Challenging the Norms

Loss of Confidence in Diabetes Management

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ABSTRACT

Using current treatment approaches, many patients with type 2 diabetes do not achieve glycemic goals — and do experience macrovascular complications that contribute to morbidity and mortality. It's time to consider other options.

Implications: Aggressive therapeutic interventions aimed at insulin resistance and cell dysfunction may alter outcomes. Managed care organizations may need to modify the way they look at diabetes and should consider changing their focus from drug costs to wellness. Value-based insurance design may provide opportunities to optimize diabetes management, resulting in improved outcomes for patients and economic benefits for managed care organizations.

INTRODUCTION

Although the prevalence of diabetes has steadily increased in this country for years, recent acceleration of this trend has prompted widespread concern. Poor eating habits and inactive lifestyles contribute to the problem. Because individuals are developing diabetes earlier in life, they will have the disease longer and will require prolonged medical management for an increasingly complex constellation of symptoms. Along with the changing epidemiology of diabetes, there has been a shift in focus from microvascular to macrovascular complications. The impact of these changes, from the perspectives of health, functionality, and economics, makes diabetes a public health concern of staggering import. Standard approaches to the problem do not seem to be working. The diabetes epidemic continues, treatment effectiveness is limited, and costs seem to spiral. The following examination of pathophysiology, treatment considerations, and the managed care perspective will hopefully illuminate issues and initiate a discussion to challenge existing norms and reshape our approach to diabetes care.

Two primary defects contribute to the development of type 2 diabetes: insulin resistance and β-cell dysfunction. Elucidation of the interrelationship of these issues with the metabolic syndrome has led to improved understanding of the underlying pathophysiology, resulting in novel treatment approaches. As clinicians increasingly recognize that diabetes is not necessarily "all about the sugar," the need for a different perspective on lifestyle management and pharmacotherapy emerges. New agents featuring distinct mechanisms and targeting a variety of defects have been introduced, which calls for an approach to drug selection that matches the strengths and limitations of particular drugs with specific patient characteristics. Managed care organizations may also need to rethink their approach to diabetes. Rather than focusing on drug costs, a broader view incorporating knowledge of the natural history of diabetes may be in order. Acknowledgement that aggressive, early management can alter the course of disease progression and prevent or minimize the impact of costly, debilitating complications can inform novel strategies. These could include value-based insurance design (Fendrick 2006) and a focus on wellness rather than disease.

DIABETES MANAGEMENT: MORE THAN BLOOD SUGAR

The formal diagnosis of diabetes requires symptoms of diabetes and a casual plasma glucose of at least 200 mg/dL, a fasting plasma glucose (FPG) of 126 mg/dL, or a 2-hour plasma glucose of 200 mg/dL during an oral glucose tolerance test (American Diabetes Association 2006).

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However, we now know that these diagnostic criteria focus on only a small part of the disease process. The two main physiologic abnormalities of type 2 diabetes are insulin resistance and β-cell dysfunction. Insulin resistant cells fail to respond to circulating insulin. As a result, skeletal muscle is unable to properly utilize plasma glucose, and the liver inappropriately synthesizes glucose. Adipose tissue, in particular, and visceral fat stores enlarge and further contribute to insulin resistance. Plasma glucose levels rise, necessitating increased insulin secretion from pancreatic β-cells. There is a period prior to the onset of symptoms in which the β-cells can keep up with the enhanced demand for insulin secretion (see figure 1). The compensatory increase in circulating insulin prevents elevation of glucose levels. Eventually, however, increasing end-organ insulin resistance coupled with β-cell exhaustion leads to the development of hyperglycemia (DeFronzo 1988, Goldstein 2002).

Insulin resistance alone does not result in the development of diabetes. When insulin resistance first occurs, insulin secretion increases so that normal glucose tolerance is maintained. When insulin demand outstrips the capacity of insulin production by β-cells, glucose tolerance is impaired. During this period of insulin resistance and hyperinsulinemia, pathophysiologic alterations to large and small blood vessels are hastening the development of diabetic complications (DeFronzo 1988, Weyer 2001).

