Family Practice News®

HIGHLIGHTS OF AN EDUCATIONAL SYMPOSIUM
Presented in San Francisco, CA, April 13, 2005

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Achieving Lifetime Glycemic Goals in Patients With Type 2 Diabetes

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This supplement is based on a symposium held April 13, 2005, in San Francisco, California.

This educational supplement to Family Practice News was supported by an educational grant from

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The supplement was produced by the medical education department of International Medical News Group. Neither the Editor of Family Practice News, the Editorial Advisory Board, nor the reporting staff reviewed or contributed to its contents. The opinions expressed in this supplement are those of the faculty and do not necessarily reflect the views of the supporter or the Publisher.

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INTERNATIONAL MEDICAL NEWS GROUP

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TARGET AUDIENCE

This activity is intended for primary care physicians who are involved in the diagnosis and treatment of patients with diabetes.

FINANCIAL SUPPORT

This supplement is supported by an educational grant from sanofi-aventis U.S.

Myth or Fact? Addressing Concerns About the Use of Insulin in Patients With Type 2 Diabetes

Stephen N. Davis, MD, FRCP

Of an estimated 21 million people with diabetes mellitus in the United States, 90% to 95% have type 2 diabetes.[1] Almost 5.2 million cases of diabetes are undiagnosed[1] and remain untreated. Prediabetes is associated with blood glucose levels that are higher than normal, but not high enough to be identified as diabetes[2]; if left untreated, prediabetes often leads to diabetes. Currently, cases of prediabetes are progressing to diabetes at a rate of 11% per year. If this trend continues, the number of people with diabetes will double over the next 8 to 10 years.[3]

A driving force behind the explosive epidemic of diabetes is the ongoing increase in obesity, which has risen by 61% during the past decade.[4] The prevalence of diabetes rose by 49% between 1990 and 2000[4] and will continue to increase along with the rate of obesity.

Over time, elevated glucose levels left uncontrolled significantly increase the risk for the development of debilitating chronic complications, including retinopathy, nephropathy, neuropathy, and coronary heart disease.[2,5] Therefore, the therapeutic goal of diabetes management is to prevent or mitigate these complications. Determining the most effective prevention or treatment plan for type 2 diabetes requires a thorough understanding of the pathophysiology of the disease.[6]

Pathophysiology

In an individual without diabetes, ingestion of carbohydrates or other nutrients triggers a rapid release of insulin from the pancreas into the portal vein. The insulin suppresses hepatic glucose release and stimulates glucose uptake from the general circulation into the liver and skeletal muscles, thereby restraining the increase in postprandial plasma glucose concentrations.[7] The normal physiologic release of insulin consists of postprandial and basal components. Postprandial insulin secretion occurs in response to a meal or snack and is released in two phases. The first phase, also referred to as the acute phase, constitutes a rapid rise in insulin, occurs within the first 1 to 3 minutes following the rise in plasma glucose levels, and lasts for about 10 minutes. The acute phase is directly related to the rate and amount of glucose entering circulation. It is primarily responsible for suppressing hepatic glucose release and stimulating the uptake of glucose into the liver.[8] Following the acute phase is a second phase wherein insulin rises more gradually and is responsible for the uptake of glucose into the skeletal muscles. The duration of this phase is directly related to the degree and duration of glucose elevation in circulation.[8] The basal component of insulin release is a low-level secretion of insulin that occurs continuously between meals and throughout the night to maintain basal glucose homeostasis. Basal insulin retards hepatic glucose production in the postabsorptive state via gluconeogenesis and glycogenolysis, and inhibits the breakdown of fat and proteins.[9]

The acute insulin response stimulated by glucose is significantly reduced in individuals with elevated fasting glucose levels. This was demonstrated in a study investigating the relationship between plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. This study was conducted in 66 subjects with a wide range of fasting plasma glucose (FPG) levels. The acute insulin response was reduced by almost 50% in subjects with an FPG level between 100 and 114 mg/dL and completely absent in subjects with an FPG level above 115 mg/dL.[10]

Currently, diagnosis of diabetes is defined as an FPG level of 126 mg/dL or higher (**Table 1** on page 4).[11] Based on this criterion, insulin deficiency is present in the prediabetic stage and, by the time a diagnosis is made, patients lack an acute insulin response and have less than

50% of normal insulin secretion.[14] The subsequent insulin deficiency results in elevated hepatic glucose production, decreased glucose transport into liver and muscle, and increased breakdown of fat. The lack of adequate suppression of hepatic glucose production leads to elevated basal and postprandial plasma glucose concentrations. This abnormality in hepatic glucose regulation can be restored by appropriate insulin therapy.[15] Due to insulin resistance, however, patients with type 2 diabetes, compared with individuals without diabetes, require two to three times more insulin to suppress hepatic glucose release and increase peripheral glucose uptake. This is an important consideration when determining the appropriate insulin dose in these patients. Thus, both insulin resistance and insulin deficiency play a fundamental role in the pathogenesis of type 2 diabetes.[6,7] The exact role that each plays in the progression of type 2 diabetes can be further understood by examining the natural history of type 2 diabetes.

