Emerging Perspectives on Type 2 Diabetes

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Roseman received his BA in sociology, specializing in social and political philosophy, from the University of Pennsylvania, his medical degree from the University of Tennessee, and his master of public health degree, specializing in epidemiology of cardiovascular diseases, from Yale University School of Medicine. He completed his cardiology fellowship and postfellowship training at Brown University and at Massachusetts General Hospital, Boston.

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3. Describe all drugs by generic name unless the use of the brand name is necessary to reduce the opportunity for confusion among readers.

4. Strive to report subjects of current interest to managed care pharmacists and other managed care professionals.

5. Seek and publish content that does not duplicate content in the *Journal of Managed Care Pharmacy*.

6. Subject all supplements to expert peer review.
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Target Audience
Managed care pharmacists, clinical pharmacists, pharmacy directors, and medical directors responsible for reviewing and implementing treatment strategies for people with type 2 diabetes in the managed care setting

Learning Objectives
Upon completion of this program, participants will be able to
1. describe opportunities and challenges to improving the overall care of individuals with type 2 diabetes as well as those at high risk for developing this disease;
2. outline the key pathophysiologic features in the development of type 2 diabetes and its complications, including the central role of metabolic syndrome;
3. discuss the latest clinical research surrounding the effective management of prediabetes and type 2 diabetes;
4. summarize the importance of achieving tight glycemic control as a means of averting diabetes-related complications and reducing managed care costs;
5. describe cost models that estimate the economic impact of diabetes-related complications and the cost savings that may be accrued by interventions that reduce the risks for these complications; and
6. discuss a case study of a health care organization's successful diabetes management program and outline the key features and achievements of this program.

This supplement was funded by an unrestricted educational grant from GlaxoSmithKline and sponsored by StrategiCare, Inc. and The GMR Group. Articles in this supplement are based on the proceedings of a symposium, “Emerging Perspective in Type 2 Diabetes: Understanding the Influence of Metabolic Syndrome,” held on March 31, 2004, in San Francisco, California, which was supported by an unrestricted educational grant from GlaxoSmithKline and sponsored by StrategiCare, Inc. and The GMR Group.

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Progression From Obesity to Type 2 Diabetes: Lipotoxicity, Glucotoxicity, and Implications for Management

HAL M. ROSEMAN, MD, MPH, FACC, FACP

ABSTRACT

OBJECTIVE: To examine the roles of lipotoxicity and glucotoxicity as critical pathogenic foundations in the development of type 2 diabetes and the potential benefits of thiazolidinediones (TZDs) in ameliorating these processes.

SUMMARY: Type 2 diabetes represents the failure of the pancreas to maintain adequate insulin secretion in response to insulin resistance, which causes impedance to glucose membrane transport. The lipotoxicity, seen in insulin resistance and the metabolic syndrome and characterized by ectopic fat storage in skeletal muscle, the pancreas, and the liver, can cause adverse effects on the endothelium and thus lead to cardiovascular disease, independent of conversion to diabetes. Once diabetes develops, the resultant hyperglycemia leads to glucotoxicity, which in concert with lipotoxicity accounts for the microvascular and macrovascular complications seen in type 2 diabetes. Accumulating evidence suggests that TZDs may blunt the lipotoxicity and glucotoxicity that underlie insulin resistance and type 2 diabetes and that early treatment may provide important therapeutic benefits.

CONCLUSIONS: The lipotoxicity of insulin resistance and the glucotoxicity resulting from pancreatic β-cell failure act synergistically to effect the clinical manifestations and complications of type 2 diabetes. Early treatment with agents that dampen both of these deleterious processes may delay or prevent the onset of type 2 diabetes in high-risk individuals and reduce the risks for microvascular and macrovascular complications in those already diagnosed with type 2 diabetes.

KEYWORDS: Lipotoxicity, Glucotoxicity, Free fatty acids, Hyperglycemia, Type 2 diabetes, TZDs, Obesity

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From Obesity to Metabolic Syndrome to Diabetes

As a result of overnutrition, sedentary lifestyle, and genetic factors, obesity, a primary driver in the development of type 2 diabetes, has increased to epidemic proportions. According to the 1999-2000 National Health and Nutrition Examination Survey (NHANES), obesity, defined as a body mass index (BMI) of ≥ 30 kg/m², describes 31% of the adult population, a disconcerting increase of 16% since 1980. During the same period, extreme obesity (BMI ≥ 40 kg/m²) also has increased substantially, from 2.9% to 4.7%.7

Obesity contributes to the development of a physiological complex called metabolic syndrome, which, according to the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III), is identified by the presence of 3 of the 5 conditions shown in Table 1.9

Overall, metabolic syndrome has been estimated to affect an alarming 22% of the adults in the United States, with prevalence highest, at 40%, in individuals over age 60.10 Approximately one third of overweight or obese individuals in the United States have metabolic syndrome, according to the NHANES III.10 Insulin resistance, a central component of metabolic syndrome, evolves out of the milieu of obesity with central truncal distribution, sedentary lifestyle, and genetic influences. Although metabolic syndrome is a cluster of phenotypic cardiovascular risk factors designed to identify insulin resistance, and the ATP III criteria for metabolic syndrome have proven to be reasonably specific for predicting insulin resistance, this definition may miss insulin resistance in nearly half of obese patients.11 However, metabolic syndrome does confer significant cardiovascular risk independent of conversion to diabetes, presumably through the cluster of multiple risk factors that alter endothelial cell function.11

Free Fatty Acids and Development of Lipotoxicity

How do FFAs facilitate the development of type 2 diabetes from metabolic syndrome? A new paradigm for the pathogenesis of diabetes highlights FFA excess as a central physiological feature in type 2 diabetes and related comorbidities such as dyslipidemia and cardiovascular disease.

The present discussion of the impact of FFAs in the development of diabetes and its atherosclerotic complications will center on (1) the effect of insulin resistance and FFAs on endothelial dysfunction and atherogenesis, (2) the impact of lipotoxicity on pancreatic β-cell function and survivability, and (3) the role of FFAs on metabolic dyslipidemia.

Insulin Resistance and Development of Atherosclerosis Through Endothelial Dysfunction

FFA excess has been closely associated with insulin resistance.14 In individuals with sedentary lifestyles and high fat and carbohydrate diets, fat is stored initially in a genetically determined number of fat cells. Once these have been saturated, fat is stored within organs such as the heart, skeletal muscle, and pancreas, among others. Adipocytes within organs are not biologically inert, however. Instead, they synthesize a wide range of hormones, called adipokines, that promote the formation of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and C-reactive protein (from the liver through interleukin-6 influence) and release FFAs into the circulation.15,16 The excess FFAs and TNF-α, together, can impair normal insulin signal transduction within the cell and inhibit the expression of glucose transporter (GLUT) 4 protein, the major glucose transporter in peripheral tissue.14,17 The pancreas responds to the resultant insulin resistance by increasing insulin production. As long as the pancreas is able to maintain adequate levels, plasma glucose levels remain normal and the clinical state of diabetes dormant.

The biological effects of insulin are normally mediated through 2 pathways within the cell: the mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K). The PI3K pathway is responsible for the anabolic effects of insulin, including glucose transport, adipogenesis, protein synthesis, glycogen synthesis, and anti-apoptosis. On the other hand, the MAPK pathway promotes growth differentiation, apoptosis, and inflammation. From a vascular standpoint, the PI3K pathway expresses anti-atherosclerotic effects, whereas the MAPK pathway is proatherosclerotic. In individuals with insulin resistance, activation of the PI3K pathway is impaired, thus favoring the MAPK proatherosclerotic pathway.17,18

Normally, in the PI3K pathway, insulin activates receptors on the cell surface that, in turn, generate a cascade of intracellular signals causing the movement of vesicles containing GLUT 4 proteins to the plasma membrane, the subsequent fusion of the vesicles to the membrane, and, finally, glucose entry via active transport.19 FFAs, in conjunction with proinflammatory mediators such as TNF-α, can interrupt this process by impairing GLUT 4 gene expression and triggering the serine phosphorylation of certain critical components of the insulin signaling cascade, contributing to insulin resistance in the PI3K pathway and preferential activation of the MAPK pathway.20,21

Indeed, in individuals with insulin resistance, insulin-preferential stimulation of the MAPK pathway yields enhanced vascular...
smooth muscle cell migration and growth; platelet aggregation and decreased thrombolysis, in part related to increases in plasminogen activator inhibitor-1 (PAI-1); and vasoconstriction secondary to elevation in endothelin-1. Together, these physiological actions on the endothelium can elevate the risk for cardiovascular disease in individuals with insulin resistance even before the onset of type 2 diabetes.23

Metabolic syndrome has now been identified as being an independent risk factor conferring significant cardiovascular mortality and morbidity. In a recent reexamination of the NHANES II, cardiovascular risk and mortality increased linearly with the addition of each component of metabolic syndrome defined by the ATP III criteria.24,25 Using the World Health Organization criteria for metabolic syndrome, another study of the Finnish and Swedish populations found that metabolic syndrome conferred a 3-fold increase in risk for cardiovascular mortality.26

**Free Fatty Acids and Development of Type 2 Diabetes Through Pancreatic β-Cell Failure**

Type 2 diabetes follows the loss of β-cell function. In the pancreas, elevated FFA levels can induce β-cell apoptosis by stimulating the production of inducible nitric oxide, which is cytotoxic to β-cells (Figure 1).21,22 In transgenic animal models replicating the human diabetic experience, FFAs rise well before the onset of diabetes and eventually infiltrate the pancreatic β-cells.27

Even in the presence of insulin resistance, the pancreas remains relatively sensitive to insulin, permitting the entry of excess glucose and FFAs. The resulting FFA excess in the pancreas induces lipotoxicity that triggers β-cell death and reduced insulin production.24 In response to the reduced availability of glucose, FFA levels rise to maintain an adequate fuel source. In turn, the liver converts FFAs through gluconeogenesis, amplifying glucose production and release into the circulation. In the United Kingdom Prospective Diabetes Study (UKPDS), it was estimated that, at the time of diabetes, at least 50% of the pancreatic β-cells are no longer functional.29 Hyperglycemia follows, as glucose levels increase through hepatic gluconeogenesis from the continued influx of FFAs to the liver and insulin production diminishes with the decline in pancreatic β-cell function.

