

Tight Control of Hyperglycemia in Type 2 Diabetes Mellitus

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ABSTRACT

Background: In the past decade, a number of new therapeutic agents have been introduced for the treatment of patients with type 2 diabetes mellitus (DM). These agents target the metabolic disturbances that characterize this disease, specifically insulin resistance, excessive hepatic gluconeogenesis, and β -cell failure.

Objective: The goal of this article was to review the options available for obtaining glycemic control in patients with type 2 DM.

Methods: Materials for this article were identified through searches (1965–present) of MEDLINE (English language only). Search terms included *treatment of type 2 diabetes, insulin therapy, oral hypoglycemic therapy, and exenatide*.

Results: Large randomized controlled trials have shown that the incidence of microvascular complications of DM can be greatly reduced by improving glycemic control. The cornerstone of glycemic control continues to be successful implementation of a diet and exercise program. These dietary modifications reduce obesity, lower glucose levels, and improve insulin sensitivity. Lifestyle changes, however, are difficult to achieve and sustain in unsupervised settings. For patients who do not respond adequately to diet and exercise therapy alone after a 3-month trial, the addition of pharmacotherapy to the treatment regimen is indicated. Five classes of oral agents are now approved by the US Food and Drug Administration for the treatment of type 2 DM: the sulfonylureas and meglitinides (both secretagogues), the biguanides (metformin), the α -glucosidase inhibitors (acarbose and miglitol), and the thiazolidinediones (rosiglitazone and pioglitazone). The recently approved glucagon-like peptide-1 analogue exenatide is an injectable hypoglycemic agent that may also be considered before starting patients on insulin. Long-term clinical trials have found that over time, most patients will require combination therapy to achieve adequate glycemic control. Insulin therapy is indicated when glycemic control cannot be achieved and maintained with lifestyle intervention, including diet and exercise, and pharmacologic treatment with oral antidiabetic agents or exenatide.

Conclusions: By combining lifestyle interventions with selected pharmacologic agents, clinicians are now able to individualize treatment regimens to better control hyperglycemia, and to help prevent the development of diabetic microvascular and macrovascular complications. (*Insulin*. 2006;1:166–172) Copyright © 2006 Excerpta Medica, Inc.

Key words: type 2 diabetes mellitus, glycemic control, exercise, pharmacotherapy, insulin.

INTRODUCTION

Large randomized controlled trials have shown that the incidence of microvascular complications of diabetes mellitus (DM) can be greatly reduced by improving glycemic control. The Diabetes Control and Complications Trial¹ showed that in 1441 patients with type 1 DM who were randomized to treatment with intensive insulin therapy and whose glycosylated hemoglobin (A1C) levels were subsequently lowered by 2%, there were marked reductions in the development of microvascular complications. The incidence of diabetic retinopathy was reduced 76%, the progression of preexisting retinopathy was reduced 54%, the incidence of diabetic nephropathy was reduced 67%, and the progression of diabetic neuropathy was reduced 60%. In the 6-year Kumamoto Study,² 110 patients with type 2 DM who were treated with intensive insulin therapy had similar reductions in the development of retinopathy, nephropathy, and neu-

ropathy. The United Kingdom Prospective Diabetes Study (UKPDS)³ found that a 0.9% reduction in A1C levels produced by lifestyle intervention, oral hypoglycemic agents, or insulin among 5102 patients newly diagnosed with type 2 DM led to a 25% to 29% decrease in the incidence of microvascular complications.

Large randomized controlled trials have shown that the incidence of diabetic microvascular complications can be greatly reduced by improving glycemic control.

The findings of these studies led to the development of current American Diabetes Association guidelines for glycemic control, which indicate the following as appropriate target goals: fasting glucose, 90 to 130 mg/dL (normal,

<100 mg/dL); 2-hour postprandial glucose, <180 mg/dL (normal, <140 mg/dL); and A1C, <7.0% (normal, 4.0%–6.0%).⁴ Lower glycemic targets have been advocated (eg, A1C <6.5% by the American Association of Clinical Endocrinologists⁵) if the risk of hypoglycemia can be minimized.