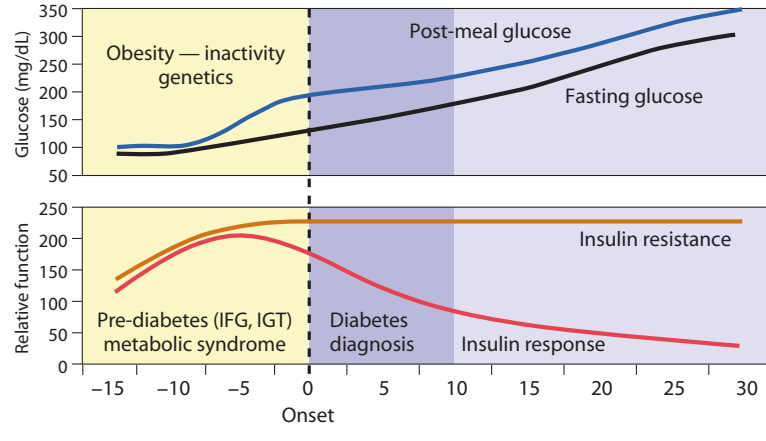
There are two main components of β-cell dysfunction. These include secretory defects in which cells show a diminished acute insulin response to glucose, a reduced ability to compensate for insulin resistance, and inhibited potentiation of non-glucose-stimulated insulin secretion. Deficiencies in the glucose-sensing mechanism of β-cells result in a reduced ability to detect and respond to oscillations in glucose levels and a shift in the relationship between glucose levels and insulin secretion (Polonsky 1996).

There is tremendous overlap between type 2 diabetes and the metabolic syndrome. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) describes metabolic syndrome as a constellation of risk factors that includes abdominal or visceral obesity; atherogenic dyslipidemia (elevated triglycerides, small dense LDL particles, and low HDL-cholesterol); elevated blood pressure; insulin resistance; and prothrombotic and proinflammatory states (Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults 2001, Grundy 2004). Visceral adiposity is closely associated with insulin resistance and elevated levels of free fatty acids. These conditions stimulate hepatic apolipoprotein B secretion and hepatic lipase activity, contributing to the dyslipidemia that is characteristic of both the metabolic syndrome and type 2 diabetes (Brunzell 1999). Hypertension, a defining component of the metabolic syndrome, is extremely common in patients with insulin resistance and/or diabetes. In addition, levels of proinflammatory cytokines including tumor necrosis factor-α interleukin-6, and C-reactive protein are elevated in insulin-resistant, obese individuals; their presence predicts the subsequent development of diabetes and cardiovascular disease.

The complications of insulin resistance and type 2 diabetes lead to staggering morbidity and mortality. Approximately 65 percent of deaths in people with diabetes are due to cardiovascular disease and stroke. Mortality due to cardiovascular disease is elevated up to fourfold among adults with diabetes compared to those without diabetes. The risk of cerebrovascular incident is similarly elevated among people with diabetes and lower-limb amputations are rampant in this population. Hypertension is also extremely common. It is critical for people with diabetes to be treated both to ameliorate hyperglycemia and to minimize the impact of cardiovascular pathology. Interventions may include controlling blood pressure, aggressive management of dyslipidemia, use of antiplatelet agents, and encouraging smoking cessation.

Microvascular changes result in compromised function in the kidneys, eyes, and nervous system. Diabetic retinopathy is the leading cause of new cases of blindness among adults ages 20 to 74, and diabetic nephropathy is the leading cause of

FIGURE 1
Natural history of type 2 diabetes



end-stage renal disease, affecting up to 40 percent of people with diabetes. Neuropathy as a consequence of diabetes can lead to impaired sensation, delayed digestion, or carpal tunnel syndrome; it contributes significantly to lower-limb amputations (American Diabetes Association 2006, National Diabetes Information Clearinghouse 2007).

Recent evidence suggests that the abnormal metabolic environment of hyperglycemia represents the primary cause for the development of both microvascular and macrovascular complications (Brownlee 2005, Brownlee 2001). Genetic factors contribute to individuals' susceptibility to the metabolic milieu characterized by insulin resistance, hyperglycemia, and hyperinsulinemia. Factors such as hypertension, diet, smoking, and hyperlipidemia can increase or decrease the risk of developing complications. Some investigators believe that during the early stages of insulin resistance and impaired glucose tolerance, there is only minimal tissue damage (i.e., reduced nerve conduction velocity, microalbuminuria) and rigorous control of glucose levels may inhibit further deterioration. However, after prolonged duration and intensity of the abnormal metabolic environment, irreversible tissue damage ensues, regardless of maintenance of euglycemia.