**Free Fatty Acids and Development of Dyslipidemia**

In individuals with metabolic syndrome, the most common dyslipidemia is characterized by high levels of triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), and a shift in the size of the LDL-C particles and HDL-C particles. The transformed small dense LDL-C particles are thought to be atherogenic.31 The mechanisms that contribute to these changes have been identified partially30,31 and are illustrated in Figure 2. These effects are directly related to the availability of FFA substrate to the liver.

In the state of insulin resistance, lipoprotein lipase (LpL), which hydrolyzes triglycerides from very-low-density lipoprotein cholesterol (VLDL-C) and LDL-C particles, is inhibited, and, therefore, triglyceride-rich lipoproteins are increased. Under the influence of hormone-sensitive lipase, whose activity is increased in insulin-resistant states, triglyceride stores in the adipocytes are released as FFAs into the circulation and exported to the liver. Under the influence of hepatic lipase, the liver packages the FFAs into the triglyceride-rich particles known as VLDL-C particles. In turn, under the influence of cholesterol transport protein (CETP), the VLDL-C particles exchange triglyceride for cholesterol with
Glucotoxicity and Development of Diabetic Cardiovascular Disease

With the onset of diabetes, multiple vascular endothelial insults, along with associated hypertension and dyslipidemia, trigger devastating complications, most notably cardiovascular disease, which account for the majority of deaths in diabetic individuals. Indeed, in individuals with diabetes, the risk for fatal and nonfatal myocardial infarction is on a par with the risk in nondiabetic individuals who have preexisting coronary artery disease. In addition, hyperglycemia has been proven to increase both microvascular and macrovascular complications, as in the Finnish Study, the Strong Heart Project, the UKPDS, and the Honolulu Heart Program.

Because of its antithrombotic, anti-inflammatory, and antioxidative properties, nitric oxide plays a pivotal role in maintaining normal endothelial functioning. FFAs, through multiple routes, trigger the production of free radicals that blunt the beneficial effects of nitric oxide, disrupting normal endothelial function and increasing the risk for thrombus formation.

With progression to hyperglycemia, the defining hallmark of diabetes, another insult is added to the vasculature. The presence of hyperglycemia accounts for the major clinical signs and symptoms of uncontrolled diabetes: polyuria and glucosuria (frequent urination to excrete excess glucose in the urine to avoid glucotoxicity), hyperphagia (overeating to compensate for the excess calories lost through glucosuria), and weight loss (a consequence of the calorie loss through urinary excretion of glucose). The added insult of glucotoxicity exerts some of its deleterious effects via multiple mechanisms. This discussion will be limited to a brief review of how the metabolic pathways are exaggerated in diabetes.

Elevated blood glucose levels exert myriad biochemical actions that impair endothelial function. Hyperglycemia, itself, can trigger abnormal glucose metabolism. In the presence of hyperglycemia, insulin resistance dampens glucose utilization in tissue that requires insulin for glucose uptake. Yet, tissue where glucose transport is not regulated solely by insulin, such as contracting skeletal muscle cells, can experience hyperglycemia. Because the normal glucose metabolic pathways become saturated in these cells, the polyol metabolic pathway activates, transforming excess glucose into sorbitol through the action of the enzyme aldose reductase. Normally, sorbitol levels are minimal; however, in individuals with type 2 diabetes, 30% to 35% of the glucose can be transformed to sorbitol. Activation of the polyol pathway and the oxidative stress secondary to sorbitol accumulation has been proposed as one mechanism underlying the development of the complications secondary to type 2 diabetes, chiefly nephropathy, neuropathy, and cataracts. Interestingly, nitric oxide may down-regulate the activity of aldose reductase; thus, interventions that elevate nitric oxide levels may alleviate some of the oxidative stress that spawns diabetes-related complications.

Moreover, hyperglycemia elevates the synthesis of diacylglycerol, which, in turn, activates protein kinase C, further damping nitric oxide production and enhancing the formation of the vasoconstrictive protein endothelin-1 and endothelial growth factors, such as vascular endothelial growth factor, epidermal growth factor, and transforming growth factor (TGF-β). Acting in concert, these
proteins contribute to thrombus formation and atherosclerosis in hyperglycemic individuals.

In addition, the formation of advanced glycation end products (AGEs) secondary to hyperglycemia has been implicated in tissue damage.46 Unstable, toxic, reactive compounds, AGEs result from the reaction between carbohydrates and the free amino group of proteins.47 In individuals with diabetes mellitus, AGEs accumulate faster than normal in the arteries and in the circulation, accelerating endothelial dysfunction and triggering increased lipid deposition and inflammation that, in turn, enhance the risk for renal failure, nephropathy, and cardiovascular disease.48-50 In addition, in the endothelium, AGEs suppress nitric oxide and activate receptors for proinflammatory cytokines, such as TNF-α, and growth factors that promote the migration and proliferation of smooth muscle cells.46 AGEs also increase vascular permeability, permitting the transmigration of macrophages and the focal deposition of lipid-rich foam cells, a central morphologic feature of atherosclerosis. The mechanism by which AGEs interact with the vessel wall is shown schematically in Figure 3.

### Impact of Thiazolidinediones

These data, together, imply that the pathogenesis of insulin resistance and type 2 diabetes and its sequelae can best be characterized by the presence of excess FFAs with resulting lipotoxicity, as well as the presence of glucotoxicity. Blunting these pathogenic features should be a principal goal of treatments for type 2 diabetes. Thiazolidinediones (TZDs) offer an opportunity to impact on both of these conditions.

All of the 4 major treatments for type 2 diabetes—insulin sensitizers, α-glucosidase inhibitors, secretagogues, and insulin—can diminish plasma glucose levels, but the insulin sensitizers, such as the TZDs, offer the added potential benefits of preserving β-cell function and reducing the risks for cardiovascular complications.50 By activating a nuclear receptor, TZDs can simultaneously exert multiple biological effects that have proven to impact positively on every aspect of the atherosclerotic process: cellular movement, coagulation, immunological reactivity, lipid metabolism, and endothelial utilization.51-53

In addition, the TZDs stand apart from other treatment options for type 2 diabetes by offering perhaps the best opportunity to enhance glucose uptake and reduce FFA levels. (Note: Although troglitazone (Rezulin) was taken off the market in 2000 because of potential hepatic toxicity, troglitazone has been used in multiple laboratory and clinical trials to demonstrate the PPAR-γ effects of the TZD class. It should be noted that a class effect has not been established for the TZDs. Therefore, generalized assumptions for the TZDs should not necessarily be derived from the studies involving troglitazone.) Normally expressed in adipose tissue, peroxisome proliferator-activated receptor-gamma (PPAR-γ) may play a central role in regulating triglyceride levels, blood glucose homeostasis, and insulin resistance.54

### Table 2: TZDs: Free Fatty Acid Effects

<table>
<thead>
<tr>
<th>TZD</th>
<th>Decrease From Baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troglitazone*</td>
<td>42*</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>38*</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>15-23*</td>
</tr>
</tbody>
</table>

* Troglitazone was removed from the market on March 21, 2000, because of hepatotoxicity. TZD = Thiazolidinedione.


TZDs may also preserve β-cell function in individuals with insulin resistance, thus delaying disease progression to frank
diabetes. A placebo-controlled, randomized, 3-month study in 266 Hispanic women with previous gestational diabetes examined the relationship between preservation of β-cell function and attenuation of insulin resistance with the use of troglitazone. In this high-risk population, troglitazone treatment was shown to delay or prevent the onset of type 2 diabetes presumably by preserving β-cell function, perhaps by reducing the demands on β-cells resulting from chronic insulin resistance. One explanation for how TZDs reverse insulin resistance is by blocking TNF-α-mediated inhibition of the insulin pathways and enhancing adiponectin, an adipokine intimately related to insulin-glucose metabolism.

**Effect of TZDs on Endothelial Function and Atherosclerosis**

Endothelial dysfunction occurs when the endothelium is too compromised to produce sufficient levels of nitric acid to maintain homeostatic vascular health. Nitric oxide can be neutralized by free radicals or reactant oxygen species or by a newly found endogenous inhibitor of endothelial nitric oxide synthetase, asymmetric dimethylarginine (ADMA). It is now well recognized that many of the known cardiovascular risk factors, including insulin resistance, diabetes, hyperlipidemia, and hypertension, are associated with elevations of ADMA level and, in turn, disruptions in endothelial cell function. Possibly, ADMA explains the common links of these seemingly disparate risk factors and their similar adverse effects on the endothelium. Rosiglitazone is the first pharmacological agent demonstrated to lower ADMA levels. In a nonrandomized trial that included 64 subjects, 7 with insulin resistance and hypertension, a significant relationship emerged between insulin resistance and plasma levels of ADMA, with rosiglitazone treatment leading to improved insulin resistance and diminished ADMA levels.

The demonstration of endothelial benefits of TZDs has been broadening. In a recent nondiabetic rat hypertensive model, TZDs were demonstrated to reverse the adverse vessel remodeling effects of hypertension. This finding was confirmed in human type 2 diabetic subjects, many without hypertension, in whom rosiglitazone was demonstrated to improve small artery elasticity.

Carotid intimal-media thickness, a known cardiovascular risk factor and surrogate marker of endothelial dysfunction, has been reversed with pioglitazone and troglitazone treatment in subjects with type 2 diabetes and with rosiglitazone treatment in even nondiabetic coronary artery subjects.

Finally, TZDs apparently have a protective effect against all phases of the atherosclerotic process: decreasing immune cell response by decreasing adhesion molecules, such as monocytic chemotactic factors (MCP-1); promoting cholesterol efflux from the foam cells (similar to HDL-C); inhibiting smooth muscle cell proliferation; reducing the production of matrix metallic proteases (MMP-1); and inhibiting plasminogen activator inhibitor (PAI1) and reducing the thrombogenic potential of an atherosclerotic plaque.

TZDs have also been shown to improve the dyslipidemia of the metabolic syndrome and diabetes by reducing the available FFAs promoting the dyslipidemia and by direct beneficial effects on multiple processes involved in lipid metabolism.

