dL [7.8-11.0 mmol/L]), or A1c levels of 5.7%-6.4%.[38] Currently, an estimated 79 million people (35% of adults aged 20 years or older) have prediabetes in the US, compared with 57 million in 2008.[39]

Prediabetes confers a 3- to 7-fold increase in the risk of developing overt type 2 diabetes compared with individuals with normal glucose values.[40] Moreover, evidence from numerous studies suggests that the chronic complications of type 2 diabetes start to develop during the prediabetic state. Thus, retinopathy, microalbuminuria, and neuropathy are already present in, respectively, 8%-19%, 5%-15%, and approximately 45% of patients with abnormal glucose tolerance,[41-48] while the risk for CVD is 2-3 times higher in patients with prediabetes compared with individuals with normal glucose values.[49-53] Therefore, to minimize the burden of complications associated with hyperglycemia, early intervention, even before overt diabetes develops, seems advisable.

Currently there are no approved pharmacotherapies for prediabetes. However, some prevention studies have shown that early intervention with lifestyle modification or pharmacotherapy may slow down the progression to diabetes by delaying the underlying pathophysiology of the disease.[54] The most recent position statement issued by the ADA regarding standards of medical care in diabetes and a consensus statement by the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) recommend lifestyle intervention as the preferred treatment option of prediabetes, as it has been shown to be safe and highly effective,[55-57] reducing the progression to type 2 diabetes by more than 40%.[58-60] For example, in the Diabetes Prevention Program (DPP), which enrolled 3234 nondiabetic individuals with impaired fasting glucose or IGT, intensive lifestyle modification, aiming to achieve at least a 7% weight loss and 150 minutes of physical activity per week, reduced the incidence of type 2 diabetes by 58% compared with placebo after 2.8 years of follow-up.[60]

Nevertheless, as prediabetes progresses, pharmacotherapy may be required. Given that the role of intensive glucose control has not been irrefutably proven to reduce the risk of CVD complications,[31-33] the ACE/AACE algorithm recommends a 2-track approach, targeting hyperglycemia and CVD risk factors separately (with the same blood pressure and lipid control goals as those recommended for diabetes patients) through multifactorial intervention, which has been shown to be highly beneficial in preventing the micro- and macrovascular complications associated with type 2 diabetes.[36,61]

Results from randomized clinical trials have shown that several antihyperglycemic agents, namely metformin, acarbose, and thiazolidinediones, can prevent the progression from prediabetes to overt diabetes, although these agents are either less effective or have safety and tolerability issues.[61] Thus, the DPP showed that patients randomized to treatment with metformin (850 mg twice daily) had a 31% reduction in the incidence of type 2 diabetes after 2.8 years of follow-up. Similarly, in the STOP-NIDDM trial, patients with IGT randomized to treatment with acarbose were 25% less likely to develop overt diabetes than those randomized to placebo after 3.3 years of follow-up.[51] Furthermore, acarbose significantly increased reversion from IGT to normal glucose tolerance and reduced the risk of CVD and hypertension compared with placebo.[51,62] Rosiglitazone and pioglitazone also have been shown to prevent the progression from IGT to type 2 diabetes, with reductions in the risk of conversion from prediabetes to type 2 diabetes of 62% and 72% after 2.4 and 3.0 years of follow-up, respectively.[52,63] Despite their proven efficacy, the thiazolidinediones are not ideal for primary prevention due to multiple safety and tolerability concerns.[64,65] In fact, as part of a risk evaluation and mitigation strategy program required by the US Food and Drug Administration, rosiglitazone has not been available from retail pharmacies since November 2011.[66] Nevertheless, despite evidence showing that some antihyperglycemic agents can prevent the progression from prediabetes to type 2 diabetes, there are no drugs approved for prediabetes and no obvious pathway for attaining approval.

Although antihyperglycemic agents have generally proved useful in delaying the progression from prediabetes to overt diabetes, there have been exceptions. In the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, for example, treatment with nateglinide, a meglitinide that enhances insulin secretion, did not reduce the incidence of diabetes or reduce CVD events in patients with IGT and at high risk for CVD.[67]

Unfortunately, awareness of prediabetes is very limited. In The National Health Interview Survey carried out in 2006, only 4% of Americans knew that they were living with this condition.[68] Therefore, despite the potential of early intervention to prevent the progression from prediabetes to overt diabetes, and thus the development and progression of chronic complications, the majority of people will never benefit from this early intervention. Screening for prediabetes may be a useful tool to increase awareness of prediabetes, and it is recommended in overweight adults (body mass index [BMI] >25 kg/m^2) with one or more additional risk factors (**Table 1**).[55]

DIAGNOSING DIABETES

Diagnosis and Classification Criteria

The World Health Organization (WHO) and the International Diabetes Federation (IDF) have defined criteria for the diagnosis of diabetes, with cutoff limits based on levels of