Previously, discussions of the clinical consequences of diabetes focused more on microvascular complications. As our understanding of the metabolic syndrome (insulin resistance syndrome) increases, we recognize that macrovascular complications may present even before patients are actually diagnosed with diabetes. As the incidence of diabetes approaches epidemic proportions, and the disease appears in younger individuals, the clinical impact of these conditions becomes markedly amplified. Clinicians would be well served, then, to use a rational, systematic approach to treating diabetes and associated conditions and to treat earlier and more aggressively.

TREATMENT: IT'S NOT ONE SIZE FITS ALL

Table 1 shows the American Diabetes Association's (ADA) recommended glycemic goals for adults with diabetes. Algorithms generated by the ADA propose routes to guide physicians' treatment decisions to achieve these goals (see figure 2). However, the previous discussion on the pathophysiology of metabolic syndrome and type 2 diabetes underscores the importance of not only working toward euglycemia but treating the disorders mediating the development of macrovascular and microvascular complications, including dyslipidemia and hypertension. To have a truly significant impact on slowing the development of vascular disease, a more individualized approach to treatment may be necessary. The importance of lifestyle modification cannot be overemphasized. In addition, a more complete understanding of the available drugs could help physicians select therapies providing even more patient benefits. Diabetes drugs vary considerably with regard to their effects on lipids and β-cells, impact on cardiovascular outcomes, and effect on weight.

Consider the insulin secretagogues. Sulfonylureas and the glinides stimulate pancreatic β-cells to increase insulin secretion. The sulfonylureas are older agents, relatively inexpensive, and of comparable effectiveness with regard to lowering blood sugar. Side effects include hypoglycemia, weight gain, and, potentially, sulfa allergy (Goke 2000). By their very mechanism of action, these agents promote hyperinsulinemia, which further contributes to cardiovascular risk in already at-risk patients. In addition, use of these agents seems to hasten β-cell failure in type 2 diabetes. Increased β-cell apoptosis has been noted (Maedler 2005). A recent report suggests that sulfonlyureas may also increase cancer incidence (Bowker 2006).

Now let's look at the thiazolidinediones, particularly in terms of cardiovascular safety. Nissen, et al, published a meta-analysis of studies of rosiglitazone which suggested that rosiglitazone use was associated with a significant increase in the risk of myocardial infarction and a borderline-significant increase in the risk of death from cardiovascular causes (Nissen 2007). A meta-analysis by Singh, et al, corroborated these findings, noting that the use of rosiglitazone for at least one year is associated with a significantly increased risk of myocardial infarction and heart failure, although these authors did not find a significantly increased risk of cardiovascular mortality (Singh 2007). A different meta-analysis reviewed studies involving over 16,000 individuals to evaluate the effects of pioglitazone on ischemic cardiovascular events (Lincoff 2007). Unlike rosiglitazone, pioglitazone was associated with a significantly lower risk