Therefore, it is unsurprising that TZDs have been shown to prevent atherosclerosis in nondiabetic animal models. The mechanisms by which TZDs exert their favorable effects on the vasculature, as well as other nonhypoglycemic effects, have been well characterized as involving beneficial endothelial effects. This effect of TZDs has recently been proven in nondiabetic cardiac patients, where improvement of endothelial surrogate markers of inflammation was demonstrated.

**Summary and Conclusions**

In individuals destined to develop type 2 diabetes, glucotoxicity and lipotoxicity act in concert to disrupt normal endothelial cell function and accelerate the loss of β-cells in the pancreas. At the time of diagnosis, substantial β-cell loss has already occurred. An accumulating body of clinical evidence suggests not only that TZDs offer the potential of treating the critical pathophysiological mechanisms implicated in type 2 diabetes and its sequelae but also that these agents show promise as a means of preserving β-cell function and thus slowing the progression of insulin resistance to type 2 diabetes or the inevitable worsening of type 2 diabetes.

To rapidly achieve optimal glycemic control and stem the further erosion of functional β-cells in type 2 diabetes, early treatment with TZDs may be a clinically prudent course of action in many patients.

Because of their antiatherosclerotic effects, TZDs may be useful in the future as part of a general treatment algorithm, such as statins and angiotensin-blocking agents are today, to prevent diabetes, independent of their hypoglycemic effects.

**DISCLOSURES**

This article is based on the proceedings of a symposium, “Emerging Perspective in Type 2 Diabetes: Understanding the Influence of Metabolic Syndrome,” held on March 31, 2004, in San Francisco, California, which was supported by an unrestricted educational grant from GlaxoSmithKline (GSK) and sponsored by StrategiCare, Inc., and The GMR Group. The author received an honorarium from GSK, StrategiCare, Inc., and The GMR Group for participating in the symposium upon which this article is based. He is on the speakers bureau and advisory board of GSK. He discloses no potential bias or conflict of interest relating to this article.

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Progression from Obesity to Type 2 Diabetes: Lipotoxicity, Glucotoxicity, and Implications for Management

Progression from Obesity to Type 2 Diabetes: Lipotoxicity, Glucotoxicity, and Implications for Management


Patient Management Strategies in Type 2 Diabetes: Current Practices and Future Considerations

LAWRENCE BLONDE, MD, FACP, FACE

ABSTRACT

OBJECTIVE: To examine current issues in the management of people with type 2 diabetes, focusing on the need for early recognition, aggressive multifactorial therapy, and a systems approach to treatment in order to reduce the development and progression of the serious and costly complications of this disease.

SUMMARY: Affecting more than 6% of the population in the United States, type 2 diabetes and its complications have become a serious public health concern that exerts a substantial toll on the individuals affected, the entire health care system, and the economy, including employers. Clinical data suggest that early intervention can diminish the risk for developing diabetes in high-risk individuals with prediabetes. Further, improved glycemic control in individuals with diabetes substantially lowers the risk for microvascular complications, and evidence is increasing that it can also decrease macrovascular complications. To maintain long-term glycemic control and reductions in diabetes-related complications, people with diabetes require lifestyle measures, and many will also require combinations of antidiabetic medications and, often, additional treatments for coexisting hypertension and dyslipidemia. Unfortunately, the majority of individuals with type 2 diabetes have not achieved the optimal glucose, blood pressure, or lipid levels recommended by national guidelines. A more aggressive multifactorial approach to treatment is required to improve treatment outcomes for the increasing numbers of people with type 2 diabetes. The comprehensive team approach needed should include early recognition of at-risk individuals, use of risk-specific therapies, regular patient education, and consistent follow-up.

CONCLUSIONS: Despite a prevalence that has reached epidemic proportions, type 2 diabetes remains underdiagnosed and suboptimally controlled. A more aggressive multifactorial approach to treatment is required to improve treatment outcomes.

KEYWORDS: Type 2 diabetes, Thiazolidinediones, Combination therapy, Treatment paradigm

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In the United States, the prevalence of type 2 diabetes has reached epidemic proportions. Accounting for up to 95% of all cases of diabetes, type 2 diabetes now afflicts approximately 17.2 million individuals, an increase of about 40% in 10 years. Of this total, almost 30%, or 5.2 million individuals, remain undiagnosed, and, thus, untreated. Furthermore, the Centers for Disease Control and Prevention (CDC) currently estimates that 41 million adults in the United States have prediabetes, defined as the presence of impaired fasting glucose (fasting glucose levels of 100 mg/dL to 125 mg/dL) or impaired glucose tolerance (glucose levels of 140 mg/dL to 199 mg/dL 2 hours after the ingestion of a 75-gram oral glucose load). Absent effective intervention, the majority of individuals with prediabetes will develop diabetes within 10 years. Based on current, but modifiable, trends, the lifetime risk for developing diabetes for an American born in the year 2000 has been estimated at close to 33% for men and 39% for women, and an astounding 53% for Latina/Hispanic women.

Type 2 diabetes has been clearly linked to an elevated risk for both microvascular and macrovascular complications. In fact, individuals with type 2 diabetes have the same elevated risk for a myocardial infarction (MI) as nondiabetic individuals who already have a history of MI. In addition, the presence of diabetes substantially increases the risk for mortality after an MI. According to 2002 estimates, if diagnosed at age 40, diabetes results in 11.6 life-years lost for men and 14.3 for women. Moreover, with at least $132 billion in direct ($92 billion) and indirect ($40 billion) costs, diabetes-related morbidity and mortality impose a substantial economic burden. Importantly, of the nearly $92 billion in direct medical costs, almost 75% can be accounted for by the costs associated with diabetes-related complications and the excess prevalence of other medical conditions in patients with diabetes. Yet, pharmacologic treatment of diabetes patients accounted for only 13% of the total direct medical costs. Lost work days, restricted activity days, permanent disability, and excess mortality account for the almost $40 billion in indirect costs associated with diabetes. In one study of a managed care organization, the average yearly cost for each patient with diabetes was high, at about $11,000, but antihyperglycemic prescriptions accounted for only about 5% of that total ($561)—markedly less than the prescription costs for the treatment of diabetes-related comorbidities ($1,267), implying that antihyperglycemic agents that can reduce the risks for expensive, long-term diabetes-related complications are perhaps underutilized in the managed care setting.

The personal health, family, employment, and other economic consequences associated with type 2 diabetes underscore the
importance of early diagnosis and primary prevention as key public health policies in stemming the growing diabetes epidemic and blunting its cost burden. To accelerate the identification and treatment of individuals with prediabetes and diabetes, the U.S. Department of Health and Human Services developed the Diabetes Detection Initiative (DDI). Targeted toward clinicians and the public, this pilot program uses education and outreach to accelerate the identification and treatment of individuals with prediabetes or undiagnosed diabetes. In addition, the National Diabetes Education Program, a joint venture of the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) and CDC, has launched a national diabetes prevention campaign, “Small Steps, Big Rewards,” to attempt to prevent or at least delay the development of diabetes in high-risk groups. The broad array of patient information available, such as diabetes fact sheets, preventive tip sheets, calorie and fat counters, and activity trackers, can be easily downloaded and provide useful educational tools for people with or at risk for prediabetes.

Without intervention, most of these individuals with prediabetes are destined to develop type 2 diabetes. However, the Diabetes Prevention Program (DPP) trial demonstrated that we can at least delay, if not prevent, the progression from prediabetes to type 2 diabetes. In this study, 3,234 nondiabetic individuals with elevated fasting glucose and postload plasma glucose concentrations were assigned to 1 of 3 treatments: lifestyle modification with goals of at least 7% weight loss and 150 minutes of exercise per week, metformin 850 mg twice daily, or placebo. After a mean 2.8 years of treatment, the incidence of diabetes declined by 58% and 31%, respectively, with lifestyle modification and metformin treatment, when compared with placebo. In this study, lifestyle modification produced a significantly greater protective effect than metformin treatment alone. Yet, for subjects with a body mass index of at least 35 kg/m² or those aged 25 to 45 years, metformin and intensive lifestyle modification were similarly effective in diminishing the risk for diabetes. Some DPP subjects also received troglitazone therapy alone for about 11 months before this treatment was prematurely terminated because of the emergence of hepatic dysfunction. During the mean 0.9 year (range, 0.5 to 1.5 years), there were 3 cases/100 person-years, compared with 12, 6.7, and 5.1 cases/100 person-years in the placebo, metformin, and intensive lifestyle participants, respectively (P < 0.001, troglitazone vs. placebo; P = 0.02, troglitazone vs. metformin; P = 0.18, troglitazone vs. ILS [intensive lifestyle intervention]).

In the Troglitazone in Prevention of Diabetes (TRIPOD) study, the investigators randomly assigned 266 Latina women who had previous gestational diabetes, and who were thus at high risk for subsequent type 2 diabetes, to treatment with troglitazone 400 mg/day or placebo. All subjects received dietary advice and were instructed to walk for 30 minutes 3 times weekly. Fasting plasma glucose was measured trimonthly, and oral glucose tolerance tests were performed yearly. The average yearly incidence of diabetes for women who returned for follow-up (average yearly dropout rates were about 15%) was 12.1% during a 20-year follow-up and 5.4% for the placebo and troglitazone groups, respectively (Figure 1).

By the study’s end, type 2 diabetes had emerged in 53% and 19% of the placebo- and troglitazone-treated subjects, respectively, reflecting a robust relative risk reduction of 54% with troglitazone treatment. Is there evidence that treating prediabetes would reduce serious complications and improve overall outcomes? Data from the Nurses’ Health Study, which included more than 100,000 women who were monitored every 2 years since 1976, revealed a significant 2.82 relative increased risk for cardiovascular disease events, such as stroke and MI, in women destined to develop type 2 diabetes even before the diagnosis of diabetes, during a 20-year follow-up. Once people were diagnosed with diabetes, their relative risk increased to 3.71 compared with those who remained without diabetes during the entire study. This does suggest that preventing the progression from prediabetes to
Management Issues in Type 2 Diabetes

In type 2 diabetes, evidence suggests that optimal treatment should focus not only on ameliorating hyperglycemia but also on insulin resistance and its accompaniments as well.

