INTRODUCTION

Over 20 million Americans suffer from diabetes, and approximately one third of these individuals are undiagnosed. An additional 40 to 50 million have prediabetes, which often leads to diabetes if untreated.1,2 Research has demonstrated that improved glycemic control will reduce the development and progression of diabetic complications. However, despite recommendations for early diagnosis and aggressive treatment in recent years and the availability of a larger selection of oral antidiabetic drugs (OADs), most people with diabetes do not attain or maintain treatment goals.3-5 Adequate glycemic control often requires initiation of insulin therapy in a timely and appropriate manner, though studies indicate that early initiation and integration of insulin into treatment is frequently not implemented.6 Earlier insulin therapy can reduce glycemia and micro- and macrovascular risk and potentially improve beta-cell function.7,8 Patient and physician barriers to the early introduction of insulin can be overcome through the use of various strategies.6

This monograph is based on a case-based symposium entitled Tailoring Insulin Therapy to Improve Clinical Outcomes for Type 2 Diabetes presented at the American College of Osteopathic Internists 66th Annual Convention on October 19, 2006, in Phoenix, Arizona.
Epidemiology and Impact of Diabetes

The prevalence of diabetes in the United States is forecasted to more than double from 2005 to 2050—increasing from 5.6% of the population in 2005 to 12.0% in 2050. This increase will affect both men and women and all age groups. In addition, overweight, obesity, insulin resistance, metabolic syndrome, and prediabetes—all risk factors for diabetes—are epidemic in our society. Largely related to its chronic complications, diabetes is associated with increased morbidity, mortality, and costs. In fact, compared to someone without diabetes, medical costs are twice as high for a person diagnosed with diabetes. Diabetes cost the United States ~$132 billion in 2002—$92 billion in direct medical expenditures and $40 billion in lost productivity. Those aged 65 years and older bear about half of all of these costs.

There is a significantly increased prevalence of diabetes in minority populations in comparison to non-Hispanic whites. Whereas 8.7% of all non-Hispanic whites aged 20 years or older have diabetes, the percentages in other populations are much higher—13.3% of African Americans, 9.5% of Hispanic Americans, and 12.8% of American Indians and Alaska Natives. Though still rare, clinically based reports and regional studies suggest that type 2 diabetes in children is being diagnosed more frequently, particularly in minority populations.

Better access to preventive care, early diabetes diagnosis, more intensive disease management, and the use of newer medical technologies could contribute to a reduction in complication risk and better quality of life for people with diabetes and their families and reduced expenditures for health care services.

Causes of the Diabetes Epidemic

The increase in the prevalence of overweight and obese persons is directly linked to an increase in the prevalence of diabetes. Almost all states have a prevalence of obesity of >20%, and for many it is 25%. This has tremendous implications for the future health of Americans, which may include a potential decline in life expectancy in the United States in the 21st century.

Contributing factors to obesity include nutritional changes, excessive portion sizes, and an increasingly sedentary lifestyle. Americans have access to an abundant selection of convenient products, including prepackaged foods, fast food restaurants, and soft drinks, and such foods are often high in fat, sugar, and calories. Portion sizes have also increased, leading to a rise in calorie consumption. Finally, despite a greater awareness of the benefits and need for regular physical activity, most Americans are sedentary, reducing the ratio of energy expended to calories consumed.

This monograph presents a longitudinal case study illustrating the progression of treatment in a patient with type 2 diabetes. The role of insulin therapy in his treatment is emphasized. We hope you find this information helpful in your practice.

Case Study:

Charles Jenkins

Charles Jenkins visits his doctor for a complete physical exam. He has a history of hypertension and dyslipidemia both presently controlled with medications. He is 45 years old, 5 feet 9 inches tall, and weighs 209 lb. His body mass index is 31.2, and he has pronounced abdominal obesity. His blood pressure is 130/78 mm Hg, and he has absent ankle reflexes. Charles has steadily gained weight since college. He has a negative family history for diabetes. Charles’ blood work revealed a fasting plasma glucose (FPG) of 182 mg/dL on initial evaluation and 189 mg/dL on reevaluation. Other blood work revealed an A1C of 8.6%, low-density lipoprotein cholesterol (LDL-C) of 99 mg/dL, triglycerides of 145 mg/dL, and a urine albumin-to-creatinine ratio of 18. His physician makes a diagnosis of diabetes and refers him to a diabetes education program recognized by the American Diabetes Association (ADA) and conducted by certified diabetes educators working in a multidisciplinary diabetes management team. This program will also provide him with medical nutrition therapy and appropriately prescribed physical activity. His physician also initiates therapy with metformin.