TABLE 1
ADA recommended levels for adults with type 2 diabetes

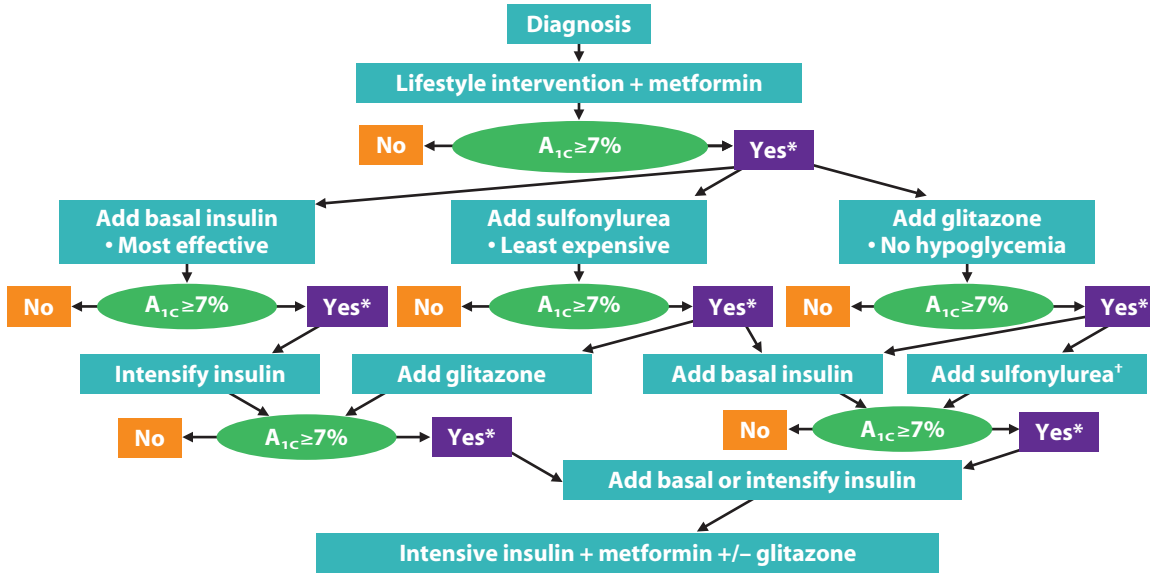
Glycemic Control	
A_{1c}	<7.0%
Preprandial capillary plasma glucose	90–130 mg/dL
Peak postpreprandial capillary plasma glucose	<180 mg/dL
Blood pressure	<130/80 mm Hg
Lipids	
LDL	<100 mg/dL
Triglycerides	<150 mg/dL
HDL	>40 mg/dL

of death, myocardial infarction, or stroke. These observations have engendered much discussion about the cardiac safety of thiazolidinediones as a class. Congestive heart failure (CHF, inability of the heart to function efficiently as a pump), heart failure, weight gain, and edema are well-recognized classwide side effects of the thiazolidinediones. In considering the cardiac safety profiles of thiazolidinediones, then, it is critical to distinguish between macrovascular events, such as myocardial infarction, and CHF. Thiazolidinediones are known to increase plasma volume through a direct effect on the kidney, a consequence of PPARγ-induced excess sodium resorption, but without a direct effect on cardiac tissue (Zhang 2005, Guan 2005). Macrovascular events represent a consequence of acute loss of blood flow to critical tissue, often resulting in permanent loss of function. Among the thiazolidinediones, there seems to be marked differences with regard to these issues.

In the PROactive trial, over 5,200 patients with type 2 diabetes and a prior history of macrovascular disease were randomized to receive either pioglitazone or placebo in addition to their current treatment regimens. Patients were followed for a mean of 2.85 years. Treatment groups were similar with regard to demographic, physical, and laboratory parameters. Ninety-six percent of patients in the study were treated with blood glucose lowering agents including sulfonylureas, metformin, and insulin. Ninety-five percent were taking cardiovascular medications that included β-blockers, ACE inhibitors, calcium channel blockers, diuretics, lipid lowering agents, and antiplatelet medications. The primary efficacy endpoint was time from randomization to first occurrence of any event: all-cause mortality, nonfatal myocardial infarction, acute coronary syndrome, cardiac intervention including cardiac artery bypass graft or percutaneous coronary intervention, stroke, above the ankle amputation, bypass surgery, or revascularization of the leg. There was no statistically significant difference between pioglitazone and placebo for the 3-year incidence of first cardiovascular event, and no increase in mortality or total macrovascular events with pioglitazone (Charbonnel 2004). Meta-analysis of 19 randomized studies of pioglitazone further demonstrated that pioglitazone use is associated with decreased risk of ischemic cardiovascular events (Lincoff 2007).