Hyperglycemia

Results from the landmark United Kingdom Prospective Diabetes Study (UKPDS) revealed a significant and clear relationship between the risk for diabetes-related complications—among them MI, stroke, lower extremity amputation, and retinal photocoagulation—and hyperglycemia. In the epidemiologic analysis of this study, for every 1% decline in glycated hemoglobin (A1c) levels, there was a 21% reduction in the risk for complications generally, including a 21% reduction in diabetes-related mortality and a 14% reduction in the risk for MI and all-cause mortality.

In addition, improved glycemic control can produce substantial medical and employer cost benefits and improvements in patient-reported quality-of-life measures. In the UKPDS, the more intensive therapy cost an additional £695 per patient over the course of the study, but it decreased the cost of treating diabetes-related complications by £957 per patient. Testa and Simonson demonstrated that improved glycemic control could also improve short-term quality of life and worker productivity. In this double-blind, randomized, placebo-controlled trial involving 569 adults with type 2 diabetes, 12 weeks of treatment with the sulfonylurea glipizide GITS (gastrointestinal therapeutic system) was associated with a mean A1c decline of 1.8% versus placebo. This improved glycemia was associated with significant improvements in quality-of-life measures such as symptom distress, general perceived health, and cognitive function compared with the same measures in placebo-treated subjects. Furthermore, active treatment and the resulting improved glycemic control was associated with reduced absenteeism, restricted activity days, and bed days, resulting in estimated savings of $91 per worker per month, $1,615 per 1,000 person-days, and $304 per 1,000 person-days, respectively. These findings provide employers with an economic rationale for investing in strategies that result in improved glycemic control for their employees with type 2 diabetes.

Insulin Resistance

There may well be benefits to treatment of type 2 diabetes that specifically address insulin resistance. Insulin resistance has been shown to be an independent predictor not only of type 2 diabetes but also of cerebrovascular disease, hypertension, cancer, and coronary heart disease, with the risk for these diseases positively correlated with the magnitude of insulin resistance. In addition, insulin resistance is associated with excess body weight, dyslipidemia, and hypertension.

Treatment Approaches

Patient Education/Lifestyle Modification

Patient education and appropriate lifestyle measures remain indispensable first steps in the management of people with type 2 diabetes. Diabetes is a self-managed disease. Thus self-management education is essential in helping patients attain and maintain target glycemic levels. Appropriate self-management not only includes regular self-monitoring of blood glucose (SMBG) but also adherence to appropriate nutritional and physical activity recommendations. These lifestyle measures can be associated with improved glycemia. Yet, in the UKPDS only about 20% of type 2 diabetes subjects treated with diet modification and exercise alone were able to attain and maintain fasting plasma glucose values < 270 mg/dL. Of these, 80% required pharmacologic intervention with sulfonylureas or insulin to reach that level. Thus, for most patients with type 2 diabetes, lifestyle measures, although necessary, are not likely to be sufficient to reach target blood glucose levels.

Pharmacologic Treatment—Focus on Thiazolidinediones

Several classes of agents are now available to treat type 2 diabetes—insulin secretagogues, α-glucosidase inhibitors, biguanides, thiazolidinediones, and several forms of insulin. These agents have different and often complementary mechanisms of action.

In the UKPDS, a progressive worsening of glycemic control was associated with a decline of β-cell function over time. Studies in animals and preliminary studies in man suggest that thiazolidinediones may be associated with reduced β-cell apoptosis and preserved β-cell function. For example, a study administered rosiglitazone, glyburide, or metformin to genetically diabetic mice for 28 days. Only the rosiglitazone-treated mice demonstrated preservation of β-cell structure and insulin production.

Studies such as the UKPDS have clearly demonstrated that
improved glycemic control in patients with type 2 diabetes can reduce the risks for microvascular complications such as retinopathy and nephropathy. Some studies have shown that treatment with pioglitazone or rosiglitazone may reduce urinary albumin excretion to a greater degree than occurs with equivalent glycerol lowering with metformin or a sulfonylurea.22-23

Evidence is also increasing for a relationship between improved glycemia and a reduction in macrovascular complications.22,24,25 Metformin, the only insulin sensitizer used in the UKPDS, was associated with a marked reduction in MI and mortality.21 It has been hypothesized that some of the nonglycemic effects of metformin, such as decreased low-density lipoprotein cholesterol (LDL-C) and triglycerides and a reduction in plasminogen activator inhibitor 1 (PAI-1), may have been responsible for some of these outcomes.

Thiazolidinediones, in addition to improving glycemia, ameliorate insulin resistance and endothelial cell dysfunction and improve levels of inflammatory markers that have been associated with increased vascular risk.26 A 12-week study of newly diagnosed type 2 diabetes subjects compared endothelial cell function in response to rosiglitazone 4 mg twice daily with that in response to nonsulfonylurea secretagogue nateglinide 60 mg twice daily.27 Glycemic control was similar in both groups. However, rosiglitazone diminished insulin resistance by 60% compared with nateglinide and significantly enhanced nitric oxide-mediated forearm vasodilation independently of glucose control, implying an improvement in endothelial cell dysfunction.

In addition, preliminary evidence suggests that thiazolidinediones may have antiproliferative effects. A study in patients with type 2 diabetes who underwent coronary stent implantation found that pioglitazone treatment for 6 months reduced tissue proliferation within the stent.28 This finding is consistent with known effects of thiazolidinediones. Thiazolidinediones have been shown to attenuate PAI-1, which potentially promotes fibrinolysis and, in turn, may be associated with antiproliferative effects.29 Further, rosiglitazone has been shown to reduce the levels of other systemic proinflammatory mediators implicated in the pathogenesis of cardiovascular disease, specifically C-reactive protein and metalloproteinase-9.30

Moreover, thiazolidinediones have beneficial lipid effects—specifically, reducing triglyceride and increasing high-density lipoprotein cholesterol (HDL-C) levels. While some studies have shown a small thiazolidinedione-associated increase in LDL-C, there tends to be a beneficial conformational change in LDL-C. For example, 8 weeks of rosiglitazone treatment of individuals with type 2 diabetes was associated with a modest increase in LDL-C levels (9%). However, there was also a transformation of the LDL-C from smaller and denser to larger, more buoyant subfractions, which are believed to be less atherogenic. In the same study there was a 6% increase in HDL-C levels.30 Furthermore, when atorvastatin therapy was added, LDL-C levels markedly decreased (by 39%) and HDL-C levels further increased (by 5%).

**Combination Therapy**

As the UKPDS revealed, most patients with type 2 diabetes will not be able to attain and maintain glycemic goals with monotherapy.31 In fact, after 3 years of therapy <50% of subjects had an A1c <7%, and after 9 years, this had decreased to <25%. Therefore, most patients with type 2 diabetes will require combinations of antihyperglycemic medications with complementary mechanisms of action in order to achieve goal glycemia. For example, metformin or a thiazolidinedione can be combined with secretagogues or with each other to improve glycemic control.32,33 Each additional oral agent added is likely to be associated with a 1- to 1.5-percent reduction in A1c. For example, in one study, the combination of glyburide 2.5 or 5 mg twice daily and metformin 500 mg daily resulted in significantly better glycemic control than either agent individually.34 After 16 weeks of combination therapy, A1c levels declined by about 1.8%.

The addition of a thiazolidinedione in subjects needing combination therapy may offer the potential to preserve or enhance β-cell function. A 2-year, randomized, double-blind study in 227 patients with type 2 diabetes aged >60 years, previously on submaximal doses of sulfonylurea therapy (converted to glipizide at study entry), compared the addition of rosiglitazone to sulfonylurea with up titration of the sulfonylurea. Early addition of rosiglitazone to sulfonylurea improved insulin sensitivity and β-cell function, resulting in reduced disease progression with superior glycemic control that was sustained over 2 years, and provided a greater likelihood of achieving glycemic targets than just maximizing sulfonylurea monotherapy.35

The thiazolidinedione/metformin combination may also improve β-cell function. A randomized, double-blind, parallel-group study examined the efficacy of the rosiglitazone/metformin combination therapy in 348 adults with type 2 diabetes.33 Subjects were assigned to treatment with metformin 2.5 g/day and rosiglitazone 4 mg/day, metformin 2.5 g/day and rosiglitazone 8 mg/day, or metformin 2.5 g/day plus placebo. After 26 weeks, the metformin/rosiglitazone combination induced dose-dependent, statistically significant improvements in A1c levels, fasting plasma glucose levels, insulin sensitivity, and β-cell function when compared with metformin monotherapy. On average, A1c levels declined by 1% in the metformin/rosiglitazone 4 mg group and by 1.2% in the metformin/rosiglitazone 8 mg group.

Other clinical studies have shown that the addition of rosiglitazone to the regimen of patients not at glycemic goals despite combination therapy with a sulfonylurea and metformin can produce significant improvement in glycemic control and is generally well tolerated.36,37

**Single-Pill Combinations**

The formulation in which multidrug antidiabetic therapy is delivered can influence adherence and, as a result, therapeutic efficacy. A retrospective analysis of a managed care pharmacy

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**Patient Management Strategies in Type 2 Diabetes: Current Practices and Future Considerations**

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Expanded access to prescribers in the United States and to health practitioners and potential patients in other countries has been facilitated by the availability of the patient support programs. These programs are offered by companies or independently by non-profit organizations, government, third parties, and related organizations. The availability of such programs varies from country to country.

For example, in the United States, the type of support program is likely to be primary among the options available. A primary support program is a program that is designed to provide information and support to the patient, the prescriber, and the pharmacist. This may include: (1) information on the diagnosis and treatment of type 2 diabetes, (2) information on the use of the drug, (3) information on the potential side effects and benefits of the drug, (4) information on the potential benefits of the drug, (5) information on the potential side effects of the drug, (6) information on the potential benefits of the drug, (7) information on the potential side effects of the drug, (8) information on the potential benefits of the drug, (9) information on the potential side effects of the drug, (10) information on the potential benefits of the drug, (11) information on the potential side effects of the drug, (12) information on the potential benefits of the drug, (13) information on the potential side effects of the drug, (14) information on the potential benefits of the drug, (15) information on the potential side effects of the drug, and (16) information on the potential benefits of the drug.
claims database revealed that patients with recently diagnosed type 2 diabetes had the same adherence rates when taking glyburide or metformin monotherapy. Yet, when both of these agents were coadministered as separate pills to patients who had failed to respond satisfactorily to monotherapy, adherence rates declined from 82% to 54%. In contrast, patients switched from monotherapy to a single-tablet glyburide/metformin combination therapy maintained adherence rates at close to monotherapy levels (77%). Another study compared subjects switching from monotherapy with rosiglitazone or metformin with either combination therapy with the 2 agents administered as separate pills or with a single-pill combination of the 2 medications. Adherence was significantly higher in those who switched to the single-pill combination than in those receiving the 2 medications as separate pills (86% vs. 61%, respectively; \( P < 0.0001 \)).