ADA Recommendations for Adults With Diabetes

Glycemic control
- A1C: <7.0% for patients in general; as close to normal (<6.0%) without significant hypoglycemia for the individual patient
- Preprandial capillary plasma glucose: 90-130 mg/dL
- Peak postprandial capillary plasma glucose: <180 mg/dL

Blood pressure <130/80 mm Hg

Lipids
- LDL-C: <100 mg/dL
- Triglycerides: <150 mg/dL
- HDL-C: >40 mg/dL
Stages of Type 2 Diabetes

Many of the pathophysiologic changes that characterize type 2 diabetes are present prior to diagnosis. Insulin resistance precedes the development of type 2 diabetes in the majority of patients and is often related to central or visceral obesity.\(^{17,18}\) However, patients cannot develop prediabetes or diabetes without at least a relative defect in the ability to appropriately secrete insulin. Insulin deficiency causes reduced insulin-mediated glucose uptake from muscle, exaggerated glucose production from the liver, and increased free fatty acid mobilization from adipose tissue.\(^{17}\) Beta-cell function begins decreasing as early as a decade before diagnosis and in most patients progressively declines over the course of the disease, which correlates with a progressive loss of glycemic control.\(^6\) The increasing impairment of beta-cell function initially leads to postprandial hyperglycemia and then to fasting hyperglycemia, at which point diabetes is often diagnosed. As beta-cell function continues to decline, insulin secretion becomes less effective and the need for pharmacologic support including insulin increases (Figure 1).\(^{17}\)

Because the average delay in diagnosis of diabetes, and subsequent treatment, is 4 to 7 years or more, as many as 50% or more of patients have some evidence of macrovascular, microvascular, or neurologic diabetic complications at the time of diagnosis.\(^{19}\) Moreover, complications, such as cardiovascular disease, blindness, end-stage renal disease, peripheral neuropathy, and amputation, are influenced by both the duration of diabetes and the average level of chronic hyperglycemia.\(^{20}\) Therefore, early diagnosis and appropriate treatment are needed to decrease diabetic complications and their impact.

**A1C Levels and Clinical Practice**

An FPG is the preferred test to diagnose diabetes in children and nonpregnant adults. Regular performance of an A1C test reflects whether the glycemia of a person with diagnosed diabetes has achieved the target range.\(^{15}\) Studies have demonstrated a direct association between higher A1C levels and increased microvascular and neurologic complications (Figure 2).\(^{21}\)

Regular testing of a patient’s A1C levels (frequency depends on the clinical situation) allows physicians to assess average glycemia, and therefore antihyperglycemic treatment efficacy, over the preceding 2 to 3 months.\(^{15}\) The ADA recommends an A1C goal of <7% for patients in general, and as close to normal (<6%) as possible without significant hypoglycemia for the individual patient.\(^{15}\) The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) recommend a target A1C goal of ≤6.5%.\(^{22}\)

Two landmark trials—the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS)—supported the fact that more intensive control of both type 1 and type 2 diabetes resulted in fewer microvascular and neurologic complications.\(^{23,24}\) The epidemiologic

---

**Figure 1: Stages of Type 2 Diabetes**\(^{17}\)

Adapted from *Diabetes Rev.* 1999;7:139-153.
analysis of the UKPDS did demonstrate that improved glycemia was associated with reduced macrovascular as well as microvascular disease. Furthermore, the observational follow-up of the DCCT in the Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that after an average of 17 years following conclusion of the DCCT, the previously intensively treated patients now had a 42% reduction in the risk for any cardiovascular event and a 57% reduction in the risk for fatal and nonfatal myocardial infarction and stroke compared with conventionally treated subjects.\(^\text{25}\)

There are 2 important messages from this study. The first is that improved glycemic control will reduce the risk for macrovascular disease. And secondly, while it is never too late to begin optimal treatment of diabetes, the earlier it is initiated, the better the outcome. There appears to be a metabolic memory of good and bad control that persists for many years afterward.\(^\text{19,23,26,27}\)