Table 2 demonstrates that reports of CHF were more common among

FIGURE 2
Algorithm for the metabolic management of type 2 diabetes



ADA = American Diabetes Association
Lifestyle intervention should be reinforced at every visit.
*A_{1c} should be checked every 3 months until it is <7% and then at least every 6 months.
†Although 3 oral agents can be used, initiation and intensification of insulin therapy is preferred based on efficacy and cost.
Adapted with permission from the American Diabetes Association

TABLE 2
PROactive: CHF data

	Pioglitazone	Placebo	*P* value
Any report of heart failure*	281 (11%)	198 (8%)	<.0001
Heart failure not leading to hospitalization*	132 (5%)	90 (3%)	.003
Heart failure needing hospitalization	149 (6%)	108 (4%)	.007
Fatal heart failure†	25 (1%)	22 (1%)	.634

*Not adjudicated
†Adjudicated cause of death.

patients taking pioglitazone vs placebo ($P<0.0001$). Although more pioglitazone-treated patients required hospitalization for CHF ($P=0.007$), there was no statistically significant difference between patients treated with pioglitazone vs placebo for fatal heart failure ($P=0.63$). This may be of particular interest in light of the excess mortality that patients with type 2 diabetes experience with heart failure as compared to patients without diabetes (see figure 3). Furthermore, the previously referenced meta-analysis of pioglitazone trials confirmed the increase in CHF with pioglitazone use, but also demonstrated that there was no increase in mortality associated with this CHF (Lincoff 2007). With regard to the thiazolidinediones, then, cardiac issues can be understood to include both macrovascular events and CHF.

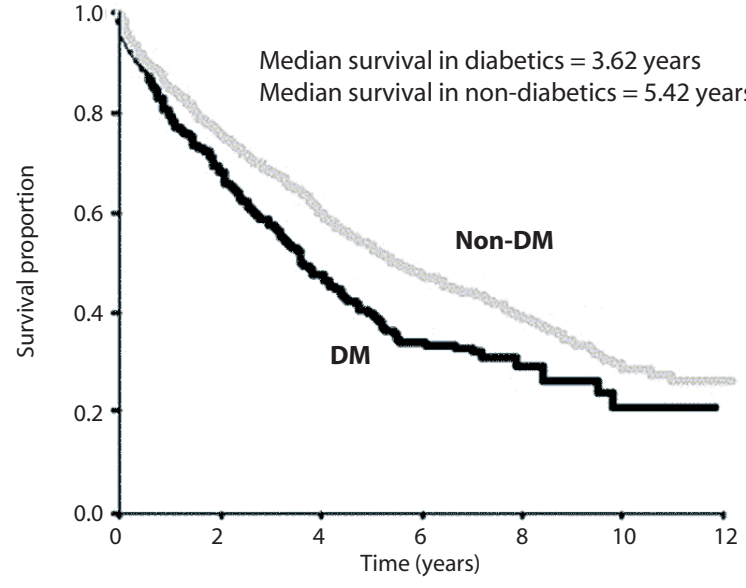
Lipid-lowering properties should be taken into consideration too since they may directly impact cardiac pathology. The effects on lipids of rosiglitazone and pioglitazone were compared in a 24-week, head-to-head study that included 735 patients with type 2 diabetes, fasting triglyceride levels between 150 and 600 mg/dL, and fasting LDL-cholesterol levels below 130 mg/dL. Although both agents provided equivalent glycemic control, results regarding lipid parameters were markedly different. With pioglitazone, fasting triglyceride levels decreased from baseline by 51.9 mg/dL (12 percent) as compared with a 13.1 mg/dL (14.9 percent) increase from baseline with rosiglitazone ($P<0.001$). Both agents increased HDL-cholesterol, although the increase was greater for pioglitazone (5.2 mg/dL) as compared with rosiglitazone (2.4 mg/dL)($P<0.001$).

Non-HDL cholesterol levels also differed. Rosiglitazone-treated patients experienced a significant increase in non-HDL cholesterol of 25.7 mg/dL from baseline to the end of treatment, whereas the increase in non-HDL cholesterol was 3.6 mg/dL for patients treated with pioglitazone ($P<0.001$). The difference in LDL-cholesterol was significant too, with a 21.3 mg/dL (23.3 percent) increase in LDL-cholesterol with rosiglitazone, and a 12.3 mg/dL (15.7 percent) increase with pioglitazone ($P<0.001$) (Goldberg 2005).