In the United States, 3 single-tablet combination oral anti-hyperglycemic medications have been approved to date: the sulfonylurea/metformin combinations Metaglip (glipizide and metformin) and Glucovance (glyburide and metformin), and the thiazolidinedione/metformin combination Avandamet (rosiglitazone and metformin).

**Insulin Treatment**

If therapy with combination oral antidiabetic agents fails to achieve glycemic control, insulin treatment should usually be considered. In a randomized, open-label, 24-week study in subjects with inadequately controlled glycemic levels despite treatment with one or two oral antidiabetic agents, the addition of systematically titrated bedtime glargine or neutral protamine Hagedorn insulin permitted about 60% of the patients to reach an A1c level of \( \leq 7% \). In this study, nocturnal hypoglycemia was significantly less common with the use of insulin glargine.

**Multifactorial Approach to Diabetes Management**

Many patients with type 2 diabetes also have hypertension, dyslipidemia, or both, and these comorbidities must also be addressed in comprehensive diabetes management. The Steno II trial demonstrated that multifactorial approaches to treatment attempting to reach recommended targets for hyperglycemia, hypertension, dyslipidemia, and microalbuminuria in addition to the administration of aspirin, resulted in marked reductions in retinopathy, nephropathy, and cardiovascular end points compared with usual care. Findings such as these suggest that an intensive, targeted treatment approach can reduce the risks for both microvascular and macrovascular complications in individuals with type 2 diabetes.

Consistent with these findings, major guidelines for the management of type 2 diabetes now advocate goals for glycemia, blood pressure, and lipid levels that are much closer to the nondiabetic range. In addition, appropriately prescribed aspirin therapy and smoking cessation can further reduce the risks for cardiovascular complications (Table 1). Despite these recommendations, glucose, blood pressure, and lipid levels remain disconcertingly uncontrolled in the majority of individuals with type 2 diabetes. In a recent report, only 37% of diabetic subjects had achieved a target A1c level of \( \leq 7% \), only 36% reached the target blood pressure goal of \( \leq 130/80 \) mm Hg, only 48% reached target total cholesterol levels of \( < 200 \) mg/dL, and only 7% simultaneously achieved all 3 goals.

Yet, there is evidence that outcomes for patients with type 2 diabetes in managed care settings can be improved. For instance, diabetes disease management programs have created registries of diabetes patients from inpatient, ambulatory care, pharmacy, and laboratory records. Patients in the registry are then risk-stratified so that risk-specific interventions can be prospectively implemented. Approaches like this, coupled with regular evaluations and subsequent evaluation-informed modifications, can improve outcomes. One such program, in a managed care setting, employed comprehensive team-oriented care that included risk-specific treatment consistent with current guidelines, ongoing patient monitoring, and patient education and demonstrated significant improvements in glycemic, blood pressure, and lipid control after 1 year.

To improve outcomes and lessen the devastating health and economic impact of type 2 diabetes, managed care organizations must consider a comprehensive systems approach to management that employs identification of individuals with, and at risk for, type 2 diabetes and taps the expertise of a treatment team to provide patient education, early treatment, and consistent monitoring. The National Diabetes Education Program recently launched the BetterDiabetesCare Web site (www.betterdiabetescare.nih.gov) to help health plans and health care professionals in practices of all sizes to develop, implement, and improve health care delivery for their patients with type 2 diabetes.

<table>
<thead>
<tr>
<th>Target</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c</td>
<td>(&lt; 7.0% ) (ADA) ( \leq 6.5% ) (ACE/AACE)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>(&lt; 130/80 ) mm Hg</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>LDL-C: (&lt; 100 ) mg/dL ( &gt; 40 ) mg/dL (men), ( &gt; 50 ) mg/dL (women) ( \leq 150 ) mg/dL</td>
</tr>
<tr>
<td>Overall cardiovascular risk</td>
<td>Aspirin (57-162 mg/day) ( &gt; 40 ) mg/dL (men)</td>
</tr>
</tbody>
</table>

**A1c** = glycated hemoglobin; ACE/AACE = American Association of Clinical Endocrinologists/American College of Endocrinology; ADA = American Diabetes Association; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol.

**Table 1: Goals for Diabetes Management**

Diabetes Care. 2005;28(suppl 1):S4-S36.
Endocrine Pract. 2002;8(suppl 1):40-89.
A New Paradigm for the Prevention and Management of Type 2 Diabetes?

Traditionally, the management of type 2 diabetes progressed through several distinct steps: diagnosis, lifestyle modifications, pharmacologic treatment with oral agent monotherapy, oral agent combination therapy, and, if needed, insulin treatment. Unfortunately, an extended period of time, sometimes measured in years, is often required to progress through these therapeutic steps, and many patients never achieve recommended glycemic goals. Instead, health care professionals need to focus on early diagnosis and intensive management of people with type 2 diabetes using a systematic and persistent treat-to-target approach to achieve and maintain glycemic goals.

Ideally, people should be identified when they still have prediabetes because, as noted above, appropriate treatment can prevent or at least delay the progression from prediabetes to diabetes. Moreover, health care professionals need to address other risk factors associated with the insulin resistance or metabolic syndrome that can lead to long-term deleterious consequences.

Summary and Conclusions

Type 2 diabetes has emerged as a serious public health issue in the United States, and epidemiologic data indicate that, without aggressive intervention, its prevalence will increase drastically in the coming decades. Initiatives are currently underway to identify the more than 5 million Americans with undiagnosed diabetes as well as high-risk individuals with prediabetes. Once identified, these individuals will require aggressive, multifactorial management encompassing not only lifestyle measures, but, when indicated, also pharmacologic interventions targeted at achieving optimal glucose, blood pressure, and lipid levels. For many individuals with type 2 diabetes, therapy-combining agents with complementary mechanisms of action will be required to achieve the glycemic control goals advocated by current guidelines and demonstrated to significantly reduce morbidity from complications.

For health care organizations, a systems approach to treatment that involves early identification of people with prediabetes and diabetes, a team approach to management, risk-specific treatments consistent with current guidelines, and regular patient education and monitoring can improve outcomes and lower long-term costs.

DISCLOSURES

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Managing the Continuum of Treatment: Modeling the Economic Impact of Treating Diabetes

DIANA I. BRIXNER, RPh, PhD

ABSTRACT

OBJECTIVE: To describe economic models that may be useful for assessing the long-term and short-term cost-effectiveness of treatment options in the management of type 2 diabetes.

SUMMARY: Because clinical studies typically focus on short-term efficacy and safety, evaluating the long-term cost-effectiveness of various treatment options in the management of type 2 diabetes remains daunting. Long-term cost-modeling approaches offer an option for estimating the true costs of type 2 diabetes, which necessarily include the cost impact of complications, and suggest that tight glycemic control is a cost-effective step in reducing the risks for costly cardiovascular and renal complications. Short-term cost models can facilitate the evaluation of the cost-effectiveness of different drug regimens used to manage type 2 diabetes, an important step in formulary decision making.

CONCLUSION: In the absence of long-term, prospective studies to assess cost-effectiveness, cost modeling may be a useful tool in assessing the full economic impact of diabetes-related complications and the cost benefits that can be realized by managed care organizations that implement treatment approaches to avert these complications.

KEYWORDS: Cost modeling, Type 2 diabetes, Complications, Cost-effective formulary, Optimized management

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The economic costs attributable to diabetes mellitus remain staggering. Indeed, the total direct and indirect costs associated with diabetes in the United States totaled a striking $132 billion in 2002. This total included $92 billion in direct costs—the costs of medical care and services—and $40 billion in indirect costs—the costs associated with diabetes-related disability, work loss, and premature death. A report from the American Diabetes Association (ADA) indicated that the mean per capita 1997 health care cost for a patient with diabetes was $10,000, 4 times the mean cost for a patient without diabetes. Further, the ADA data indicated that inpatient care was the largest contributor (62%) to the direct medical expenses related to diabetes treatment, and almost half of these expenses (44%) were attributed to diabetes-related chronic and acute complications.

Clearly, there is ample opportunity to lower the high cost associated with type 2 diabetes and its complications with improved medical management. Reducing microvascular and macrovascular complications may dramatically lower the largest cost component of this disease—those requiring inpatient treatment. This article examines how managed care organizations (MCOs) can effectively lower diabetes-related costs and discusses approaches to economic modeling of these costs.

Cost-effectiveness in the Management of Type 2 Diabetes

How can an MCO begin to improve outcomes in type 2 diabetes and lower diabetes-related costs? Optimizing the management of type 2 diabetes is essential for reducing the risks for serious sequelae and the attendant medical costs.

The first approach is to target improvement in glycemic control. Compared with conventional insulin treatment, intensive glycemic control—glycated hemoglobin (A1c) < 6.5%, fasting blood glucose < 110 mg/dL, and 2-hour postprandial glucose < 180 mg/dL—achieved with multiple insulin injection therapy has been found to substantially delay the onset and deterioration of diabetic retinopathy, nephropathy, and neuropathy in patients with type 2 diabetes. But does improved glycemic control actually reduce treatment costs? That question was answered in a 1997 landmark study by Gilmer and colleagues. These investigators assessed the link between glycemic control and medical care charges for 3,017 adults continuously enrolled in a large health maintenance organization (HMO). Over a 3-year period from 1993 to 1995, charges for medical care were closely associated with A1c levels. Medical care charges increased significantly for every 1% increase in A1c above the ADA target of 7%. These researchers found that for each successive percentage increase in A1c levels above 6%, cumulative medical charges increased by about 4%, 10%, 20% and 30%.
respectively. Notably, the increase in charges accelerated rapidly as A1c levels progressively elevated, and this relationship converged in patients with isolated type 2 diabetes and in patients with diabetes and comorbid conditions. These findings underscore an important link between improved glycemic control and reduced medical costs.