Though treatment regimens among US adults diagnosed with type 2 diabetes have changed substantially over the last decade or so, in one study, only 36% of patients with diabetes reached glycemic control. There are many reasons why so many people with diabetes have difficulty achieving goal glycemia. One of these may be the reluctance to initiate therapy with insulin. Virtually all clinicians would agree that insulin is the most effective antihyperglycemic agent and is able to reduce glucose to a greater degree than other therapies. Yet, in the above study, only 27% of patients with type 2 diabetes were being treated with insulin, and this number had not improved during the previous decade.\(^\text{5}\) Barriers to the early introduction of insulin may be partly due to its route of administration, perceived complexity, the belief that insulin is not effective in type 2 diabetes, and the fear of hypoglycemia and weight gain.\(^\text{27}\)

**Hyperglycemia Management Through Oral Antihyperglycemic Drugs**

Type 2 diabetes is a multifactorial metabolic disease involving both insulin resistance and insulin deficiency, as well as inappropriate glucagon secretion. Addressing these defects forms the cornerstone of current and future therapies for this disease.\(^\text{26}\) It is important to note that blood glucose control is especially effective in preventing the initial development of microvascular complications.\(^\text{28}\)

Lifestyle recommendations are central to the therapeutic regimen of all people with diabetes. However, most patients will require pharmacologic as well as lifestyle therapy to achieve glycemic goals. Most patients will initiate pharmacologic antihyperglycemic therapy with an OAD. There are now 6 classes of OADs that have been developed, each with a different mechanism of glycemic control: sulfonylureas (SUs), non-SU secretagogues (meglitinides), biguanides (eg, metformin), thiazolidinediones (TZDs), alpha-glucosidase inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors. The average A1C reduction with any single oral agent is between 0.5% and 1.5%.\(^\text{28,29}\)
Patients with very poor and symptomatic glycemic control (eg, A1C ≥10% and/or FPG ≥300) are best treated with insulin, at least initially. Insulin-induced improvements in glycemia and glucose toxicity might then allow a downward titration of the insulin, and some patients will subsequently be able to be treated with OADs alone.

Most patients not requiring insulin will begin with an OAD. Frequently, metformin is the first choice if there are no contraindications or intolerance to its use. A recently published ADA/European Association for the Study of Diabetes (EASD) algorithm suggested initiating metformin therapy along with lifestyle measures at the time of diagnosis in most patients.10

The majority of patients with type 2 diabetes will not achieve glycemic goals with lifestyle measures plus a single OAD. Instead, most will require combination therapy with 2 or more agents that have complementary mechanisms of action.11-13 Patients with A1C levels >8.5% to 9% who do not require insulin initially might best have pharmacologic therapy initiated with a combination of 2 agents. Over the past several years, several single-pill combination products incorporating SUs with metformin or a TZD, or metformin with a TZD, have become available.14 Additional single-pill combination products will be available in the near future.

Another antihyperglycemic therapy option is exenatide, an incretin mimetic with glucoregulatory activities similar to the human incretin hormone glucagon-like peptide (GLP)-1. Exenatide, which is administered as a twice-daily subcutaneous (SC) injection, enhances insulin secretion in a glucose-dependent way, slows accelerated gastric emptying, suppresses inappropriately high glucagon secretion reducing hepatic glucose output, and enhances satiety. In 30-week clinical trials, exenatide at a dose of 10 µg SC twice daily reduced A1C levels by a placebo-subtracted 0.9% to 1.0% in patients with type 2 diabetes who had not achieved satisfactory glycemic control despite receiving treatment with metformin and/or a sulfonylurea. These trials also reported a dose-dependent weight loss of 1.6 to 2.8 kg from baseline with exenatide at the 10-µg twice-daily dose. Nausea is the most frequent adverse event with exenatide. It is usually mild to moderate and decreases over time. Hypoglycemia did not occur more frequently than with placebo when exenatide was used in combination with metformin. Increased rates of hypoglycemia have been observed with exenatide compared to placebo added to the regimen of patients treated with SUs or SUs plus metformin. As a result, clinicians should consider reducing the SU dose when adding exenatide to the regimen of patients taking an SU. Exenatide has been approved as add-on therapy to patients with type 2 diabetes receiving metformin and/or an SU and was recently approved to be used in combination with a TZD or a TZD plus metformin in type 2 patients who have not achieved glycemic targets.14,36