Table 1 Criteria for Testing for Type 2 Diabetes or Assessing the Risk of Future Type 2 Diabetes in Adults*

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2†) and have additional risk factors:
   - Physical inactivity
   - First-degree relative with diabetes
   - High-risk race/ethnicity (eg, African American, Latino, Native American, Asian American, Pacific Islander)
   - Women who delivered a baby weighing >9 lb or were diagnosed with gestational diabetes
   - Hypertension (≥140/90 mm Hg or on therapy for hypertension
   - High-density lipoprotein cholesterol level <35 mg/dL (0.90 mmol/L) or triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovarian syndrome (PCOS)
   - A1c >5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing
   - Other clinical conditions associated with insulin resistance (eg, severe obesity, acanthosis nigricans)
   - History of cardiovascular disease
2. In the absence of the above criteria, testing for diabetes should begin at age 45 years
3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

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†At-risk body mass index (BMI) may be lower in ethnic groups.

glycemia associated with microvascular complications (in particular, retinopathy) and the population distribution of plasma glucose.[69] Fasting plasma glucose ≥126 mg/L (7.0 mol/L) or 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test have traditionally been used for diagnosis. More recently, the value of A1c for diagnostic purposes has been recognized with A1c ≥6.5% as the cutoff point for a positive diagnosis.[70] The diagnostic criteria recommended by the ADA are the same as those of the WHO/IDF, but also include a random plasma glucose ≥200 mg/dL (11.1 mmol/L) as a criterion for diagnosis in patients with severe hyperglycemia such as those who present with severe classic hyperglycemic symptoms or hyperglycemic crisis, including in rapidly evolving diabetes, such as the development of type 1 diabetes in some children.[38] Therefore, the diagnostic process is relatively straightforward: an individual that meets any of these criteria (confirmed by repeat testing) will be diagnosed with diabetes. Once a patient is diagnosed, most diabetes cases are classified based on its etiology as type 1 (accounting for 5%-10% of cases and characterized by autoimmune beta-cell destruction generally leading to absolute insulin deficiency) or type 2 (accounting for most of the remaining 90%-95% of cases and characterized by insulin deficiency and insulin resistance), although the ADA recognizes up to 8 other subcategories, including genetic defects of the beta-cell or insulin action, diseases of the exocrine pancreas, and endocrinopathies.[38]

Undiagnosed Diabetes: The Importance of Screening

Because of the long asymptomatic period that characterizes type 2 diabetes,[71] a large proportion of people with this disease remains undiagnosed (WHO). In the US, about 9 million people are believed to fall into this category.[4] Given that a substantial proportion of patients newly diagnosed with type 2 diabetes already have complications associated with the disease,[72] and the large body of evidence showing that these complications can be prevented by early intervention to control glycemia and other comorbidities,[29,35,36] it seems reasonable that a screening program should be implemented to facilitate early diagnosis. Thus, the ADA recommends that testing for type 2 diabetes should be considered in overweight adults (BMI >25 kg/m^2) with one or more additional risk factors (**Table 1**) and overweight children (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height) with 2 or more additional risk factors (**Table 2**).[55]

INITIAL INTERVENTION: LIFESTYLE CHANGES AND METFORMIN

Lifestyle Changes

Overeating and low levels of physical activity are commonplace in many modern societies and are 2 major factors behind the global epidemic of obesity. As overweight and obesity are major risk factors for developing type 2 diabetes, it seems unsurprising that changes in lifestyle such as decreased caloric intake and increased physical activity have a positive impact on glycemic control and other CVD risk factors.[73] Given that this lifestyle intervention is generally safe and cost-effective, its importance should be stressed not only upon the diagnosis of diabetes, but throughout the course of the disease.[74] Unfortunately, the long-term success of lifestyle intervention to maintain good glycemic control in patients with type 2 diabetes is limited, due to a failure to lose weight, weight regain over time, the progressive nature of the disease, or a combination of these factors, and most patients will therefore require pharmacotherapy to maintain adequate glycemic control.[74]

Table 2 Criteria for Testing for Type 2 Diabetes in Children*

Criteria

- Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height
- Plus any 2 of the following risk factors
  - Family history of type 2 diabetes in first- or second-degree relative
  - Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
  - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome [PCOS], or small-for-gestational-age birth weight)
  - Maternal history of diabetes or gestational diabetes during the child's gestation
  - Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age

Frequency: every 3 years

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Metformin

Unless contraindicated or not tolerated, metformin is generally the recommended initial pharmacotherapy in combination with lifestyle changes, as it has been shown to reduce glycemia effectively (A1c reductions of approximately 1.5% can be achieved with metformin monotherapy) with a low risk of hypoglycemia and no weight gain or modest weight loss. In addition, it is generally well tolerated, with gastrointestinal side effects being most common, affecting up to 63% of patients on initiation of treatment.[74,75] For this reason, metformin should be titrated slowly; the ADA/European Association for the Study of Diabetes (EASD) consensus algorithm recommends beginning with low-dose metformin (500 mg) once or twice a day with meals or 850 mg once a day, increasing the dose after 5-7 days if gastrointestinal side effects have not occurred. The maximum effective dose can be up to 1000 mg twice a day.[74]

