

## **Virtual Mentor**

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### **CLINICAL PEARL**

#### **Type 2 Diabetes: Lifestyle Changes and Drug Treatment**

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More than 23 million individuals in the United States have diabetes—a figure that creates great urgency for finding the most effective and safest methods for treatment. Data show that therapies that lower hyperglycemia to the normoglycemic range can reduce morbidity, cardiovascular mortality, and microvascular complications in type 1 diabetes [1-3]. Likewise, intensive treatment strategies for type 2 diabetes have demonstrated a reduction in microvascular disease, but more recent data show no reduction in macrovascular disease [4-7]. Due to the potential for complications, initial treatment for decreasing hyperglycemia should be patient-specific and adjusted to achieve the American Diabetes Association (ADA) target A1c level of less than 7 percent [8]. While oral and injectable pharmacotherapies and insulin are often needed to maintain this level, the importance and benefit of lifestyle changes should not be undervalued. According to the 2008 consensus statement from the ADA and European Association for the Study of Diabetes, lifestyle interventions and metformin therapy should be started concurrently upon diagnosis of type 2 diabetes [9].

#### **Macrovascular Disease Reduction**

In selecting treatment for chronic disease, the mechanism of the disease should be considered. Obesity and a sedentary lifestyle, for example, contribute to the risk for and development of type 2 diabetes. Obesity is also a factor in insulin resistance, which is a major cause of elevated glucose levels. Weight reduction and an increase in physical activity improve glycemic control by reducing insulin resistance and lowering fasting blood glucose. Weight loss also lowers risk of cardiovascular disease by reducing hypertension and serum makers of inflammation and improving the lipid profile. One study noted that intentional weight loss, such as with bariatric surgery, reduced mortality [10]. Likewise, the Diabetes Prevention Program showed a 58 percent decrease in the incidence of type 2 diabetes among patients with impaired glucose tolerance who achieved at least a 7 percent weight loss over 2.8 years [11].

Diabetes treatments in general reduce hepatic glucose output, enhance insulin secretion, improve insulin sensitivity, and prolong the effects of glucagon-like peptide-1 (*GLP-1*). Despite these mechanisms and their abilities to lower blood glucose, pharmacotherapies for diabetes have shown varying effects on macrovascular disease outcomes. Metformin monotherapy reduced mortality from all causes by 26 percent compared to other conventional therapies in the 1998 UK Prospective Diabetes Study 34, while the controversial yet classic University Group Diabetes Program suggested that sulfonylureas may increase cardiovascular disease

mortality [5, 12]. Thiazolidinediones have mixed data, with meta-analyses showing a 30 to 40 percent increase in the risk for myocardial infarction with rosiglitazone [13]. Conversely, a 16 percent reduction in death, myocardial infarction, and stroke was seen in patients treated with pioglitazone in the PROactive trial [14]. Intensive insulin treatment given to critically ill patients in an intensive care unit reduced mortality by 42 percent compared to the conventional-treatment group [15]. No published clinical trials have examined the effects of exenatide, pramlintide, and sitagliptin on cardiovascular outcomes.

### **Tolerability and Contraindications**

Side effects and contraindications figure importantly in selection of individualized treatment. In general, few side effects are associated with lifestyle modifications. Exercising may result in myalgias, and dietary changes may cause gastrointestinal symptoms. Patients with arthritis or neuropathies should follow strict physician recommendations to avoid injury. While there is no consensus on which type of diet is most appropriate for patients with type 2 diabetes, most clinicians agree that a plan that results in gradual and sustained weight loss provides the most benefit. Patients should learn from a registered dietitian or other health care professional how to develop a plan that is balanced and safe. Common side effects of medications used to treat type 2 diabetes include hypoglycemia, gastrointestinal discomfort, weight gain, and fluid retention. Some medications are contraindicated in patients with renal or liver impairment or congestive heart failure, which limits their use.

### **Sustaining Glycemic Control**

One of the most important topics a patient and his or her physician should discuss prior to selecting therapy is the potential for sustaining the desired result. Patients often have difficulty introducing new dietary and exercise regimens into their daily routines due to time constraints or other logistical factors. Svetkey et al. studied patients who had lost at least 8 pounds during a 6-month weight-loss program to determine which of several factors—monthly personal contact, unlimited interactive technology, or self-directed control—produced the most sustainable weight loss over a 30-month period [16]. While personal contact and interactive technology were superior to self-control, 71 percent of all patients remained at or below their trial entry weight at the end of the trial.

The international multicenter study, A Diabetes Outcome Progression Trial (ADOPT), evaluated the glycemic-lowering sustainability of monotherapy with maximum doses of metformin, rosiglitazone, and glyburide in patients newly diagnosed with type 2 diabetes [17]. At 5 years, rosiglitazone significantly reduced the risk of monotherapy failure—defined as fasting blood glucose levels greater than 180 mg/dl—by 32 percent when compared with metformin, and by 63 percent when compared with glyburide. A 2008 trial reported that intensive insulin therapy in newly diagnosed patients sustained the acute insulin response at 1 year compared to oral hypoglycemic agents, suggesting preservation of B-cell function [18]. Of course, adherence to the therapies is necessary to realize the benefits. As with other chronic disease states that require medication, adherence is influenced by patient perceptions

of the benefits of treatment and their understanding of the regimen, the complexity of the regimen, and patients' emotional well-being. Adherence rates to oral diabetes medications range from 65 to 85 percent and for insulin, from 60 to 80 percent [19].

### **Cost**

Because lifestyle modifications and medications are usually recommended throughout life to maintain adequate glycemic control, the cost-effectiveness of each therapy should be taken into consideration. A subgroup of the Diabetes Prevention Program Research Group performed a within-trial, cost-effectiveness analysis comparing lifestyle intervention—defined as achieving and maintaining a 7 percent weight loss—with metformin (850 mg twice daily) [20]. Costs were based on the way the interventions would be implemented into routine, clinical practice and also from a societal perspective that considered direct medical cost, direct nonmedical cost, and indirect cost. In the 2003 report on the study, lifestyle intervention cost \$13,200 and metformin cost \$14,300 to prevent or delay one case of diabetes over 3 years.

When selecting the most appropriate therapy for treatment, the percent reduction needed to achieve the A1c target should be taken into account. The A1c-lowering potential for available therapies are listed in Table 1 [21]. When A1c levels are above 8.5 percent, combination therapies may be needed. If lifestyle modifications or the initial medications fail to achieve glycemic control in 2 to 3 months, additional therapy should be initiated. Fifty percent of patients initially controlled with monotherapy required a second agent after 3 years, and 75 percent needed multiple therapies by 9 years to achieve the target A1c [22]. It is agreed that initial treatment for patients with type 2 diabetes should include education on lifestyle modifications, diet, exercise, and setting reasonable goals to achieve a 5 to 10 percent initial weight loss. Regardless of the initial response to therapy, glycemic control and health behaviors should be continually evaluated to manage hyperglycemia most effectively. Therapies should be patient-specific and selected based on the potential for microvascular and macrovascular disease reduction, tolerability, sustainability, and expense.

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