Natural History of Type 2 Diabetes

Insulin resistance is the initial metabolic defect in type 2 diabetes. Most patients have insulin resistance for many years prior to the consequent diagnosis of type 2 diabetes. Insulin resistance remains relatively constant over the course of the disease.[6] The progression from impaired glucose tolerance or prediabetes to early type 2 diabetes is marked by the reduction in insulin secretion caused by progressive pancreatic β-cell dysfunction. As long as the β cells are able to compensate for insulin resistance by increasing insulin production and secretion, blood glucose levels remain normal or near normal. Eventually, β-cell function begins to deteriorate and insulin secretion fails. Over time, the failure of β cells to compensate for insulin resistance marks the beginning of type 2 diabetes (**Figure 1** on page 5).[6] It has been estimated that about 50% of β-cell function is already lost by the time of diagnosis.[16,17] Earlier diagnosis and more aggressive forms of intervention to achieve and maintain good glucose control in the prediabetic stage may prevent the progressive loss of β-cell function and may decrease long-term microvascular and macrovascular complications.[14]

Treatment of Type 2 Diabetes

Lifestyle Interventions

Dietary measures and increased physical activity are key nonpharmacologic treatment approaches and the foundation for the management of type 2 diabetes.[18] The improvement in outcomes following lifestyle changes has been demonstrated in a large, randomized clinical trial in adults who were at high risk for developing diabetes. A 7% loss in body weight and 150 minutes of physical activity per week reduced the progression of prediabetes to diabetes by 58% over an average follow-up of 2.8 years.[19] By increasing physical activity and reducing caloric intake, subjects improved their blood pressure and triglyceride and cholesterol levels.[4] Furthermore, lifestyle modification was more effective in delaying or preventing diabetes than treatment with the oral antidiabetic agent metformin (Glucophage®): a 58% reduction in the incidence of diabetes was obtained with lifestyle modification, compared with a 31% reduction with metformin.[19] Unfortunately, the long-term impact of these interventions is frequently disappointing, and most patients will require pharmacotherapy to achieve and maintain adequate glycemic control.

Oral Antidiabetic Agents

Pharmacotherapy is generally initiated with an oral agent, such as a sulfonylurea, metformin, the α-glucosi-

Table 1. Criteria for the Diagnosis of Diabetes Mellitus[11-13]*†

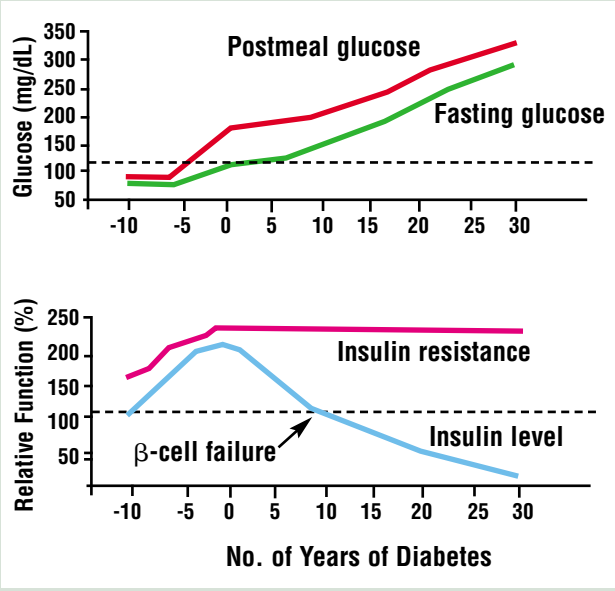
1. Symptoms of diabetes plus a casual plasma glucose concentration of ≥200 mg/dL (11.1 mmol/L).
   Casual is defined as any time of day without regard to time since last meal.
   The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
   or
2. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L).
   Fasting is defined as no caloric intake for at least 8 hours.
   or
3. 2-hour postload glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT.
   The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

OGTT = oral glucose tolerance test.

*In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use.

†Reprinted with permission from The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.[11]

Figure 1. Natural History of Type 2 Diabetes: Obesity IGT Diabetes (Uncontrolled Hyperglycemia)*



IGT = impaired glucose tolerance.
*Reprinted with permission from Bergenstal RM et al.[6]

dase inhibitor acarbose (Precose®), or a thiazolidinedione.[20] However, sustained success with monotherapy for more than a few years is unusual.[20] The failure to maintain glycemic control with oral agents is due to the progressive decline in β-cell function, which leads to insulin deficiency. This has been illustrated in the United Kingdom Prospective Diabetes Study (UKPDS), wherein 6 years of treatment with diet, metformin, or a sulfonylurea resulted in deterioration of glycemic control. However, treatment with a sulfonylurea improved glycemic control via a greater improvement in β-cell function at year 1 compared with treatment with diet or metformin.[17] Additionally, the UKPDS demonstrated that good glycemic control reduces the risk of macrovascular and microvascular complications.[21] Each 1.0% reduction in glycosylated hemoglobin (A1C) was associated with a 21% decrease in any end point related to diabetes, a 14% decrease in risk of myocardial infarction, a 12% decrease in risk of stroke, and a 37% decrease in risk of microvascular complications. The lowest risk for these complications was observed in subjects with A1C levels below 6.0%.[21] However, evidence of a risk for myocardial infarction and microvascular disease existed even at the A1C concentration of 5.5%. Therefore, it is best to achieve an A1C level as low as possible without causing unacceptable side effects, such as hypoglycemia.