Several studies have also correlated the severity of hyperglycemia with the incidence of macrovascular disease. The Wisconsin Epidemiologic Study of Diabetic Retinopathy,⁶ a trial of 996 patients with type 1 DM, found that a 1% higher A1C level correlated with a 10% increase in the risk of ischemic heart disease and a 17% increase in the risk of stroke. The Honolulu Heart Program⁷ in 8006 men found that the increase in the risk of death due to cardiovascular causes was proportionate to the increase in glucose levels in patients with type 2 DM. The UKPDS⁸ showed that a 1% reduction in A1C was associated with a 21% reduction in DM-related deaths ($P < 0.001$) and a 14% reduction in myocardial infarction ($P < 0.001$).

The goal of this article was to review the options available for obtaining glycemic control in patients with type 2 DM.

MATERIALS AND METHODS

Materials for this article were identified through searches (1965–present) of MEDLINE (English language only). Search terms included *treatment of type 2 diabetes, insulin therapy, oral hypoglycemic therapy, and exenatide*.

THE CORNERSTONE OF GLYCEMIC CONTROL: DIET AND EXERCISE

The cornerstone of glycemic control continues to be successful implementation of a diet and exercise program. Medical nutritional therapy is aimed at reducing caloric intake, increasing fiber intake, and moderating carbohydrate intake. These dietary modifications reduce obesity, lower glucose levels, and improve insulin sensitivity. Regular aerobic exercise, ideally ≥ 20 minutes daily, increases energy expenditure, promotes weight loss, and improves insulin sensitivity.⁹ Adopting a healthier lifestyle, including diet and exercise, can lead to up to a 2% reduction in A1C,¹⁰ and a modest 5% to 10% loss of body weight may substantially improve metabolic control and reduce the need for pharmacologic therapy.¹¹ Lifestyle changes, however, are difficult to achieve and sustain in unsupervised settings.¹² Clinician reinforcement of healthy lifestyle choices throughout the course of the disease helps promote long-term patient adherence. Pharmacologic therapy is unlikely to be effective in patients who fail to adhere to some degree of medical nutritional therapy and regular exercise.

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PHARMACOTHERAPY

For patients who do not respond adequately to diet and exercise therapy alone after a 3-month trial, the addition of

pharmacotherapy to the treatment regimen is indicated. Five classes of oral agents are now approved by the US Food and Drug Administration for the treatment of type 2 DM: the sulfonylureas and meglitinides (both secretagogues), the biguanides (metformin), the α -glucosidase inhibitors (acarbose and miglitol), and the thiazolidinediones (TZDs) (rosiglitazone and pioglitazone). The recently approved glucagon-like peptide-1 (GLP-1) analogue exenatide is an injectable hypoglycemic agent that may also be considered before starting patients on insulin.

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Secretagogues

The sulfonylureas—glipizide, glyburide, and glimepiride—work by binding to receptors on pancreatic β -cells to enhance basal and glucose-stimulated insulin secretion. The meglitinides—repaglinide and nateglinide—have a similar mechanism of action; however, because they bind less effectively to the receptor, they are shorter-acting agents given before meals to augment mealtime insulin secretion.^{13,14} These agents may be beneficial for patients taking sulfonylureas who become hypoglycemic if they miss or delay a meal. The sulfonylureas and repaglinide lower A1C levels by 1.0% to 2.0%, and nateglinide lowers A1C levels by 0.5% to 1.0%.^{15,16} The major risks of the sulfonylureas and meglitinides include hypoglycemia and weight gain. Rates of hypoglycemia range from 1% to 2% annually for most of these agents, although the rate is $\sim 3\%$ with glyburide.¹⁷ Weight gains of up to 10 pounds can be seen with the use of these agents.¹⁸