It is clear that important distinctions exist between drugs in the same class that can influence physician drug choice. The CHF associated with thiazolidinediones seems to be a class effect specific to actions of PPARγ on a renal sodium receptor; CHF is typically clinically mild and does not result in excess cardiac mortality. However, differences between agents in lipid effects and with regard to macrovascular outcomes may be related to properties of specific agents within the class.

A novel treatment approach may focus on treating the pathophysiology of diabetes, namely, treating both insulin resistance and β-cell dysfunction. Table 3 prioritizes goals of dia-

FIGURE 3
Kaplan-Meier plot showing reduced survival among diabetic heart failure patients relative to non-diabetic heart failure patients



Source: Varela-Roman A, et al. Influence of diabetes on the survival of patients hospitalized with heart failure: a 12-year study. *Eur. J. Heart Failure*. 2005;7:859–864.

betes treatment according to this approach. To utilize this idea, physicians must match the characteristics of a particular drug or therapy to specific patient characteristics such as preexisting cardiovascular compromise, CHF, renal or hepatic compromise, advanced age, obesity, and whether the patient is symptomatic. Clinicians also need to evaluate patient characteristics that would make the potential for hypoglycemia particularly threatening.

We will briefly consider a number of drugs and the patients for whom they may be appropriate (see figure 4 and table 4). Metformin improves hepatic insulin resistance. It is clearly effective at enhancing glycemic control. Potential gastrointestinal side effects necessitate gradual dose increase for maximal effectiveness. Metformin is not appropriate for patients with underlying renal disease because of the threat of lactic acidosis.

Thiazolidinediones act via the PPARγ receptor. They decrease insulin resistance in the periphery and in the liver, resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Insulin action is enhanced, leading to a reduction in insulin secretion. Consequently, serum glucose is reduced due to increased peripheral glucose utilization and decreased hepatic glucose production. β-cell function is enhanced as well. As outlined above, both pioglitazone and rosiglitazone are comparable with respect to glycemic effectiveness but clear differences exist with regard to changes in lipid parameters and cardiovascular safety. Data from the PROactive trial suggests that pioglitazone may reduce macrovascular events. Thiazolidinediones are safe for patients with renal insufficiency, hypoglycemia is not an issue, and glycemic benefits are durable over time.

Incretin mimetics are another class of agents for treating diabetes. Animal studies demonstrate that these drugs act to improve β-cell function. Both the GLP-1 analog, exenatide, and the DPP-4 inhibitor, sitagliptin, improve glucose-dependent insulin secretion and suppress glucagon release. Sitagliptin is not associated with nausea or other gastrointestinal side effects, and patients usually experience no weight loss or gain. On the other hand, exenatide use may be complicated by nausea, the result of a central satiety effect. Patients who continue with exenatide typically lose weight.

The insulin secretagogues — sulfonylureas and glinides — were discussed earlier. They act rapidly to lower glucose by driving insulin release. Hypoglycemia may occur with these agents, and weight gain is common. The α-glucosidase inhibitors delay absorption of glucose from the duodenum to farther along in the intestines, and represent an effective way to decrease postprandial glucose levels. However, side effects are considerable and include bloating and diarrhea. Nevertheless, among certain populations, such as patients in nursing homes who are typically constipated, increased gastrointestinal motility could represent a potential benefit of therapy.

The current treatment paradigm is too simple; a single algorithm cannot possibly take into account the many different and evolving patient- and drug-related factors that impact treating the pathophysiologic defects in diabetes. Some consider the current treatment approach as offering "too little, too late." The interval between initiating a treatment, evaluating it, and possibly changing dose or adding another agent needs to be shortened. By treating aggressively, physicians can safely help patients achieve optimal glycemic control while diminishing insulin resistance and preserving β-cell function. In this way, the development of complications can be delayed or even pre-

TABLE 3
A novel approach to diabetes treatment

Goals of therapy

- Reduce HbA_{1c} levels as low as possible without undue hypoglycemia
- Select agents that will aid weight loss, or at least result in no weight gain
- Consider potential cardiovascular benefits of any agents
- Utilize agents with the potential to preserve β-cell function
- Employ combination therapy to address multiple pathophysiologic defects
- Minimize potential side effects