Patients who fail to achieve and maintain good glycemic control with two oral agents could be switched to triple oral therapy.[22] Even combination treatments, however, have shown limited success in achieving glycemic targets. In a randomized, double-blind, placebo-controlled trial, 200 type 2 diabetic subjects experienced a 1.4% reduction in A1C levels after receiving combination therapy with a sulfonylurea, metformin (Glucophage®), and troglitazone (Rezulin®) for 6 months. In addition, only 14% of these subjects were able to achieve an A1C level of 7.0%.[23] In another open-label trial, 365 subjects received treatment with a combination of glyburide (Diabeta®, Glynase®, Micronase®), metformin, and rosiglitazone (Avandia®) for 6 months, resulting in a 1.0% reduction in A1C levels and 42% of subjects attaining the target A1C level of less than 7.0%.[24]

Insulin Therapy

Alternatively, patients can be switched from oral therapy to insulin therapy. A substantial number of patients with type 2 diabetes require long-term therapy with insulin to achieve and maintain optimal glycemic targets.[6,18] Additionally, initiating insulin therapy early in patients with type 2 diabetes could halt disease progression and provide long-term glycemic control.[25]

Barriers to Insulin Therapy

Although the benefits of insulin therapy have been well established, there are several patient and professional barriers to using insulin that need to be first addressed and then dispelled before this therapy can be initiated effectively. The major barriers to initiating insulin therapy include patients' concerns regarding injecting insulin, hypoglycemia, and weight gain.[25] In addition, there are some misconceptions among physicians that insulin treatment worsens insulin resistance and increases the risk of cardiovascular disease.[24,26] Syringe needles now have finer gauges; therefore, injections are relatively painless.[6] Although treatment with insulin can cause hypoglycemia, the risk of a severe episode is uncommon if insulin is used appropriately. Initiation of insulin therapy is associated with a modest weight gain, especially in the first 3 to 6 months of therapy. Weight gain with insulin glargine (Lantus®) vs neutral protamine Hagedorn (NPH; Novolin®) insulin is 0.4 kg vs 1.4 kg; $P<0.0007$.[25,27] This is a consequence of the improvement in glycemic control, wherein patients continue to follow the same dietary practices but no longer have the caloric loss from glucosuria.[25] Another reason for the observed weight gain is that patients using insulin increase their caloric intake to raise their blood glucose levels to avoid hypoglycemia. This problem can be avoided by selecting appropriate agents that are associated with a low incidence of hypoglycemia.

Contrary to the concern that insulin therapy may

cause even more insulin resistance, insulin therapy actually improves insulin sensitivity. This is supported by findings from several glucose-clamp studies that measured insulin sensitivity before and after treatment with insulin. In all of these studies, insulin sensitivity substantially improved in subjects after restoration of glycemic control with insulin. The increase in insulin sensitivity has been attributed to the reduction of glucose toxicity and lipotoxicity resulting from insulin treatment.[26]

In addition, an improvement in lipid profiles has been demonstrated by a 60% reduction in serum triglyceride levels and a 24% reduction in total cholesterol levels in patients with type 2 diabetes after 6 months of treatment with insulin.[28] Similarly, cardiovascular outcomes also improve during treatment with insulin. In a prospective, randomized study, insulin therapy significantly reduced the mortality rate in subjects who had type 2 diabetes and an acute myocardial infarction.[29] In a separate study, insulin therapy reduced morbidity and mortality in critically ill subjects and did not increase the risk for cardiovascular disease.[30] In a 3.5-year study, treatment with insulin glargine, which is a long-acting basal insulin, not only induced a sustained improvement in glycemic control but also improved endothelial function markedly.[31] Overall, these data provide compelling evidence for the lack of cardiovascular risk with insulin therapy.

A KEY PRINCIPLE OF INSULIN THERAPY IS TO MIMIC THE NORMAL PHYSIOLOGIC PATTERN OF INSULIN RELEASE AS CLOSELY AS POSSIBLE WITH ADEQUATE BASAL AND PRANDIAL SUPPLEMENTATION.

Principles of Insulin Therapy

Once barriers to initiating insulin therapy have been dispelled, physicians must develop the most appropriate strategy for initiating insulin therapy that will be effective in achieving the target A1C goals. A key principle of insulin therapy is to mimic the normal physiologic pattern of insulin release as closely as possible with adequate basal and prandial supplementation. There are several strategies to initiating insulin therapy. One approach is to use twice-daily, split-mixed or premixed insulin formulations.[25] These formulations are mixtures of regular human insulin (RHI) and a long-acting insulin.[32] In a 24-week study of 188 subjects with inadequately controlled type 2 diabetes who were currently taking two oral medications, treatment with a 70/30 insulin mixture plus metformin was as effective as triple oral therapy in lowering A1C and FPG levels.[33] However, a higher percentage (16.3%) of subjects using the triple oral regimen did not complete the study due to either the lack of efficacy or drug-related side effects.[33] Although premixed insulin formulations are effective and simple to use, they lack flexibility for specific insulin adjustments based on the individual needs of each patient. Because the insulin components cannot be adjusted separately, meals must be taken on a regular schedule to avoid hypoglycemia.[32]