More than 30 years ago, concerns about the safety of sulfonylureas were raised by the University Group Diabetes Program,¹⁹ which found an increase in the rate of cardiovascular events in type 2 DM patients treated with sulfonylureas. On a cellular level, sulfonylureas work by inhibiting adenosine triphosphate-sensitive, potassium-positive channels. It has been speculated that these agents might inhibit ischemic preconditioning, an adaptive mechanism by which ischemic injury to the myocardium is reduced in chronic ischemia. Studies in isolated rabbit hearts²⁰ and in humans²¹ who underwent transient balloon occlusion of high-grade coronary stenoses found that treatment with glyburide, but not glimepiride, can reverse the benefits of ischemic preconditioning.

In a retrospective Canadian study of 5795 newly treated patients with type 2 DM, higher rates of mortality per 1000 patient-years were found among users of older first-generation sulfonylureas (67.6) and users of glyburide (61.4) compared with users of metformin (39.6).²² However, the UKPDS³ actually showed a nonsignificant trend toward fewer cardiovascular events with sulfonylurea use plus lifestyle

intervention compared with lifestyle intervention alone, and no difference in mortality between sulfonylurea and insulin users.

Biguanides

Metformin is a member of the biguanide class of drugs. Although its cellular mechanism of action remains unknown, metformin has been shown to suppress hepatic gluconeogenesis and, to a lesser degree, to increase glucose utilization by skeletal muscle.²³ Because it does not stimulate insulin secretion, metformin is not associated with hypoglycemia when used as monotherapy.²³ Many patients using metformin will experience weight loss, as well as reductions in triglycerides, low-density lipoprotein (LDL) cholesterol, plasminogen activator inhibitor-1 (PAI-1), and fibrinogen.²³ Metformin also leads to a 1% to 2% reduction in A1C levels.²⁴ The UKPDS²⁵ found that metformin monotherapy, in contrast to monotherapy with diet, insulin, or a sulfonylurea, was associated with a 30% to 40% reduction in the risk of macrovascular complications in overweight patients. Metformin also improves glycemic control when used in combination with sulfonylureas.²⁶

The most common adverse effects with metformin are gastrointestinal symptoms, including nausea, diarrhea, and decreased appetite.²³ These tend to be mild and self-limited, and are minimized by slow titration of the dose and dosing with meals. Adverse effects have led to discontinuation of therapy in only 5% of patients treated with metformin.²⁷ A modest decrease in gastrointestinal events has been reported in studies using the longer-acting metformin extended release.²⁸ Unlike other biguanides, the risk of lactic acidosis is very low with metformin and typically is seen only in patients with preexisting contraindications (eg, impaired renal or hepatic function) or disorders associated with ischemia.²³

The nonglycemic benefits of metformin and the reduction in cardiovascular events shown with obese patients support its early use in overweight patients.²⁹

α -Glucosidase Inhibitors

The α -glucosidase inhibitors, acarbose and miglitol, delay carbohydrate absorption and lower postprandial glucose and insulin levels. Most studies have found that these agents reduce A1C levels by 0.5% to 1% when used either as monotherapy or in combination with sulfonylureas, metformin, or insulin.³⁰⁻³² As monotherapy, there is no risk of hypoglycemia with the α -glucosidase inhibitors, and their effects on the lipid profile are clinically insignificant.^{10,27} The major adverse effects of these agents include diarrhea, bloating, and flatulence.³⁰⁻³² These effects can be alleviated by slowly titrating the medication or by reducing the dose; however, reducing the dose may limit the ability to achieve maximally effective doses.

Thiazolidinediones

The TZDs act by enhancing insulin action in fat and muscle tissue without stimulating insulin secretion.