The Food and Drug Administration recently approved a new OAD generically known as sitagliptin. It is one of a new class of medication called DPP-4 inhibitors that work by enhancing endogenous GLP-1 and glucose-dependent insulinotropic peptide levels. These incretin enhancers increase glucose-dependent endogenous insulin secretion and lower inappropriately increased glucagon secretion. They have been weight neutral in clinical trials to date and adverse events have been similar to placebo. Sitagliptin is approved for use as monotherapy or as an add-on therapy to metformin or a TZD.37,38

In spite of initial improvement in glycemic control with OAD monotherapy and combination therapy, deterioration in glycemic control may resume as early as 6 months.39 Many patients will eventually need insulin in order to achieve glycemic targets, but initiation of insulin therapy is often long delayed and not used aggressively enough.37 Indeed, in a study by Brown et al, the average patient had nearly 5 years of elevated A1C levels >8.0% from diagnosis until starting insulin and about 10 years of elevated A1C levels >7.0%.40

A recent study of insulin-naïve patients with type 2 diabetes who were inadequately controlled on dual-OAD combination therapy with SU and metformin found that the addition of insulin glargine resulted in similar A1C improvements to that achieved with the addition of the TZD, rosiglitazone. However, when the baseline was ≥9.5%, glargine was associated with greater glycemic reduction compared to add-on maximum-dose rosiglitazone. Insulin glargine was also associated with more hypoglycemia, but less weight gain, no edema, and salutary lipid changes at a lower cost of therapy.41

Case Study:

**Treating Charles Jenkins**

Two years after beginning treatment for his diabetes, Charles is on metformin 2 g/day and rosiglitazone 4 g/day. His A1C initially decreased to 7.1% but is now at 8.2%. His doctor recommends intensification of lifestyle measures and adds basal insulin to his present OAD therapy.
In February 2005, the AACE, ACE, and the American Association of Diabetes Educators, in collaboration with a number of other organizations, conducted the Implementation Conference for Outpatient Management of Diabetes Mellitus. Based on some of the information presented at that meeting, the AACE developed a Road Map for treating patients who are naïve to therapy, patients under treatment, and for patients at risk for diabetes. Both the conference and the subsequent Road Map recommended that effective intervention requires an uncompromising insistence to treat to target through early initiation of appropriate therapies with timely and persistent titration to achieve glycemic targets.

The recently published ADA/EASD diabetes consensus algorithm for the management of hyperglycemia in type 2 diabetes supports the goal of achieving and maintaining glucose levels as close to a nondiabetic range as possible. For many patients, insulin therapy plays a key role in achieving these aggressive goals. The algorithm suggests that for patients who are unable to reach an A1C level of <7% through lifestyle interventions and metformin, physicians should add an SU, a TZD, or insulin. For initiating insulin they recommended bedtime intermediate-acting insulin or bedtime or morning long-acting insulin with titrations until FPG levels are 70-130 mg/dL without hypoglycemia (Figure 3).

This insulin approach has been supported by 2 controlled clinical trials. A treat-to-target trial demonstrated that systematically titrating bedtime basal insulin (neutral protamine Hagedorn [NPH] or glargine) added to oral therapy can safely achieve an A1C of <7% in the majority of patients not at goal on OADs alone. Glycemic efficacy was similar with the 2 treatments, but insulin glargine was associated with a significant reduction in nocturnal hypoglycemia compared with NPH, addressing one of the barriers to the introduction of insulin. A second study determined that the addition to OAD therapy of twice-daily insulin detemir compared to NPH resulted in less variation in preprandial plasma glucose, lower risk of hypoglycemia, and less weight gain at a similar clinically relevant level of improvement in glycemic control.

The ADA/EASD algorithm authors noted that using basal insulin analogs (insulin glargine or insulin detemir) with longer, nonpeaking profiles may decrease the risk of hypoglycemia compared with NPH.

**Case Study:**

**Following Charles Jenkins—Initiation of Basal Insulin Therapy**

Six months after basal insulin analog was added to Charles’ treatment plan and the dose titrated to 45 units at bedtime, his FPG is 110 mg/dL and his A1C is 7.4%. Charles is told to continue lifestyle

---

**Figure 3: Consensus Algorithm for the Initiation and Adjustment of Therapy**

Algorithm for the metabolic management of type 2 diabetes. Reinforce lifestyle intervention at every visit. *Check A1C every 3 months until <7% and then at least every 6 months.* Although 3 oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and expense.