Basal Insulin

Alternatively, insulin therapy can be initiated with an evening dose of basal insulin,[32] while continuing the use of oral agents.[16] The options available for providing basal insulin include human NPH insulin, lente (Humulin® L), ultralente (Humulin® U), insulin glargine, insulin detemir (Levemir®), and continuous subcutaneous insulin infusion. Lente and ultralente were removed recently from the market and insulin detemir is not yet available in the United States. Human NPH insulin has a mean duration of action of less than 24 hours[25] and, therefore, requires multiple daily injections. Additionally, treatment with NPH insulin shows substantial fluctuations in blood glucose levels with erratic peaks, which result in significant daily variations in its action and unpredictable hypoglycemia.[25]

Insulin glargine provides a continuous 24-hour basal coverage with no pronounced peaks.[34] The beneficial effect of adding insulin glargine to oral therapy in patients with inadequate glycemic control with one or two oral agents was demonstrated clearly in the Treat-to-Target Trial.[35] In this study, the addition of insulin glargine or NPH insulin to oral therapy led to similar efficacy results by effectively reducing A1C levels (to 6.96% and 6.97% with glargine and NPH, respectively) and mean FPG levels (to 117 mg/dL and 120 mg/dL, respectively). However, nearly 25% more subjects achieved these beneficial effects without documented nocturnal hypoglycemia with insulin glargine than with NPH insulin.[35] Additionally, adding insulin glargine to oral therapy has been shown to be more effective in reducing fasting blood glucose and A1C levels when compared with the conventional practice of using twice-daily premixed insulin without oral agents.[36] Importantly, the risk of hypoglycemic events was reduced about twofold with insulin glargine compared with premixed insulin.[36] Thus, insulin glargine provides a simple regimen for providing effective and safe 24-hour basal coverage. This can facilitate earlier and effective use of insulin in routine medical practice.[35]

Prandial Insulin

In addition to providing continuous 24-hour basal insulin coverage, an effective insulin regimen should provide appropriate prandial insulin replacement.[16,32] Postprandial glucose levels are an independent risk factor for predicting mortality, as shown in the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study. In this study, the overall risk of death for subjects with impaired glucose tolerance was greater than the risk in subjects with impaired fasting glucose levels. Furthermore, the increase in postprandial glucose levels resulted in a linear increase in mortality.[37]

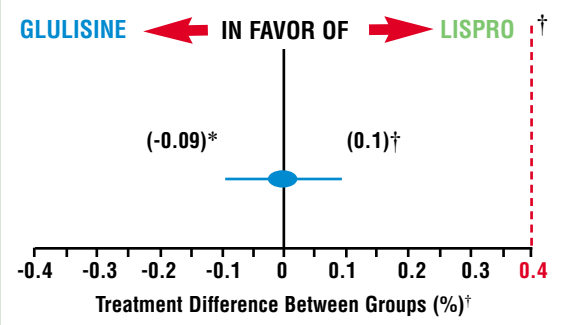
The options available for providing prandial insulin include RHI and the rapid-acting insulin analogues.[38] Regular human insulin has a slow onset of action, and its action profile does not mimic physiologic mealtime insulin secretion. Due to the slow onset of action, RHI must be administered 30 to 45 minutes before mealtime to obtain optimal prandial coverage. This requirement for mealtime planning is sometimes difficult for patients to follow.[38] The rapid-acting analogues, such as insulin lispro (Humalog®) and insulin aspart (NovoLog®), reach peak levels within an hour and have a duration of action of 2 to 4 hours.[32] Thus, by closely mimicking the physiologic postmeal rise of insulin, these agents provide better prandial insulin coverage[38] and a lower risk of hypoglycemia compared with RHI.[32]

Recently, insulin glulisine (Apidra®), a new rapid-acting insulin analogue that closely mimics physiologic insulin, was introduced. The efficacy and safety of insulin glulisine have been demonstrated in several well-designed clinical trials. In a randomized, multicenter, multinational, open-label, parallel-group study involving 876 subjects with a mean A1C level of 7.55%,[32] insulin glulisine produced a greater reduction in A1C levels (–0.46% vs –0.30%) as well as lower postbreakfast (156 mg/dL vs 162 mg/dL) and postdinner (154 mg/dL vs 163 mg/dL) blood glucose levels compared with RHI.[39] Direct comparisons of rapid-acting analogues in type 2 diabetes are not available; however, in a 26-week, multicenter, randomized, controlled trial in 672 subjects with type 1 diabetes, insulin glulisine was shown to be comparable to insulin lispro in efficacy (**Figure 2**) and incidence of hypoglycemic episodes (**Figure 3**).[40] Additionally, rapid-acting analogues offer a more convenient option for patients without the requirement of stringent mealtime planning because these agents can be used either before or a few minutes after the beginning of a meal.[41]