TABLE 4
Pathophysiologic basis for combination therapy of type 2 diabetes

- Diminish insulin resistance
  - Weight redistribution: thiazolidinediones
  - Weight loss: diet; exercise
  - Hepatic insulin resistance: metformin decreases hepatic glucose production
- Minimize β-cell dysfunction
  - Potentiate insulin release: incretins; secretagogues
  - Decrease insulin demand: thiazolidinediones, metformin, α-glucosidase inhibitors
  - Stimulate new β-cells: incretins; thiazolidinediones
- Replace insulin (when endogenous production is inadequate)
- Prevent, delay or reverse long-term complications
  - Treat hypertension, dyslipidemia, dysfibrinolysis, endothelial dysfunction, pro-inflammatory state; encourage smoking cessation

FIGURE 4

Type 2 diabetes mellitus treatment guide

Created for the University of Pennsylvania Diabetes Disease Management Program by Stanley Schwartz, MD, under the auspices of David Horowitz, MD.

Pathophysiologic approach to hyperglycemia

Principles of Guideline		
	1. Consider therapies for prevention	5. Don't forget diet, exercise, and no smoking
	2. Early therapy, even with IFG, IGT	6. Combination frequently required
	3. Fast therapeutic changes (2–4 weeks)	7. When using insulin, use with insulin sensitizing agent, if possible
	4. Avoid hypoglycemia	

Asymptomatic — **Symptomatic**

Prevention — **IGT** — **Diabetes** — **Diabetes Out of Control**

5.6 → 8.5 ← A1C → 12.0

Monotherapy metformin, pilglitazone, or incretin (or secretagogue)	Combination therapy 2 of 4 or 3 of 4 — metformin, pioglitazone, incretin (secretagogue)
	Insulin any point in time, but with any/all (met, pio, incretin)

Diet and exercise

Choices based on matching drug and patient characteristics

	Metformin	TZD-Pioglitazone	Incretin Exenatide/DPP4-I	Secretagogue SUs | Glinides Repag | netag
Practical				
Speed of action	Slow	Slow	Fast	Fast
FBS-PPG	FBS	FBS-PPG	PPG/FBS-PPG	FBS-PPG | FBS-PPG | PPG
Goals-Priorities				
No hypoglycemia	✓	✓	✓	
CV benefit	✓	✓		
Weight	↓ Neutral ↑	↑	↓ /Neutral	↑
β-Cell preservation	Unknown	✓	✓	No (increased apoptosis)
Special populations				
Elderly	?> age 70, not > age 80	Use	Use	Carefully, ideally avoid
Renal disease (RD)	Not if Cr>1.4 F, 1.5 M	Use	OK mild RD/USE, ↓ dose	Carefully, ideally avoid
Edema	Use	Carefully	Use	Use
CHF (class 3,4)	Can use	Not	Use	

*This table was constructed based on the clinical experience and expert opinions of physicians who participated in the Consenus Panel (July 2007).
IFG = impaired fasting glucose IGT = impaired glucose tolerance FBS = fasting blood sugar PPG = Postprandial glucose

vented. Better yet, the natural history of diabetes may be altered. For this to occur, however, clinical decision making must become more dynamic and fluid, with rapid, real-time responses that include changing therapy or adding agents to achieve the goals listed in table 3.

IMPACT TO MANAGED CARE: IT'S NOT ALL ABOUT DRUG COSTS

Traditionally, managed care organizations have focused primarily on drug costs in analyzing treatment choices. However, with a disease such as diabetes, which is commonly only one component in a constellation of pathologic conditions, an economic analysis must be broader and more wide ranging. Numerous factors are involved in evaluating the true costs of a disease, including expenditures for treating complications of the disease itself and for the side effects of treatment. Sophisticated analyses go beyond cost per pill and should include an examination of the potential costs/benefits to using multiple drugs or more expensive unit-cost agents, given an understanding that benefits accrue not only to enhanced glycemic control but to improvements in blood pressure, weight, and lipids. The economic impact of preventing complications — for example, a potential reduction in macrovascular events or forestalling the onset of renal failure necessitating dialysis — could be significant. Furthermore, such investigations should likely include the costs due to side effects of treatment. Some, such as the edema and mild CHF seen with thiazolidinediones, may be minimal, especially with adequate provider education to mitigate their impact. However, the potential costs of others, such as hypoglycemia associated with insulin use, may be significant.