These findings underscore the importance of controlling postmeal glucose levels in order to achieve recommended A1C goals. When patients require prandial insulin, the use of rapid-acting insulin analogs (insulin aspart, insulin glulisine, or insulin lispro) offers a time-action profile, which will match the timing of food absorption better than regular human insulin. The authors of the ADA/EASD algorithm pointed out that analog insulins with very short durations of action may reduce the risk of hypoglycemia compared with regular insulin.

In summary, the newly published ADA/EASD treatment algorithm suggests the following:

- If a patient's A1C is ≥7% after 2 to 3 months of basal insulin therapy and the fasting glucose is in target range (70-130 mg/dL), the patient should perform SMBG before lunch, dinner, and bedtime. Postprandial SMBG measurements may also be helpful.

- Depending on the SMBG results, the patient and his/her health care professional could consider the addition of a premeal dose of a prandial insulin. As noted above, the authors of this manuscript would usually prefer one of the rapid-acting insulin analogs (insulin aspart, insulin glulisine, or insulin lispro) rather than human regular insulin. For example, if the prelunch SMBG is above the target range, rapid-acting insulin should be added before breakfast. If the predinner SMBG is above target, rapid-acting insulin should be added before lunch; or if the prebedtime SMBG exceeds the target, rapid-acting insulin should be added before the evening meal. Usually there might be some initial reduction in the basal insulin dose when initiating a prandial insulin dose. One can usually begin with about 4 units of a rapid-acting insulin analog administered about 10 minutes before the meal and adjust by 2 units every 3 days until SMBG values reach the target range.

- Eventually, patients may need to add an injection of a rapid-acting insulin before each meal in addition to basal insulin. This is commonly referred to as a basal-bolus regimen.

**Benefits of Insulin Therapy**

Macrovascular disease (atherosclerosis) accounts for 70% of deaths in people with type 2 diabetes, with heart attacks and strokes 2 to 4 times more frequent in comparison with the nondiabetic population. It is increasingly accepted that insulin resistance is proatherogenic, and that exogenous insulin itself has a potent anti-inflammatory effect that may inhibit atherogenesis in the long term. Lowering blood glucose levels will have an indirect effect by helping reduce proinflammatory factors and cytokines, adhesion molecules, and reactive oxidative stress. The use of insulin and TZDs, which can improve insulin sensitivity, may well have a direct effect by enhancing anti-inflammatory factors; increasing nitric oxide; reducing reactive oxygen species and proinflammatory cytokines; reducing the initiation of thrombosis, in which tissue factor is a major factor; decreasing free fatty acids; and decreasing plasma concentration of soluble intercellular adhesion molecule-1, monocyte chemoattractant protein-1, plasminogen activator protein-1, and C-reactive protein.

As noted above, the EDIC study assessed individuals an average of 17 years after they had participated in the DCCT. Those who had been intensively treated during the DCCT had a 42% reduction in risk for any cardiovascular event and a 57% reduction in the risk for fatal or nonfatal myocardial infarction or stroke. Furthermore, a number of studies have demonstrated improved outcomes in critically ill hyperglycemic patients who received intensive insulin therapy.

Early insulin replacement reduces hepatic glucose output, enhances insulin-mediated glucose uptake, and decreases lipolysis in muscle and adipose tissue, and may also help to preserve beta-cell function.

**Diabetes Self-management Education**

Diabetes self-management education (DSME) is an indispensable component of the treatment program for people with diabetes. The goals of DSME are to optimize metabolic control, prevent acute and chronic complications, and enhance the quality of life for people with diabetes. DSME includes an assessment of patients’ specific measures, but also to perform self-monitoring of blood glucose (SMBG) pre- and postprandially. When he returns for a follow-up visit, his glucose profile shows values between 90 and 130 mg/dL at fasting and before meals. Charles has significant hyperglycemia 2 hours after his evening meal and at bedtime. A rapid-acting insulin analog given 10 minutes before his evening meal is added to Charles’ treatment regimen.
educational needs and goals, an educational and behavioral intervention directed toward helping achievement of these goals, and an evaluation of goal attainment.53

Two studies examining the effectiveness of DSME demonstrated that involving patients in decision making was associated with improvements in glycemic control as well as psychosocial and health outcomes.54,55 Diabetes self-management education is most effective when the emphasis is placed on culturally relevant behavioral strategies.56 A major component of Charles’ diabetes medical care has been instruction in lifestyle interventions, including medical nutrition therapy (MNT) and appropriately prescribed increased physical activity. His MNT emphasized portion control, food awareness, and the use of SMBG feedback as an educational tool. Web sites of the National Diabetes Education Program (www.ndep.nih.gov), the AACE (www.powerofprevention.com), and the ADA (www.diabetes.org) have extensive resources to help clinicians and their patients better implement lifestyle changes.