Conclusions

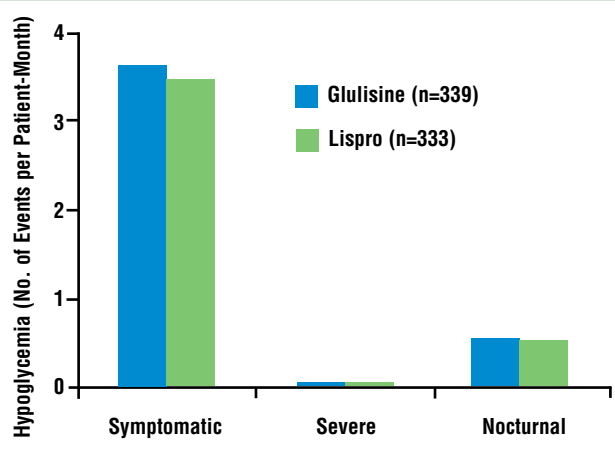
The presence of type 2 diabetes increases an individual's risk of developing debilitating microvascular and macrovascular conditions,[5] and its occurrence is increasing at a startling rate.[43] While we know that diabetes-related complications can be prevented by controlling glycemic levels,[14] achieving and maintaining long-term control is challenging. Although lifestyle changes to diet and exercise and pharmacotherapy with oral agents may be effective in providing glycemic control initially, these interventions do not successfully maintain glycemic control in the longer term.[18,20] Most patients with type 2 diabetes will eventually require treatment with exogenous insulin.[6,18] A combination of basal insulin with a rapid-acting insulin analogue for prandial coverage closely mimics physiologic insulin patterns and provides patients with an effective, flexible, and simple strategy to achieve their glycemic goals.

Figure 2. Difference in Mean A1C Values at Endpoint (26 Weeks) With Insulin Glulisine Versus Insulin Lispro[40]



*Mean (95% confidence interval). *P*=0.93, glulisine versus lispro.
†Treatment difference: Insulin glulisine – insulin lispro. Predicated on the predefined inferiority margin of 0.4%, glulisine was proven to be noninferior compared with lispro (upper bound of the 95% CI was <0.4%).

Figure 3. Incidence of Hypoglycemia With Insulin Glulisine Versus Insulin Lispro*



*Adapted with permission from Dreyer M et al.[40]

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Achieving Lifetime Glycemic Goals in Patients With Type 2 Diabetes

Frank Lavernia, MD

CASE STUDY

History and Laboratory Assessment

MP, a 52-year old Hispanic male with a 7-year history of type 2 diabetes, presents for his yearly physical examination. A year ago, his glycosylated hemoglobin (A1C) level was well controlled at 6.6%. MP has been taking metformin 1,000 mg twice daily and glyburide 5 mg twice daily. Although MP feels healthy, he has gained 16 pounds over the past year. He is 5'7" tall and weighs 210 lb. MP admits not following a good diet and resists monitoring his blood glucose level. His blood work reveals a random glucose level of 230 mg/dL and an A1C level of 9.4%. As is the case in most patients with type 2 diabetes, MP also has a history of hypertriglyceridemia and hypertension. Although his total and low-density lipoprotein cholesterol levels are well controlled with fenofibrate (Tricor®) at 180 mg/dL and 88 mg/dL, respectively, his triglyceride level is elevated (240 mg/dL), and his high-density lipoprotein level is very low (27 mg/dL). MP's hypertension is under control with candesartan (Atacand®) (32 mg) and hydrochlorothiazide (12.5 mg). His kidney and liver function test results are normal. Based on these results it is clear that, in addition to having inadequately controlled type 2 diabetes, MP appears to have the metabolic syndrome.

Background

Diabetes mellitus is a common chronic disease affecting approximately 6.3% of the US population.[1] The prevalence of type 2 diabetes is significantly higher in certain minority groups and is rapidly increasing among children and adolescents.[2] As a leading cause of morbidity and mortality in the United States, type 2 diabetes is a significant economic burden to the health care system.[3] More than 1 of every 10 health care dollars is spent on diabetes care.[2] This economic burden can be substantially reduced by improving diabetes management. Once a diagnosis of diabetes is made, the first step is to develop an effective plan to manage all the components of diabetes care, including hyperglycemia, dyslipidemia, hypertension, and, most important, prevention and management of complications.[4] Achieving good glycemic control is fundamental to the prevention and management of diabetes complications.[3] Diabetes management should also emphasize patient education regarding (1) appropriate behavior changes, (2) the importance of self-monitoring of blood glucose levels, and (3) the role of diet and exercise, which will enable patients to improve diabetes care.

CASE STUDY

Initial Therapy

At this visit, MP is advised to improve his eating habits and increase his physical activity. To assist MP in making these changes, he is referred to a dietician and a diabetes educator. He is also counseled about self-monitoring his blood glucose levels at least once or twice daily and four times daily during the week prior to his follow-up visit. Unfortunately, as is the case with most patients with type 2 diabetes, MP has not been successful in achieving glycemic control through lifestyle interventions. At the 2-month follow-up visit, the premeal and postmeal blood glucose levels are elevated despite exercise, and his A1C level is 9.0%.