Cardiovascular disease remains a common and costly comorbidity in type 2 diabetes. Diabetes markedly elevates the risk for cardiovascular disease and, according to ADA, diabetes-related cardiovascular disease directly accounts for $500 million yearly in lost productivity. Improving cardiovascular outcomes in patients with type 2 diabetes is a critical, but often challenging, step in controlling long-term costs. A retrospective study that included 2,790 subjects with type 1 or type 2 diabetes examined whether treatment with the angiotensin-converting enzyme inhibitor (ACEI) lisinopril within 24 hours of the onset of the symptoms of a myocardial infarction (MI) would lower morality risk. Lisinopril treatment reduced 6-week mortality, the primary study end point, by a statistically significant 30% when compared with an untreated control group. This decrease was sustained through 6 months despite drug withdrawal at 6 weeks. The results imply that early treatment, in this case with an ACEI, is a key to reducing cardiovascular complications in at-risk individuals with diabetes.

### Measuring Long-term Cost Outcomes

Although short-term costs are more easily quantified, a total cost consideration of diabetes is not complete without assessing the costs associated with the long-term consequences of poorly managed diabetes. However, an accurate assessment of these long-term consequences and, thus, their attendant costs, can be difficult for the following reasons:

- Clinical trials measure efficacy and safety, not cost-effectiveness.
- Postlaunch observational studies are expensive and take years to complete.
- Cardiovascular complications related to type 2 diabetes often emerge years after initiation of treatment.
- Health plans tend to focus on short-term costs, but significant disease-related costs can emerge long-term.

Clinical trials provide scant information on the cost-effectiveness of a drug in actual clinical use. Many pharmaceutical companies are beginning to conduct more observational studies that compare the cost-effectiveness of new drugs with that of standard therapy. Yet, observational studies are typically conducted postlaunch, after the drug is already available in the marketplace. Even though such studies are naturalistic, not experimental or controlled, they often retain the advantage of being prospective. This advantage permits the direct comparison between a newly launched and an already established drug. To validly make this comparison, however, a large study population and an extended evaluation period are required to capture the expected small differences in outcomes between the 2 treatments. An observational study may take a year or more to complete, however. During that time, the market for the drug under study may have changed substantially and, as a consequence, the results of the study—even if statistically and clinically significant—might no longer be relevant to formulary decision making.

### Modeling Long-term Cost Outcomes

If postlaunch observational studies will not provide usable information in a timely manner, how can the difficulty of determining long-term outcomes in type 2 diabetes be addressed? This is where modeling becomes useful. A decision-analysis model based on currently available data can be developed to estimate the potential impact of a new market entry. The model can be validated in conjunction with a particular managed care plan or several managed care plans represented in a consolidated database. But again, modeling becomes complex when evaluating the long-term cost impact of diabetes-related cardiovascular complications, delayed events that occur many years after an initial diagnosis of type 2 diabetes. This delay becomes an issue in the managed care setting, where the focus is typically on short-term costs.

When modeling long-term diabetes outcomes, it is highly important to define the unfavorable health outcomes or consequences of type 2 diabetes and then to delineate the progressive costs associated with these complications over time. O’Brien and colleagues estimated the direct medical costs of managing the microvascular and macrovascular complications of type 2 diabetes in the United States. This analysis used a combination of direct data and cost modeling to estimate the costs associated with the complications of type 2 diabetes in 2000. In this approach, average per-patient total costs were estimated by applying unit costs to the likely course of treatment for each complication or to its typical resource-use profile. A complication has 2 forms of cost: an initial cost when an event first occurs and during the first year thereafter and a subsequent, ongoing, annual cost. For an MI, the initial estimated medical cost was about $30,000, and the subsequent annual cost—assuming no additional event occurs—was about $1,700. For the early-stage complications of type 2 diabetes, microalbuminuria, for example, the initial cost was $63 and the subsequent cost, $15. The costs of early-stage complications seem modest, but the model demonstrated that these early complications can deteriorate over time into costly advanced disease, such as end-stage renal disease (ESRD), which was associated with $37,000 yearly in medical costs from the time of diagnosis. The authors concluded that a consideration of the costs associated with diabetes-related complications is essential for any model analysis examining the true ongoing economic burden of type 2 diabetes. Yet, direct information on the cost impact of these complications, especially cardiovascular and renal sequelae, has remained sparse.

To shed some light on the progressive costs associated with type-2 diabetes-related complications, Brown et al. analyzed 9 years of clinical data from 11,768 patients with suspected type 2 diabetes from a large group-model HMO. The investigators
determined the number of cardiovascular and kidney complications, staged the deterioration of these complications, and estimated the incremental costs by stage. Baseline health care costs, established at $2,500 in this study, were those of a patient without diabetes as reported by ADA. The results revealed that per-person costs increased by more than 50% ($1,087) after initiation of cardiovascular drug therapy or the use of a cardiologist, or both, and by a striking 360% ($7,352) after a major cardiovascular event. Abnormal kidney function increased diabetes treatment costs by 65% ($1,337), advanced kidney disease by 195% ($3,979), and ESRD by 771% ($15,675). These results imply that, for the type 2 diabetes population as a whole, the greatest cost savings would be achieved by preventing major cardiovascular events. For individuals, the greatest savings would be achieved by preventing deterioration to ESRD. These findings further suggest that the aggregate cost across a population with type 2 diabetes, not just the actual cost of individual events, is a critically important factor in assessing the true cost of complications and in measuring cost savings. Because cardiovascular complications affect about half the entire type 2 diabetes population, the effective management of these complications may yield the greatest cost savings.

Another approach to modeling long-term diabetes cost outcomes uses statistical methods to project forward short-term clinical trial findings into the future. For instance, a study published in the Journal of Managed Care Pharmacy started with clinical end points from a 6-month randomized controlled clinical trial, the Microalbuminuria Reduction With VALsartan (MARVAL) study, which compared the angiotensin II receptor blocker valsartan with the calcium channel blocker amlodipine in treatment of patients with type 2 diabetes and microalbuminuria. From these results, the investigators estimated 8-year health and economic outcomes by using the Markov model, a model of a sequence of events in which the probability of the occurrence of an event depends on the fact that a preceding event occurred. Urinary albumin excretion rate data were used to project the distributions of participants to 7 possible health states over 8 years. For each health state, quality-adjustment weights (health utilities) and medical care costs were identified from public sources. The model then calculated mean quality-adjusted survival, medical care costs, and cost-effectiveness ratios for each treatment arm. Treatment arms were compared with the incremental cost-effectiveness ratio. The model data indicated that subjects treated with valsartan gained a mean of 77 months of quality-adjusted survival, statistically significantly higher than the mean gain of 70 months for subjects treated with amlodipine. Mean health care cost for valsartan-treated subjects, $92,000, was statistically significantly lower than the $124,000 mean costs associated with amlodipine treatment. The Markov modeling analysis in this study projected actual 6-month clinical trial outcomes out to an 8-year period, translated health outcomes from technical clinical end points to quality-adjusted survival, and estimated the economic consequences of therapeutic outcomes. This approach to modeling can be an efficient alternative to performing long-term studies to examine cost outcomes in type 2 diabetes. However, typical pharmacoeconomic models can be based on national data and validated in a particular plan with 1-year data from that plan. In contrast, the Markov modeling analysis used by Smith et al. would require 8 years for a particular plan to validate. It should be pointed out that the practical value of long-term outcomes and cost modeling in type 2 diabetes remains controversial in the managed care setting.

### Short-term Modeling

Managed care pharmacists who make decisions about what drugs will be listed on drug formularies and about pharmacy budgets frequently compare short-term costs among the different therapeutic options available for diseases such as type 2 diabetes.

### Budget Impact Model: Pharmacotherapy Outcomes Research Center

The final part of this article describes an example of a short-term cost-effectiveness modeling project: the validation of a budget-impact model conducted at the Pharmacotherapy Outcomes Research Center in Salt Lake City, Utah. The center was approached by a pharmacy benefit manager (PBM) to evaluate the economic modeling section of the fixed-dose thiazolidinedione/metformin (TZD/Met) Economic Dossier. The analysis section examined the potential economic benefit to a particular MCO of using a single medication with a fixed combination of 2 drugs, a thiazolidinedione (pioglitazone or rosiglitazone) and metformin, instead of dispensing the drugs separately. The overall review included a summary of the economic data presented in the dossier and a description of the budget-impact model with baseline numbers. Finally, the report described the implications of the analysis in terms of pharmacy costs and offered recommendations for formulary decisions.

### Summary of the Economic Data

The summary of the economic data discussed the importance of tight glycemic control in reducing the occurrence of complications and in achieving medical cost savings in type 2 diabetes management. The summary further noted that MCOs, in general, have poor adherence to ADA standards for achieving glycemic control, defined as an A1c of <7%. Short-term costs associated with type 2 diabetes included an average of $10,500 per patient with a mean hospital length-of-stay of 4.6 days for the treatment of hyperglycemia. Long-term costs secondary to diabetes-related complications included $27,630 for the treatment of MI, $40,616 for ischemic stroke, and $53,659 for ESRD. The summary also pointed out that health economic models suggest that improved glycemic control is cost effective, with savings of $17,229 to $107,229 per life-year gained. Further, medication adherence, underscored as a necessary step in optimizing glucose control, was...
by providing an alternative to insulin therapy. Because of the potential clinical and economic benefits highlighted in the short-term cost analysis, in this MCO, the fixed-dose TZD/Met was recommended as the preferred fixed-dose combination anti-diabetic treatment.

Conclusions

Type 2 diabetes has a substantial impact on direct and indirect health care costs. Estimating the long-term cost impact of type 2 diabetes remains a daunting process. Several long-term and short-term modeling approaches, some controversial in the managed care setting, have proven valuable in evaluating the cost-effectiveness of treatment approaches to type 2 diabetes. Results from these models highlight the continued importance of tight glycemic control in reducing long-term diabetes-related costs. Short-term economic models can provide information on the potential benefit of fixed dose combinations versus separate individual prescriptions to the pharmacy budget.