**Value of Self-monitoring of Blood Glucose**

Self-monitoring of blood glucose provides feedback on the impact of nutrition, physical activity, and OAD and/or insulin therapy. It allows for the design, implementation, and adjustment of physiologic insulin replacement therapy.3 Increased frequency of SMBG is also associated with better glycemic control, even in patients being treated with OADs.57,58 Moreover, because SMBG is useful in detecting hypoglycemia, patient safety is improved.59 Teaching patients to record their blood glucose at various times during the day, such as preprandially, 1 to 2 hours postprandial, and at bedtime, helps them identify glycemic patterns that can guide diabetes management. The results can be used to adjust MNT, exercise, and/or pharmacologic therapy to achieve glycemic goals.59

**Barriers to Insulin Treatment**

Because of the progressive impairment of beta-cell function in type 2 diabetes patients, obtaining target glycemic control often requires insulin supplementation therapy. While patients may agree with their doctors on the need for better control, they need support and education in accepting and initiating this step. The Diabetes Attitudes, Wishes, and Needs (DAWN) study found substantial resistance to insulin therapy on the part of both patients and their health care professionals.60 The DAWN study results indicated that patients had a lower belief in the efficiency of insulin, blamed themselves for the need for insulin therapy,
and felt insulin would restrict their lives. An informal survey of diabetes educators in 2005 identified the following additional barriers to starting insulin: concern about pain from needles and injections; fear that starting insulin is associated with diabetes complications; the belief that insulin is actually toxic and causes weight gain; inadequate support and resources; and a lack of updated information. There was also concern about the potential cost of insulin therapy.

The DAWN study also pointed out that health care professionals often felt insulin therapy should be delayed as long as possible and had varied beliefs about its efficacy. Insulin use is often seen as a last resort to be used only when patients have “failed” oral therapy. Unfortunately, insulin has sometimes been used as a “threat” to try to compel adherence to therapy.

To overcome patients’ barriers to, and improve acceptance of, insulin therapy initiation, professionals can reinforce the progressive nature of diabetes and the role of insulin therapy in reducing deterioration of metabolic control. This may require multiple conversations with patients over several visits. Patients can be informed that, with appropriate insulin therapy, they will reduce the risk for micro- and macrovascular complications and increase the likelihood of improved overall health and quality of life.

**Patient Self-management of Insulin Therapy**

Patients who require both basal and prandial insulin therapy can be taught to observe SMBG patterns and their response to variation in insulin doses, nutrition, physical activity, and other factors. They can learn to self-manage a basal/bolus insulin regimen to obtain better glycemic control.

Basal insulin is usually adjusted to achieve target fasting glucose values. Premeal rapid-acting insulin doses are adjusted to achieve target postmeal glucose values. Patients need to take into account the amount of food, especially carbohydrate, to be consumed and the amount of subsequent anticipated physical activity. Ideally, patients should record information about the time of the meal, its caloric and carbohydrate content, insulin dose, and pre- and postprandial SMBG readings, while initially eating consistent amounts of carbohydrate at meals and snacks. Once pre- and postprandial SMBG values are in target range, insulin-to-carbohydrate ratios can be determined by dividing the number of grams of carbohydrate eaten at a meal by the units of premeal insulin (eg, 45 g carbohydrate divided by 3 units of insulin is an insulin-to-carbohydrate ratio of 1 unit of insulin to every 15 grams of carbohydrate). Patients could then use this insulin-to-carbohydrate ratio to calculate appropriate insulin coverage for meals with varying content of carbohydrate. One should remember, however, that ratios can be different at different times of day and can be influenced by stress, illness, and variations in physical activity.