Modification of Treatment Regimen

This case illustrates the failure of lifestyle modifications and oral therapy to achieve target A1C levels. When treatment with two agents fails to achieve and maintain glycemic targets, choices include the addition of either a third oral antidiabetic agent, an incretin mimetic, or insulin. Adding a third oral agent is unlikely to decrease the A1C level from 9.0% to the target A1C level of less than 7.0%. A randomized, double-blind, placebo-controlled trial[5] studied 200 subjects with type 2 diabetes whose glucose levels were inadequately controlled taking two oral agents. Adding a third oral agent, troglitazone (Rezulin®), to a regimen of a sulfonylurea and metformin lowered the A1C level by 1.4%. Additionally, only 14% of subjects were able to achieve an A1C level of 7.0% or less.[5] Therefore, with an A1C level of 9.0%, MP will require insulin to achieve an A1C below 7.0%.[3]

Insulin Therapy

Insulin therapy should replace the two components of physiologic insulin secretion: basal and prandial.[6] Basal insulin secretion occurs continuously between meals and throughout the night to maintain basal glucose homeostasis.[7] The basal insulin secretion meets about 50% of the patient's daily insulin needs.[6] Prandial insulin secretion provides an additional 10% to 20% of the daily requirement at each meal. It promotes the dispersal of glucose into the periphery and thus limits postmeal hyperglycemia.[7] Ideally, each component of insulin replacement therapy should come from a different insulin analogue with a specific profile. Over the years, several insulin preparations have been developed using recombinant DNA technology to closely match physiologic insulin requirements.[7] A comparison of the kinetics of these agents is presented in **Table 1**.[8-10]

Once the decision has been made to use insulin, the addition of a basal evening dose of insulin at bedtime to a regimen of oral agents is a convenient and effective strategy to use when initiating insulin therapy.[6] For several years, neutral protamine Hagedorn (NPH) insulin has been used to provide basal insulin coverage.[11] However, NPH insulin has a mean duration of action of <24 hours and, therefore, requires multiple daily injections to provide 24-hour coverage.[12] Treatment with NPH insulin also results in unwanted plasma insulin peaks. This causes significant day-to-day variation in action and unpredictable hypoglycemia.[12] Insulin glargine is a long-acting insulin analogue that provides continuous 24-hour basal coverage with no pronounced peaks. Thus, with a time-action profile very similar to that of normal basal pancreatic secretion, insulin glargine is an ideal agent to use for initiating basal insulin therapy.[11,13] The beneficial effects of adding insulin glargine to oral therapy have been demonstrated in several clinical trials.[11] In the Treat-to-Target Trial,[14] 756 subjects with inadequately controlled type 2 diabetes (levels >7.5%) received either insulin glargine or NPH insulin for 24 weeks while continuing to take the oral agents they had been taking prior to the study. Both insulins were administered once daily at bedtime with a starting dose of 10 U/d. The dose was titrated weekly using a simple algorithm with a fasting plasma glucose (FPG) level target of 100 mg/dL.[14] Both glargine and NPH insulin achieved similar FPG values (117 mg/dL vs 120 mg/dL and an A1C level of 6.96% vs 6.97%). However, nearly 25% more patients receiving insulin glargine reached these targets without experiencing nocturnal hypoglycemia. In addition, the rates of other categories of symptomatic hypoglycemia were 21% to 48% lower with insulin glargine than with NPH insulin.[14]

Table 1. Kinetics of Human Insulin and Insulin Analogs*

Insulin Preparations	Onset of Action	Peak of Action (h)	Duration of Action (h)
Rapid-acting			
Regular human insulin	30–60 min	2–4	6–8
Insulin glulisine†	5–15 min	1–2	3–4
Insulin lispro/insulin aspart	5–15 min	1–2	3–4
Intermediate-acting			
NPH insulin	1–3 h	5–7	13–16
Long-acting			
Insulin glargine	1 h	No pronounced peak	>24
Insulin detemir‡	0.8–2 h		6–23 (dose dependent)

NPH = neutral protamine Hagedorn.
*Adapted with permission from Leahy JL.[8]
†Insulin glulisine (Apidra®) prescribing information, 2004.[9]
‡Plank J et al.[10]

CASE STUDY

Initiating Insulin Therapy

Insulin glargine 10 U/d at bedtime is added to MP's regimen. MP is counseled to maintain a fasting blood glucose target of 100 to 110 mg/dL by following a simple algorithm for insulin dose titration. After a month of basal therapy with insulin glargine, MP's fasting blood glucose level is consistently in the 170 to 180 mg/dL range even with 30 U of insulin glargine. MP is frustrated and complains that the insulin is not working. At this point, MP is advised to increase his total insulin dose in a forced titration manner (an increase of 2 U of insulin glargine every 3 days)[15] to 66 U/d. This is comparable to the method followed in the Treat-to-Target Trial,[14] wherein an increase in insulin dose from 10 U/d at week 1 to 47.2 U/d at week 24 was required to achieve target A1C levels. (Patients should be informed that it usually takes 20 to 24 weeks to achieve target A1C levels.) With a daily dose of 66 U, MP's A1C level drops to 6.4%. However, MP experiences some midmorning hypoglycemia, especially when he exercises on weekend mornings. To prevent the hypoglycemia, glyburide (Diabeta®, Glynase®, or Micronase®) is switched to long-acting glipizide (Glucotrol®) and his insulin glargine dose is lowered to 60 U/d. With this modified regimen, MP's hypoglycemia is eliminated and he is able to maintain his A1C level below 7.0% by strictly adhering to his treatment regimen. Following this period, MP misses several appointments and does not follow up for almost 2 years. At this point, MP continues to feel healthy and his weight remains unchanged but he admits to eating large portions during dinner. His A1C level has increased to 8.7% and his 2-hour postprandial glucose level at bedtime is consistently greater than 200 mg/dL.