Rosiglitazone and pioglitazone have been available since 1999 for use as monotherapy or in combination with sulfonylureas, metformin, or insulin. Troglitazone, the first available TZD, was withdrawn from the market in 2000 due to cases of idiosyncratic hepatic failure.³³

The TZDs have been shown to improve A1C levels by 0.8% to 2% when used as monotherapy or in combination with a sulfonylurea or metformin.³⁴⁻³⁶ Because these agents do not stimulate insulin secretion, there is no risk for hypoglycemia when they are used as monotherapy. The TZDs also have nonglycemic effects. Increases in high-density lipoprotein cholesterol levels of 6% to 15% have been seen in clinical trials.^{35,37,38} In a meta-analysis of 23 randomized, controlled clinical trials, the effects of TZDs on cardiovascular risk factors were compared.³⁴ Pioglitazone was found to significantly lower triglyceride levels (-40 mg/dL; 95% CI, -53 to -26) and to have a neutral effect on total and LDL cholesterol levels. Rosiglitazone was found to significantly increase LDL cholesterol (15 mg/dL; 95% CI, 13 to 17) and total cholesterol (21 mg/dL; 95% CI, 18 to 25) and to have a neutral effect on triglyceride levels.

Because of improvements in insulin resistance, the small, dense, atherogenic LDL particles commonly seen in patients with type 2 DM become larger and less atherogenic with TZD treatment. TZDs also lower C-reactive protein and PAI-1 levels, reduce intimal hyperplasia, and improve endothelial function.³⁷ Studies suggest that the modest reductions in blood pressure seen with TZD treatment may be due to reductions in adipocyte production of angiotensinogen and angiotensin II. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events,³⁹ which included 5238 patients with type 2 DM at high risk for cardiovascular events who were already receiving optimized standard-of-care therapies, treatment with pioglitazone for 3 years reduced the combined risk of death, stroke, and heart attack by 16%. Additional cardiovascular outcome studies with TZDs are under way.

In large preclinical trials, rosiglitazone and pioglitazone have not been shown to be associated with hepatocellular injury.⁴⁰ Causality was not able to be determined in several cases of hepatic failure reported with these agents in the post-marketing experience. Because of their chemical similarity to troglitazone, however, neither drug should be prescribed if alanine aminotransferase (ALT) activity is >2.5 times the upper limit of normal at baseline. Additionally, these drugs should be discontinued if ALT activity rises to >3 times the upper limit of normal during treatment. TZDs are associated with salt and water retention, as well as edema, and are contraindicated in patients with New York Heart Association class III or IV congestive heart failure in whom heart failure may be precipitated.⁴¹ Weight gain, with increases in SC fat and reductions in visceral fat, is common with these drugs.^{42,43}

Newer Treatment Option

Exenatide is a new GLP-1 analogue that binds to GLP-1 receptors on pancreatic islets as well as the brain, heart, kid-

ney, and gastrointestinal tract. Exenatide enhances glucose-dependent insulin secretion, reduces postprandial glucagon secretion and hepatic glucose output, slows gastric emptying, promotes satiety, and reduces appetite.^{44,45} Exenatide is approved for use in combination with sulfonylureas and/or metformin. Studies have shown dose-related reductions in A1C levels of 0.4% to 1.1%.^{46–48} Mean weight losses of 1.4 to 1.9 kg and 3.5 to 4.5 kg have been seen after 30 weeks and 82 weeks of treatment, respectively.^{46,48} Exenatide is administered subcutaneously BID before meals via a fixed-dose, pre-filled pen. The most common adverse effects include nausea, vomiting, and diarrhea, which typically are mild to moderate in intensity and decrease in frequency over time.^{46–48} Dropout rates of 3% on average were seen in randomized, placebo-controlled, clinical trials.^{46–48}

PRESERVING β -CELL FUNCTION WITH ORAL THERAPY

The UKPDS demonstrated that patients newly diagnosed with type 2 DM had already lost nearly 50% of their β -cell function,⁴⁹ indicating that the disease and the decline in function had progressed over time, and suggesting that most patients with type 2 DM will eventually require the addition of insulin to maintain adequate glycemic control. Preliminary studies in patients taking TZDs found better maintenance of β -cell function compared with other oral agents.^{50,51} Studies with exenatide in laboratory animals⁵² and in humans⁵³ found maintenance of β -cell mass. Additional studies are needed with both agents to investigate whether they are able to postpone the need for insulin therapy in patients with type 2 DM.