Another method of calculating the insulin-to-carbohydrate ratio uses the 450 or 500 rule. This does not account for individual variation as much as using detailed records. If using rapid-acting insulin as the premeal insulin, one divides 500 by the total daily dose of basal plus premeal insulin (use the number 450 if one is using regular human insulin). For example, if the patient is using basal insulin at night plus premeal rapid-acting insulin and their total daily dose of basal plus premeal insulin is 33 units, one would divide 500 by 33 to give an insulin-to-carbohydrate ratio of 1:15. One would then adjust the ratio over time based on pre- and postprandial SMBG results.

In addition, patients whose premeal SMBG readings are above target can add a correction dose calculated by a formula that divides the difference between the patient’s present glucose value and the target glucose value by an insulin sensitivity factor determined by his/her physician. For example, if the patient’s premeal SMBG is 180 mg/dL, the target glucose is 120 mg/dL, and the insulin sensitivity factor is 30, the calculation would be $180 - 120 = 60 ÷ 30 = 2$ units, which would then be added to their premeal insulin dose. The insulin sensitivity factor is an estimate of the number of mg/dL that a patient’s glucose would be lowered by 1 unit of insulin. One can initially estimate the insulin sensitivity factor in a patient using basal insulin and premeal rapid-acting insulin analog by dividing 1800 (if the patient is using a rapid-acting insulin analog as their premeal insulin; if the patient is using human regular as the premeal insulin the number would be 1500) by the patient’s total daily dose of basal plus premeal insulin. So if a patient’s total daily dose of basal plus premeal insulin is 60 units and he/she is using a rapid-acting insulin analog, one would divide 1800 by 60 giving an insulin sensitivity factor of 30. This, of course, is a rough estimate, and the insulin sensitivity factor would need to be adjusted based on the patient’s response.

If a patient’s premeal SMBG is in the hypoglycemic range (blood glucose ≤70 mg/dL), the hypoglycemia should be treated with 10 to 15 g of fast-acting carbohydrate if the glucose is between 51 and 70 mg/dL, and with 20 to 30 g of fast-acting carbohydrate for blood glucose levels ≤50 mg/dL. Glucose levels should be retested 15 minutes after
ingestion and repeat treatment taken as needed based on SMBG. Once blood glucose is >70 mg/dL, the patient should use the appropriate insulin dose to cover carbohydrate intake at the meal. Patients will usually need education provided by a certified diabetes educator and a dietitian to learn carbohydrate-counting and correction-dosing skills.


A recent multicenter 24-week study, conducted by Bergenstal and colleagues, evaluated starting a fixed dose of mealtime glulisine and using an algorithm to adjust the dose to target based on preprandial glucose patterns compared with starting and adjusting glulisine using an insulin-to-carbohydrate ratio. Subjects had type 2 diabetes uncontrolled on ≥2 daily insulin injections and were switched to basal-bolus therapy plus or minus metformin with daily glargine titrated to FPG <95 mg/dL and glulisine before meals with minimal metformin with daily glargine titrated to A1C targets of <95 mg/dL and glulisine befor e meals with minus metformin with daily glargine titrated to were switched to basal-bolus therapy plus or minus metformin with daily glargine titrated to individualized target goals.

Failure to initiate insulin therapy in a timely or optimal manner is associated with longer time periods with elevated blood glucose levels, resulting in damaged or lost beta-cell function, leading to fewer complications and enhanced quality of life. Patient education can overcome barriers to insulin use, and the use of a basal/bolus system can help to achieve individualized target goals.

Summary

Overweight, obesity, insulin resistance, metabolic syndrome, prediabetes, and diabetes are epidemic in our society. Additionally, despite a greater number of treatment options available and an increasing realization of the necessity for achieving more optimal glycemic control, national statistics clearly show that most people with type 2 diabetes are not achieving treatment targets. Failure to initiate insulin therapy in a timely or appropriate manner contributes significantly to inadequate glycemic control. Earlier insulin therapy can reduce glycemia and micro- and macrovascular risk and potentially even improve beta-cell function, leading to fewer complications and enhanced quality of life. Patient education can overcome barriers to insulin use, and the use of a basal/bolus system can help to achieve individualized target goals.

References


42. Hermansen K, Derezenski T, Kim H, Gall M-A. Treatment with insulin detemir in combination with oral agents is associated with less risk of hypoglycaemia and less weight gain than NPH insulin at comparable levels of glycaemic improvement in people with Type 2 diabetes. Presented at: 40th Annual Meeting of the European Association for the Study of Diabetes; September 5-9, 2004; Munich, Germany.