Optimizing Insulin Therapy With Prandial Replacement

In most patients with type 2 diabetes, basal insulin in combination with oral antidiabetic agents can provide adequate glycemic control for a while, but over time the majority of patients fail to achieve their glycemic goals due to progressive insulin deficiency. Optimizing insulin therapy in response to disease progression requires appropriate replacement of prandial insulin to control mealtime glucose excursions, in addition to basal insulin replacement.[16] Controlling the postprandial glucose levels is extremely important because epidemiologic data suggest that 2-hour postprandial levels have a greater influence on cardiovascular outcomes than FPG levels do. In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study,[17] among 22,514 subjects not known to have diabetes, fasting blood glucose levels were less satisfactory than 2-hour postprandial levels for predicting mortality from all causes, including cardiovascular disease. The highest number of deaths was found in the group with impaired glucose tolerance and normal fasting blood glucose concentrations.

A study by Monnier et al[18] found that the impact of postprandial glucose levels on overall glycemia is most prominent at lower A1C levels. At an A1C level of less than 7.3%, postprandial glucose contributes about 70% to overall diurnal hyperglycemia. The impact gradually decreases as A1C increases.[18] Therefore, to minimize the deleterious effects of postprandial blood glucose level excursions, 2-hour postprandial levels must be closely examined, especially with A1C levels below 8.0%. Regardless of FPG levels, postprandial hyperglycemia persists if not treated.[18] In many cases, the postprandial hyperglycemia drives the increasing preprandial hyperglycemia throughout the day. Therefore, an effective treatment regimen must be designed to control both FPG and postprandial glucose levels while achieving the target A1C levels.

Postprandial glycemic control can be achieved by following a stepwise transition from basal to basal-prandial therapy (**Table 2** on page 12).[19] Traditionally, regular human insulin (RHI) has been used as mealtime therapy.[16] To obtain optimal prandial coverage, however, RHI needs to be administered 30 to 45 minutes prior to meal ingestion.[19] This requirement for mealtime planning is inconvenient and, therefore, is unlikely to obtain optimal glycemic control.[16] Additionally, because its duration of action is 6 to 8 hours,[20] therapy with RHI most often results in hyperinsulinemia and late postprandial or nighttime hypoglycemia.[21] Alternatively, the rapid-acting human insulin analogues, such as glulisine, lispro, and aspart, have a time-action profile that mimics the physiologic postmeal rise in insulin. These agents reach peak levels in an hour and their duration of action is 4 hours. Thus, these agents can provide better postprandial glucose coverage with less risk of hypoglycemia.[3] Furthermore, use of these analogues provides more mealtime flexibility because these agents can be used immediately before or a few minutes after the beginning of a meal.[21]

Table 2. Stepped Transition From Basal to Basal-Prandial Therapy in Type 2 Diabetes*

Step	Insulin	Oral Agents	Advance When A1C Is >7.0%
1	Insulin glargine or evening NPH insulin Titrate weekly based on FPG	Continue all unless contraindicated	Average weekly FPG <120 mg/dL
2	Add prandial insulin to main meal Dose 0.05-0.1 U/kg	Continue metformin and TZD Secretagogues†	Next largest meal PPG >180 mg/dL
3	Add prandial insulin at next largest meal May need to adjust basal insulin dose	As in step 2	As in step 2
4	Add prandial insulin at last meal	As in step 2	As in step 2

FPG = fasting plasma glucose;
NPH = neutral protamine Hagedorn;
PPG = postprandial plasma glucose;
TZD = thiazolidinediones (rosiglitazone [Avandia®], pioglitazone [Actos®]).

*Adapted with permission from Karl DM.[19]
†Secretagogues bind to receptors on beta cells to stimulate insulin secretion, eg, sulfonylureas, miglitinides, etc.

CASE STUDY

Introducing Prandial Insulin

To control the 2-hour postprandial glucose excursions, MP is advised to take 9 to 10 U of a rapid-acting insulin analogue at dinnertime. (This dosage was calculated based on 0.1 U/kg of body weight). MP is provided with a simple algorithm, which will enable him to adjust his mealtime dose based on the simple concept of carbohydrate counting and level of physical activity. MP is also asked to supplement an additional 1 U for every 25 mg/dL increase in premeal blood glucose above 130 mg/dL. Following this visit, MP does not present for a follow-up for a year. At this visit, MP complains that his daytime glucose levels are not well controlled. His weekly blood glucose profile shows that MP's blood glucose levels are actually elevated throughout the day. Because MP has elevated glucose throughout the day, he will now require prandial insulin with every meal to obtain optimal 24-hour glycemic control.