COMBINATION ORAL ANTIDIABETIC THERAPY

The UKPDS found that, over time, most patients required combination therapy to achieve adequate glycemic control.³ Patients presenting with very poor glycemic control (A1C >9.0%) should be considered for combination therapy at the onset to more rapidly achieve tight control since monotherapy with oral hypoglycemic agents or exenatide would not be expected to lower A1C levels >2%. Tablets containing a combination of 2 agents from the sulfonylurea, biguanide, and TZD classes are now available, and may lessen the cost and inconvenience of combination therapy.

INSULIN THERAPY

Insulin therapy is indicated when glycemic control cannot be achieved and maintained with lifestyle intervention (including diet and exercise) and treatment with oral antidiabetic agents or exenatide. Treatment with insulin is also indicated when patients have markedly elevated blood glucose levels, experience profound weight loss, or have a tendency toward ketosis. Initially, a single bedtime dose of neutral protamine Hagedorn (NPH) insulin or a daily dose of insulin glargine or insulin detemir is recommended to help reduce nocturnal hepatic glucose production and to achieve more normal fasting plasma glucose levels. A starting dose of

0.1 to 0.2 U/kg is recommended. Studies comparing NPH insulin and insulin glargine found similar reductions in A1C levels but less frequent hypoglycemia with insulin glargine, especially overnight.^{54,55}

Insulin therapy is indicated when glycemic control cannot be achieved and maintained with lifestyle intervention and treatment with oral antidiabetic agents or exenatide.

Adding insulin to therapy with oral agents can lead to reductions in A1C levels of 1% to 2.5%.¹⁰ When adding insulin to the treatment regimen, it is useful to continue oral insulin secretagogues to support prandial insulin secretion. Insulin sensitizers should be continued to reduce insulin requirements, reduce weight gain, and for their beneficial cardiovascular effects.⁵⁶

In patients whose fasting plasma glucose levels are well controlled but who have inadequate control of postprandial or predinner glucose levels, additional insulin injections are required. Such patients are best controlled with intermediate- or long-acting insulin preparations combined with rapid-acting insulin before meals, similar to regimens used in treating patients with type 1 DM. Rates of severe hypoglycemia or significant weight gain are generally low when physiologic insulin regimens are used.⁵⁷

Inpatient Insulin Therapy

Tight management of hyperglycemia has historically focused on the prevention of long-term complications in the outpatient setting. Recent studies have confirmed that tight glycemic control among inpatients is associated with reductions in mortality, infection rates, and other complications, as well as reductions in length of hospital stay.^{58,59} Oral antidiabetic medications are often contraindicated for hospitalized patients because of decreased appetite, the possibility of lactic acidosis, and the potential for adverse effects such as nausea or diarrhea (metformin), edema or congestive heart failure (TZDs), or hypoglycemia in patients with poor or unpredictable food intake (sulfonylureas). Insulin has become recognized as the best therapeutic modality for hyperglycemic patients in the inpatient setting.⁶⁰ Rapid glucose control can be achieved with insulin, and insulin doses can be customized to match patients' physiologic needs.

CONCLUSIONS

The therapeutic agents now available to treat type 2 DM target the metabolic disturbances that characterize the disease—insulin resistance, excessive hepatic gluconeogenesis, and β -cell failure. Clinicians can now combine lifestyle interventions—the cornerstone of DM treatment—with selected pharmacologic agents, including oral agents and/or insulin, and thereby individualize treatment regimens to aggressively control hyperglycemia and to help prevent the development of diabetic microvascular and macrovascular complications.

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