Representing a new perspective in managed care, value-based insurance design seeks to eliminate or minimize barriers to treatment for certain chronic diseases, recognizing that such barriers ultimately increase costs and worsen patient outcomes. For some plans, this may mean discontinuing co-payments for high-value medications and/or physician appointments. The objective is to optimize disease management, with the goal of interrupting the typical path of disease progression. Several large employers, such as Proctor & Gamble and the University of Michigan, have implemented such a program with success (*New York Times* 2007). However, employer groups or businesses that contract with managed care organizations may not appreciate the long-term benefit inherent in this approach. A conflict may arise as they are responsible for the immediate expenditure to provide coverage, yet the time frame of their responsibility to individual subscribers is uncertain. Employer groups, managed care organizations, and health care providers all need motivation to treat aggressively. To encourage such an approach, the short-term payoff of intensive treatment of the pathophysiology of diabetes with regard to potential minimization of cardiovascular outcomes and the advantages of β-cell preservation should be convincingly demonstrated.

One can logically argue that early and aggressive treatment of type 2 diabetes using combination therapy, with the goals of achieving improvements in blood pressure and dyslipidemia, decreasing insulin resistance, and enhancing β-cell function while providing excellent glycemic control, will improve patient outcomes and minimize the impact of macro- and microvascular complications, thereby decreasing the economic implications of caring for people with diabetes. To more rigorously examine this premise statistical models such as CORE can be employed. Modeling is especially useful for patient segmentation, to identify populations for whom a specific drug or intervention is likely to have the most impact. CORE is a peer-reviewed, validated diabetes model that takes into account baseline characteristics, past history of complications, current and future diabetes management, and concomitant medications (Palmer 2004, Palmer 2004). CORE utilizes simple, widely used mathematics and is based on submodels that simulate important complications of diabetes. Country-specific costs can be incorporated to calculate the development of complications, life expectancy, quality-adjusted life-years, total costs to a population, and cost-effectiveness. CORE is internet-based and includes a variety of user-defined and standard values. It represents a useful tool for evaluating potential outcomes and the budgetary impact of different diabetes treatments. Several leading managed care organizations, including Premera Blue Cross/Blue Shield and Humana, have utilized CORE models as one component of their decision-making processes. To test the impact of some of the approaches described in this paper, a CORE analysis could be performed to include costs of agents in combination therapy and expenditures due to management of drug side effects. It would also take into account savings accrued as a consequence of prevention of myocardial infarction and stroke.

Changing the focus of health care from treating disease to a wellness model is a radical departure from current thinking. However, for chronic diseases characterized by numerous complications and associated conditions that amplify disease effects, worsen outcomes, and vastly increase health care-related expenditures, such a change may be necessary. As the pathophysiology of diabetes becomes better understood, and novel therapeutic approaches target different defects, an argument can be made for early, effective treatment to preserve β-cell function, diminish insulin resistance, and improve dyslipidemia and hypertension, ultimately

decreasing macrovascular events and long-term associated costs.

CONCLUSIONS

The clinical and economic ramifications of the growing diabetes epidemic are staggering. Limitations of current management strategies are evident as only limited numbers of patients achieve glycemic goals, and other manifestations of disease, most notably macrovascular events, exact a huge toll, both financially and on a human level. Recent advances in our understanding of the pathophysiology of diabetes coupled with the introduction of novel therapeutic agents allow us to challenge existing ideas about approaches to treatment. For many patients, dedication to lifestyle changes and aggressive, early combination therapy to address β-cell compromise and insulin resistance will ultimately offer a way to improve outcomes. To effect widespread change, however, we expect that managed care organizations will need to modify their vision and policies. Rather than focusing on drug costs per se, an orientation toward wellness, including goals of minimizing complications and maximizing functionality and health, is appropriate. Value-based insurance design looks toward an approach of optimizing disease management through a variety of strategies. Although these ideas need to be evaluated through models and ultimately tested in real-world populations, it appears that good medical practice will result in better outcomes overall, both for individual patients with regard to long-term health consequences and for managed care organizations based on economic impact.

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