Conclusions

The prevalence of type 2 diabetes has increased in epidemic proportions. Achieving good glycemic control will reduce the morbidity, mortality, and economic burden associated with type 2 diabetes. Over time, the majority of patients will require insulin therapy in addition to dietary modification, increased physical activity, and oral antidiabetic agents to maintain glycemic control. Insulin therapy should be initiated with a low daily dose of 10 U of basal insulin, such as insulin glargine. The dose of insulin glargine should be gradually increased in a forced titration manner using a simple treatment algorithm to achieve FPG levels of 100 to 110 mg/dL. In the presence of more marked insulin deficiency, insulin therapy should be intensified with the addition of a rapid-acting insulin analogue administered prior to the largest meal of the day at a dose of 0.1 U/kg and adjusted using a simple algorithm for optimal mealtime coverage. By minimizing postprandial blood glucose excursions, patients can minimize the deleterious effects on the cardiovascular system and predictably achieve targeted glycemic control.

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Question-and-Answer Session

Audience: Is there evidence that decreasing glycosylated hemoglobin levels (A1C) with insulin actually leads to improved outcomes in clinical events?

Davis: Yes. Recently, there were two large trials on control of diabetes-associated complications: one in Japan called the Kumamoto study and another in the United Kingdom. It was found that lowering levels between 1.0% and 2.0% leads to significant reductions in mortality, heart attacks, and strokes as well as microvascular complications.

Audience: Does it matter whether you use insulin or oral agents?

Davis: There are currently two large studies going on in the United States: the Action to Control Cardiovascular Risk in Diabetes study, which will evaluate the relative merits of a sulfonylurea versus insulin sensitizers versus insulin. There is also a Department of Veterans Affairs study, which is investigating the difference of targeting an A1C level of less than 6.5% compared with 8.0% with combination therapy.

Audience: You mentioned the importance of recognizing the metabolic syndrome. The National Cholesterol Education Panel (NCEP) guidelines recommend observing waist circumference, whereas the World Health Organization guidelines recommend observing body mass index (BMI). If you work in a community health center with mainly an Asian population, it's well known that Asians don't have centripetal obesity. Which guidelines should be followed?

Davis: I think we need to understand that in the Asian population, the risk for type 2 diabetes probably increases dramatically at a BMI of about 22, maybe even 21. So, it's a different disease, and those of us who have been fortunate to go to the Far East over the last 10 years are now actually starting to see Asian individuals with some visceral adiposity. But, you are correct. All measures are lowered about 10 kg/m^2 in the Asian population.

Audience: So, do you think there are going to be race-specific guidelines with the NCEP Adult Treatment Panel IV or V?

Davis: Yes. Probably as we go forward, that's what we're going to have to do.

Audience: Would you like to treat patients with prediabetes based on the Diabetes Prevention Program Trial?

Davis: I think in time all the agents we use to treat type 2 diabetes will be used to treat prediabetes. It is an off-label use, but I think it is reasonable to use an agent for a patient whose fasting blood glucose is between 100 and 126 mg/dL.

Audience: What is the role of glucose in pancreatic failure?

Davis: I don't believe there's any evidence to show that glucose, per se, is a pancreatic toxin. From what I understand, according to the South Beach Diet and other types of diets, if you limit your carbohydrate intake, you can lose weight. However, I don't think one should extrapolate from this that glucose is harming pancreatic β cells. I don't think there's any evidence to support that, even though it may seem logical.

Lavernia: What is the cause of decreasing β-cell insulin production in type 2 diabetes? That's an important pathophysiology question that we need to go over.

Davis: I think the latest view is that you need to burn fuels in a β cell, which is a metabolically active cell. That is, you need to burn fat and glucose. If you can't oxidize the fuel you start storing the substrate, which triggers a signal transduction cascade and gene activation, which leads to increased apoptosis.* So, that's the latest thinking on why β-cell insulin production decreases in people with type 2 diabetes. This action is very different from what is seen in type 1 diabetes, in which an autoimmune attack occurs that actually kills off the β cells.

Lavernia: Why continue using a sulfonylurea when insulin is used? And, as alluded to earlier, β cells are still functioning, although not as much. Between 4% and 5% of β-cell function is lost every year. At the time of diagnosis, a patient with type 2 diabetes typically has lost 50% of their β cells. Some insulin, however, is still being produced, and the sulfonylurea will be helpful in that regard. Therefore, use of a sulfonylurea should be continued unless there's a problem. Hypoglycemia is a possibility with use of rapid-acting insulin analogues, in which case you must consider cutting back the dosage or even stopping using them altogether.

*Apoptosis: The process by which cells, no longer needed, commit suicide by activating a programmed intracellular death mechanism (Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. The cell cycle and programmed cell death. In: *Molecular Biology of the Cell*. 4th ed. New York, NY: Garland Publishing; 2002:983-1026).