DISCLOSURES

This article is based on the proceedings of a symposium, “Emerging Perspective in Type 2 Diabetes: Understanding the Influence of Metabolic Syndrome,” held on March 31, 2004, in San Francisco, California, which was supported by an unrestricted educational grant from GlaxoSmithKline (GSK) and sponsored by StrategiCare, Inc. and The GMR Group. The author received an honorarium from GSK, StrategiCare, Inc., and The GMR Group for participating in the symposium upon which this article is based. She served on an advisory board for GSK in the area of diabetes management. She discloses no potential bias or conflict of interest relating to this article.

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Best Practices in Innovative Type 2 Diabetes Program Management: A Case Study

H. ERIC CANNON, PharmD

ABSTRACT

OBJECTIVE: To illustrate, through a case study format, a successful type 2 diabetes disease management program.

SUMMARY: Intermountain Health Care (IHC) has implemented an evidence-based, integrated approach to the management of type 2 diabetes that includes multiple interventions: (1) a regularly updated treatment algorithm; (2) a comprehensive data registry to rapidly identify patients with type 2 diabetes; (3) a system of regular patient reminders for laboratory and other relevant testing, such as eye and foot examinations; (4) patient education that fosters an understanding of the benefits of antidiabetic medications and the need for consistent treatment; (5) pharmacist and nurse involvement to facilitate physician appointments when needed, track medication use, ensure consistent compliance, and answer questions; and (6) physician performance reports that provide an opportunity for rapid peer-to-peer outcomes comparisons. The implementation of this program has yielded a substantial increase in the number of patients within the system identified with type 2 diabetes and an increase in the percentage of patients with improved glycemic control based on HbA1c, as well as an unexpected benefit—an increase in the number of patients with improved low-density lipoprotein cholesterol levels.

CONCLUSION: An integrated, evidence-based disease management program, such as the one developed by IHC, can improve type 2 diabetes outcomes in the managed care setting and, perhaps, reduce long-term costs.

KEYWORDS: Case study, Disease management program, Type 2 diabetes, Evidence-based, Integrated treatment, Intermountain Health Care

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A publication from the Institute of Medicine (IOM) of the National Academies, Crossing the Quality Chasm: A New Health System for the 21st Century, lamented the poor state of affairs in health care in the United States. According to this publication, reducing the burden of illness and improving health requires a systems approach to health care delivery, entailing sophisticated information systems and goal development founded on evidence-based medicine, with a focus on improving the care of 15 priority conditions, including diabetes. The Disease Management Association of America takes a similar approach. The association defines disease management as "a system of coordinated health care interventions and communications for populations with conditions in which patient self-care efforts are significant." Disease management supports the physician/patient or practitioner/patient relationship, emphasizes prevention of complications by use of evidence-based practice guidelines and patient empowerment strategies, and evaluates clinical, humanitarian, and economic outcomes on an ongoing basis with the goal of improving overall health.

This article describes an innovative program for disease management at Intermountain Health Care (IHC), a not-for-profit integrated health care system based in Salt Lake City, Utah, that emphasizes an integrated management approach to type 2 diabetes.

Intermountain Health Care

When the pioneers arrived in Salt Lake City, Utah, during the 1800s, they established a health care system that came under the auspices of the Church of Jesus Christ of Latter-day Saints. The Church stepped away from managing health care in the community, but IHC, founded in 1975, has extended the culture of being a community-based health plan. So when IHC considers initiatives such as approaching formulary decisions, it believes that it has a real duty to the community to improve health care.

IHC now has about 470,000 enrollees receiving services through the integrated health system, and it uses a contract network to provide health care services to another 500,000 people. IHC’s 22 hospitals and 150 medical facilities are located throughout Utah and Idaho, and 350 of its 400 physician-employees provide primary care. An additional 2,500 physicians are affiliated through the contract network.

IHCs members, providers, facilities, and plan management work together as a patient-centered team to better integrate care and improve delivery. Integration provides a fertile environment for higher quality health care and improved value. About 90% of the members reside in a 90-mile corridor north and south of Salt...
Lake City, making it easy for IHC to reach providers and patients to implement disease management programs.

The Risk Continuum in Health Care

In discussions of health and wellness, the focus is typically on management of disease in high-risk patients, often to the exclusion of low-risk patients. This results in “risk-churning,” in which low-risk patients become high-risk ones. In developing disease management programs, IHC has focused on the entire risk continuum (Figure 1).

Crossing the Risk Chasm

IHCs fundamental philosophy, in agreement with the recommendations of the IOM report,1 promotes the use of evidence-based medicine to develop clear, manageable, and measurable goals to implement change. In the IHC integrated approach to disease management, physicians, pharmacists, hospital, and health plan staff collaborate to review and define clinical “best practice.” At IHC, disease management programs are considered a system of coordinated health care interventions and communications for populations with chronic conditions in which patient self-care efforts are significant. The chief goals are to support the physician or practitioner/patient relationship, emphasize prevention of complications utilizing evidence-based practice guidelines and patient empowerment, and measure clinical and economic outcomes on an ongoing basis with the goal of improving overall health. Essentially, disease management programs in primary care, cardiovascular, neuromusculoskeletal, oncology, and pediatric specialties were developed to foster the consistent and integrated delivery of health care. Health care management process manuals for various disorders, such as diabetes, asthma, heart failure, depression, otitis media, bronchitis, and low back pain, are published annually and placed on the IHC Web site (www.ihc.com/xp/ihc) for easy access by physicians and patients. Although IHC has not yet completed development of a new, sophisticated information systems called for in the IOM report,1 implementation is imminent. The current system links the health plan, hospitals, and physicians within the same system, as shown in Figure 2.

FIGURE 1 Risk Continuum in Health Care

Medical Management
- Clinical Programs
  - Primary Care
  - Women & Newborns
  - NMS
  - Oncology
  - Pediatric

Disease Management
- Asthma
- Diabetes
- Heart Failure
- Migraines
- PBMs

Prevention and Health Management
- Health and Productivity Workshop
- Health and Productivity Newsletter
- Total Fitness Newsletter
- Personal Health Assessment
- Flu Shots
- Smoking Cessation
- Walk-a-Day
- Calendar of Events

FIGURE 2 Integrated Information Technology*

IHC Disease Management

Health Plans
- QI – coordinate NCQA/HEDIS initiatives on systemwide basis and tracks ongoing compliance
- Provider Relations – distribute Care Process Models (CPM) to physicians
- Claims/Membership Services – collect claims and service quality data such as member complaints
- Advocates – schedule appointments for preventive care
- Advocates – channel members to appropriate providers
- HCS – provide acute and chronic care management (medicine, surgery, Rx)
- HCS – monitor and act on CP and delivery system census reports
- HCS – meet with delivery system to monitor and improve CPMs

Hospitals/Health Services
- Lead Clinical Program Leadership Team to manage/monitor performance
- Provide inpatient and outpatient care management support
- Provide disease specific education – refer to HPI for long-term care management
- Produce patient and physician education materials
- eBusiness group Web enables education and reporting materials

Physician Division
- Oversee development of CPMs
- Implement standard physician orders
- Provide physician communication, education, and monitoring

NMS = neuromuscular skeletal; PBMs = pharmacy benefit managers.

Claims, Rx, Lab, Pathology, Radiology, Hospital, Clinic, Home Care, Medicine/Surgery, Mental Health

* Diagram of IT developed by Lisa Faller, RN, VP Health Care Services, IHC Health Plans.

CP = clinical program; HCS = health care services; HPI = Health Plans, Inc.; NCQA/HEDIS = National Committee for Quality Assurance/Health Plan Employer Data and Information Set, Rx = prescription; QI = quality improvement.
IHC’S Type 2 Diabetes Program

IHC’s initial type 2 diabetes program began in the early 1990s. However, by 1997, it had become apparent that care under this program was inconsistent, and, as a result, the program was subsequently reorganized. As with other clinical programs at IHC today, such as those for asthma and other respiratory conditions, the program for type 2 diabetes is now subsumed under primary care because primary care physicians treat most patients with type 2 diabetes. IHC offers an integrated diabetes disease management program that provides patient, provider, and caregiver support to achieve optimal disease management. Components of the current type 2 diabetes program are shown in Table 1.

Treatment Algorithm

Figure 3 shows the algorithm that IHC follows in managing patients with type 2 diabetes. The algorithm is revised every other year. As part of the IHC Clinical Program for Diabetes, a work group meets every other month to discuss ongoing issues and changes needed in current guidelines and to review progress toward clinical goals. The diabetes work group consists of physician leaders in the field of diabetes, diabetes educators, and representatives from nursing and pharmacy. Recommendations and changes are distributed to various departments for comment and feedback. Once revisions are finalized, the clinical guidelines are published both in hard copy and electronically on the Web.

Patient Registry

Originally, data for all the separate components of the program were in separate databases. The key to success was developing an entire type 2 diabetes data warehouse for tracking comprehensive medical, hospital, laboratory, and pharmacy information. The database is used to identify patients with type 2 diabetes at high risk for complications. Pharmacy data, medical claims data, and hospital census information are evaluated using predictive modeling software.

The main issue IHC faces in the efficient management of type 2 diabetes is that employers fragment care by separating and dividing medical management. For instance, pharmacy responsibilities may be handled by one provider entity, such as a carve-out pharmacy benefit manager, and disease management and health and wellness by separate entities. These functions need to be kept together and integrated to optimize treatment and effectively reduce costs in the management of type 2 diabetes.

Reminders to Patients

Patients with type 2 diabetes receive a periodic newsletter with postcard reminders for laboratory tests as well as an annual calendar with testing reminders. About twice yearly, patients with type 2 diabetes receive a report card summarizing the results of laboratory tests, such as glycated hemoglobin (A1c) and low-density lipoprotein cholesterol (LDL-C), and other required exams, such as eye or foot exams. Dates, results, and explanations of the tests, as well as a schedule of the future tests required, are provided directly to the patient.