Metformin is contraindicated in patients with renal disease or renal dysfunction (serum creatinine clearance $\geq$1.5 mg/dL in males or $\geq$1.4 mg/dL in females) as it may increase the risk of lactic acidosis. Other contraindications include hypersensitivity to the active ingredient (metformin hydrochloride) and conditions such as acute or chronic metabolic acidosis, including diabetic ketoacidosis with or without coma.[76]

CURRENT TYPE 2 DIABETES TREATMENT ALGORITHM

Until the early 1990s only 2 therapies, insulin and SUs, were available for the treatment of type 2 diabetes. Since then, as a result of the increasing prevalence of type 2 diabetes,[1,2] research in the field intensified markedly. Thus, our knowledge about the mechanisms behind the pathophysiology of the disease increased rapidly, fostering the development of drugs with new or improved mechanisms of actions. Today, there are over 10 drug classes approved for the treatment of type 2 diabetes in the US. In addition, numerous studies have been carried out with the purpose of identifying the best way to manage the disease to minimize the enormous burden of its complications.

Given the enormous proliferation of medical evidence and pharmacotherapy that has taken place over the past 2 decades, the importance of developing evidence-based guidelines for the treatment of type 2 diabetes is paramount. These guidelines should enable physicians to deliver the best possible care by providing objective and up-to-date information on the available interventions and their efficacy and safety. Although general recommendations to optimize patient care, such as treatment goals for A1c, blood pressure, and lipids can be made globally, the specific intervention recommended to achieve these goals will vary from country to country, depending on the resources of their health care systems. Most countries, therefore, have their own individual guidelines.

The most recent ADA/EASD position statement recommends a patient-centered approach for the treatment of type 2 diabetes. Lifestyle changes alone are appropriate for highly motivated patients with A1c levels close to target. Otherwise, lifestyle changes and metformin (unless contraindicated) are to be initiated upon diagnosis.[77] After that, if individualized A1c targets are not met, treatment should be intensified, usually by stepwise addition of 1 or 2 other antihyperglycemic agents. Options for intensifications include SUs, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 receptor agonists, and insulin (usually basal) with no specific preference (see article by Bailey in this issue[78]). If target A1c is not achieved with 3-drug combinations, more complex insulin strategies with multiple daily doses of insulin may be needed. The appropriate combination should be decided in conjunction with the patient on an individual basis, considering patient/drug characteristics and with the goal of improving glycemic control while minimizing side effects.[77]

Similarly, the American College of Physicians recently issued guidelines based on a systematic evidence review of the comparative effectiveness and safety of type 2 diabetes medications. The American College of Physicians recommends the addition of metformin—unless contraindicated—as first-line pharmacologic therapy when lifestyle modifications do not improve hyperglycemia sufficiently. If hyperglycemia persists, the addition of a second agent is advised. Recommendations on specific combination therapies were, however,

not issued, given the lack of good evidence supporting one combination over another.[79]

The AACE guidelines, on the other hand, apply a different treatment strategy based on level of glycemic control at the time of diagnosis[56,80]: in addition to lifestyle changes, monotherapy for patients with A1c 6.5%-7.5%, dual therapy for patients with A1c 7.6%-9.0%, and insulin therapy or dual/triple therapy for patients with A1c >9.0% (see article by Bailey in this issue[78]). Agents for use as mono, dual, or triple therapy are listed in order of priority, with GLP-1RA and DPP-4 inhibitors preferred after metformin.

CONCLUSION

Type 2 diabetes has reached epidemic proportions and is one of the leading causes of premature morbidity and mortality worldwide. Evidence suggests that the burden of type 2 diabetes can be lowered substantially with intensive, multifactorial intervention to target hyperglycemia, the hallmark of the disease, as well as hypertension and hyperlipidemia, which often coexist with type 2 diabetes. In addition, the burden of the disease could be further reduced with early intervention to address prediabetes, as mounting evidence suggests that this approach could prevent, or at least delay, progression to overt diabetes. However, most people do not benefit from this, as prediabetes is largely underdiagnosed.

The diagnosis of overt type 2 diabetes is not without challenges. Although clear guidelines exist on the criteria for diagnosing and classifying diabetes, a large number of patients are undiagnosed, as the disease can remain asymptomatic for long periods of time. Therefore, screening patients with increased risk for type 2 diabetes may help to reduce the burden of the disease.

Once type 2 diabetes is diagnosed, it is of utmost importance that patients receive optimum standard of care to avoid complications. Although they vary by location, evidence-based country-specific guidelines provide recommendations on how to achieve optimum standard of care in a safe and effective manner, choosing the most appropriate intervention from the available pharmacotherapy.

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