The newsletter contains topical information about effectively managing diabetes. The bottom half includes a tear-off form with an order for one of the laboratory tests recommended for monitoring diabetes, such as A1c. The patient tears off the order form, writes his or her name on it, and uses it at the laboratory as the order form. As soon as A1c results become available, they are inserted into the integrated database and brought to the attention of the care managers and the disease management team. For instance, A1c levels of 8% or higher trigger a series of corrective steps: a case manager receives an alert that the patient’s A1c is high, and he or she telephones the patient to schedule an appointment with a diabetes educator or dietician. A clinical pharmacist reviews the medical and pharmacy history of the patient with a high A1c and exchanges electronic messages with the physician and care manager to determine whether the patient is currently receiving optimal pharmacotherapy or whether adherence may be an issue. Lack of adherence to therapy may, many times, be the cause of uncontrolled disease. Included in the routine, computer-generated reports is a list of medications recently filled by the patient. Clinical pharmacist involvement is crucial since the current reports do not make a determination of compliance with or adherence to therapy. After a clinical evaluation is complete, the care manager contacts the patient to provide education, reinforce the need for adherence to therapy, or provide additional information about changes needed in treatment.

Patient Education

Patient education is an essential component of the IHC diabetes management program. IHC’s patient education materials are available on the Web site (www.ihc.com/xp/ihc) in portable document format (PDF). When a case manager, nurse, or pharmacist talks with a patient on the telephone, they can direct the patient to the Web site or print out and mail a copy of the pertinent information. Additionally, members of the pharmacy staff assure that patients own a blood glucose monitor and understand the value of regular glucose monitoring. IHC has found that, to enhance medication adherence, patients need to more fully understand the benefits of their diabetes medications and the need for consistent treatment.
Pharmacist and Nurse Involvement

Specially trained nurses and pharmacists work with physicians and patients to arrange physician appointments, track medication use, evaluate the patient’s physical activity and dietary needs, and answer any questions. Telephone outreach by these health care professionals is the “nagware” that actually makes things happen. Clinical pharmacists perform telephone outreach, discussing medication issues, such as adherence and the emergence of any adverse events with patients. Pharmacists are also involved in weekly meetings with care managers, affording an opportunity to improve management for difficult cases. Current pharmacist involvement in the IHC diabetes management program is worth noting because they were not included in the care management team until 1977, when it became apparent that the existing team of physicians, case managers, educators, and dietitians would be more effective if pharmacists also were involved.
Physician Performance Reports

For physicians at IHC, peer-to-peer outcomes comparisons and patient outcomes information have been valuable tools for successfully changing clinical practice patterns. In an integrated system with a centralized database, physicians can access reports via the Internet that are specific to their practice and compare their patients’ outcomes with those of other physicians’ patients. Health plan management, particularly the medical directors, can also access these reports to monitor the progress of the program and identify specific physicians who may need follow-up discussions regarding their practice patterns.

Program Accomplishments

Ongoing monitoring of the IHC diabetes management program is considered essential to the program’s success. Results of the most recent analysis are summarized below. As a result of this program, recognition of patients with type 2 diabetes has increased dramatically in recent years (Figure 4), and longitudinal assessment over 8 years showed significant improvements in key outcome measures.

Between June 1999 and December 2003, the number of patients identified with type 2 diabetes more than doubled, from 3,000 to 7,000. An increase in the general prevalence of diabetes...
over that period may account for some of this increase, but improved diagnosis by clinicians and, in turn, more accurate disease coding in the database were likely major contributors. During the same evaluation period, the percentage of patients with type 2 diabetes reaching target A1c levels of <7% increased notably, from about 33% in June 1999 to 60% by the end of 2003 (Figure 5). Further, during the evaluation period, the percentage of members who had an A1c level >9% decreased from about 20% to >10%, while the mean A1c level decreased from about 8.1% to about 7.4%. In addition, improvements were also noted in lipid levels. From the end of 1999 to the end of 2003, the percentage of patients with type 2 diabetes and LDL-C levels of <100 mg/dL increased by 10%, from 37% to 47%. A main focus of the IHC diabetes program was a clinically meaningful reduction in A1c, not LDL-C. However, based on these encouraging findings, lowering LDL-C concentration has also become a major focus of the program.

Analysis of the IHC type 2 diabetes management program clearly indicates that an integrated health management program can improve the identification of patients with this disease and yield clinically meaningful improvements in glucose control. Nonetheless, employers remain interested in quantifying the medical cost savings associated with the improved glycemic control observed in this integrated program, and IHC is currently working to provide them with this cost-benefit information.

Conclusions

Optimal disease management requires an integrated clinical approach supported by the use of information technology. IHC recognizes the critical nature of this approach to disease management. Indeed, the integrated management of type 2 diabetes at IHC has substantially improved patient outcomes in terms of notable improvements in glycemic control. The cost benefits of these improvements are currently being evaluated at IHC, however. Taking a consistent approach to managing diabetes through the use of treatment algorithms and physician report cards, providing patient education and reminders for follow-up laboratory monitoring and specialty evaluations, and tracking patient outcomes through an integrated database are critical features of the IHC program and have clearly advanced the management of type 2 diabetes in the managed care setting and perhaps provides a basis for reduced long-term costs.

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DISCLOSURES

This article is based on the proceedings of a symposium, “Emerging Perspective in Type 2 Diabetes: Understanding the Influence of Metabolic Syndrome,” held on March 31, 2004, in San Francisco, California, which was supported by an unrestricted educational grant from GlaxoSmithKline (GSK) and sponsored by StrategiCare, Inc. and The GMR Group. The author received an honorarium from GSK, StrategiCare, Inc., and The GMR Group for participating in the symposium upon which this article is based. He discloses no potential bias or conflict of interest relating to this article.

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The Academy of Managed Care Pharmacy is approved by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. A total of 0.20 CEUs (2.0 contact hours) will be awarded and a continuing education statement will be sent to pharmacists for successful completion of this continuing education program, which is defined as receiving a minimum score of 70% on the posttest and completion of the Program Evaluation form. ACPE Universal Program No. 233-000-05-038-H04. (Release date: August 1, 2005; Expiration date: August 1, 2008)

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The posttest worksheet (below) is provided to assist you in marking your answers prior to entering the online CE center for submission; these pages cannot be submitted for CE credits.

In order to receive CE credit for this program, you must complete the following forms online:

1. Posttest form for this program, “Emerging Perspectives on Type 2 Diabetes,” on the AMCP.org Online Learning Center site—to receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the posttest.

2. Program Evaluation form

Upon successful completion of this program, you will automatically receive your CE statement. Your CE credits will be automatically archived and tracked for you on the AMCP.org Online Learning Center site. All information is kept confidential.

Note: There will be a $10 processing fee for nonmembers. (See payment instructions on site.)

Posttest Worksheet: Emerging Perspectives on Type 2 Diabetes

1. In the United States, obesity now affects about what percentage of the population?
   a. 50%
   b. 40%
   c. 30%
   d. 20%

2. Metabolic syndrome includes which of the following features?
   a. Waist circumference >40 inches in men
   b. High triglyceride levels of >150 mg/dL
   c. Impaired fasting glucose of >100 mg/dL
   d. All of the above

3. Adiposities within organs promote the formation of
   a. TNF-α
   b. nitric oxide
   c. HDL-C
   d. β-cells

4. In individuals with insulin resistance, insulin preferentially stimulates the
   a. PI3K pathway
   b. MAPK pathway
   c. GLUT4 pathway
   d. All of the above

5. The MAPK insulin pathway can be considered prothrombotic.
   a. True
   b. False

6. In the pancreas, elevated free fatty acid levels induce apoptosis primarily by enhancing the production of
   a. VLDL-C
   b. endothelin
   c. C-reactive protein
   d. inducible nitric oxide
7. Within the cell, excess glucose metabolism via the polyol pathway has been implicated in
   a. β-cell preservation.
   b. the development of diabetes-related complications.
   c. activation of the MAPK pathway.
   d. HDL-C suppression.

8. Activation of the PPAR-γ receptor by thiazolidinediones
   a. improves insulin sensitivity.
   b. diminishes free fatty acid mobilization.
   c. may reduce atopic fat deposition.
   d. All of the above

9. Type 2 diabetes now affects about what percentage of the U.S. population?
   a. 25%
   b. 10%
   c. 6%
   d. 3%

10. What percentage of the $92 billion in direct type-2 diabetes costs can be attributed to complications and the emergence of comorbidities?
    a. 90%
    b. 75%
    c. 50%
    d. 25%

11. Prediabetes has been linked to an elevated risk for cardiovascular disease.
    a. True
    b. False

12. A 1% reduction in A1c level has been shown to lower diabetes-related mortality by about
    a. 30%.
    b. 20%.
    c. 10%.
    d. 5%.

13. Typically, to achieve glycemic goals in type 2 diabetes, the regimen must include
    a. diet modification.
    b. exercise.
    c. pharmacologic treatment.
    d. All of the above

14. Thiazolidinediones may convey which of the following benefits in the management of type 2 diabetes?
    a. Reduced β-cell apoptosis
    b. Improved β-cell function
    c. Reduced insulin resistance
    d. All of the above

15. In UKPDS, what percentage of patients with type 2 diabetes maintained tight glycemic control (A1c < 7%) after 3 years' monotherapy?
    a. 75%
    b. 50%
    c. 25%
    d. 10%

16. The use of fixed-dose, single-agent combination antidiabetic therapy has been shown to
    a. maintain compliance levels similar to that seen with monotherapy.
    b. result in a marked reduction in compliance.
    c. elevate compliance above that seen with monotherapy.
    d. compromise glycemic control.

17. In the managed care setting, an integrated, evidence-based type 2 diabetes program, such as the one implemented by IHC, has been shown to
    a. decrease the number of members identified with type 2 diabetes.
    b. substantially increase member costs.
    c. almost double the number of members with type 2 diabetes reaching a glycemic goal of an A1c level of <7%.
    d. increase HDL-C levels.

18. Major components of the IHC diabetes management program include
    a. updated treatment algorithm and computerized patient registry.
    b. patient reminder system and patient education programs.
    c. pharmacist and nurse involvement in the treatment team.
    d. All of the above

19. Long-term cost models indicate that major cost savings can be achieved by averting diabetes-related cardiovascular complications.
    a. True
    b. False

20. Short-term, budget-impact models suggest that thiazolidinedione plus metformin given as a fixed-dose combination, rather than as single-agents, offers advantages in terms of
    a. reduced side effects.
    b. lower pharmacy cost.
    c. demonstrated improvements in clinical outcomes.
    d. All of the above

To complete this activity, go to www.amcp.org (Learning Center/Online CE), where you will access the posttest and evaluation form.