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Implementing intensified treatment strategies for patients with type 2 diabetes mellitus

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Primary care physicians play central roles in the management of patients with diabetes, providing care for approximately 90% to 95% of adult patients with type 2 diabetes mellitus (DM).[1] Treatment goals are well established, although treatment guidelines continue to evolve in response to new evidence and advances in therapy. Clinicians face significant challenges in managing this multifaceted and complex disease. Less than 12% of diagnosed patients reach treatment goals for blood glucose, cholesterol, and blood pressure (BP).[2]

Treatment typically begins with the use of single-agent pharmacotherapy in conjunction with lifestyle modifications. As the disease progresses, other pharmacologic agents are added as treatment is intensified to achieve target goals. This CME activity examines the clinical uncertainties resulting from disease progression and provides recommendations for the long-term management of patients with type 2 DM.

PATIENT CASE Eric, age 45 years, presents to his family physician, Dr Moore, for his first routine examination in 7 years. Eric would not have scheduled this visit had his wife not insisted that he discuss his 8-lb weight gain over the past year and seek prompt initiation of an exercise regimen. Eric notes that he wakes nightly to urinate and asks if this is normal. Family history is notable for a brother with type 2 DM.

FREE 2 CME CREDITS

LEARNING OBJECTIVES

After reading this section, the reader should be better able to:

- Identify the physiologic and clinical data supporting weight loss, cardiovascular risk reduction, and tight glycemic control in managing patients with diabetes
- List the target values for glycemic control and other cardiovascular risk factors
- Apply nonpharmacologic and pharmacologic treatment in the management of patients with diabetes
- Establish a specific time period to achieve an A1C level of less than 7% for each patient with diabetes
- Discuss when, why, and how to add insulin to the treatment regimen
- Design a timeline to add, change, or adjust the dosage of medications in patients with diabetes whose glycemic control is suboptimal on current antidiabetic agents

FACULTY DISCLOSURE STATEMENTS

Dr Brunton receives consulting fees from Novo Nordisk, Inc., Pfizer Inc, Amylin Pharmaceuticals, Inc., and Abbott Laboratories.

Dr Rolla receives consulting fees from Eli Lilly and Company, Novo Nordisk, Inc., and Roche Pharmaceuticals; is on the speakers' bureau for Eli Lilly and Company, GlaxoSmithKline, Novo Nordisk, Inc., and Roche Pharmaceuticals.

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CLINICAL PRACTICE RECOMMENDATIONS FOR AAFP EB CME DESIGNATION

1) Practice Recommendation: Clinical trials using insulin that have demonstrated the value of tight glycemic control have used self-monitoring of blood glucose as an integral part of the management strategy.

Evidence-based Source: National Guideline Clearinghouse

Web site of Supporting Evidence: http://www.guideline.gov/summary/summary.aspx?doc_id=10400&nbr=005446&string=diabetes

Strength of Evidence: Consistent, good quality patient-oriented evidence

2) Practice Recommendation: Lowering A1C has been associated with a reduction of microvascular and neuropathic complications of diabetes

Evidence-based Source: National Guideline Clearinghouse

Web site of Supporting Evidence: http://www.guideline.gov/summary/summary.aspx?doc_id=10400&nbr=005446&string=diabetes

Strength of Evidence: Consistent, good quality patient-oriented evidence

3) Practice Recommendation: A consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes on the approach to management of hyperglycemia in individuals with type 2 diabetes has recently been published. Early intervention with metformin in combination with lifestyle changes (MNT and exercise) with continuing, timely augmentation therapy with additional agents (including early initiation of insulin therapy) as a means of achieving and maintaining recommended levels of glycemic control (ie, A1C <7% for most patients) are highlights of this approach.

Evidence-based Source: National Guideline Clearinghouse
Web site of Supporting Evidence:
http://www.guideline.gov/summary/summary.aspx?doc_id=10400&nbr=005446&string=diabetes

Strength of Evidence: Consensus statement

STATEMENT OF SUPPORT

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Physical examination reveals Eric is 5 feet, 9 inches tall and weighs 180 lb, with a body mass index (BMI) of 26.6 kg/m^2. His blood pressure (BP) is 138/88 mm Hg. Other than the somewhat overweight body habitus, ophthalmologic, neck, cardiovascular, abdominal, extremity/skin, and neurologic examination results are normal.

Because of Eric's age, reported inactivity, and slightly elevated BMI and BP, laboratory work is ordered. Results show several abnormalities: fasting glucose (FG) of 165 mg/dL; high-density lipoprotein cholesterol (HDL-C), 45 mg/dL; low-density lipoprotein cholesterol (LDL-C), 110 mg/dL; total cholesterol (TC), 189 mg/dL; triglycerides (TG), 170 mg/dL; creatinine, 0.9 mg/dL; urinalysis, no albumin and trace glucose; and electrocardiogram, normal. Repeat FG is 162 mg/dL. Dr Moore orders a glycosylated hemoglobin test (A1C), which shows a level of 7.8%.

Issues for clinicians

Eric's infrequent medical care history–not uncommon for men in his age group–presents an additional treatment issue. Aggressive blood glucose regulation is essential to prevent diabetes complication; normalization of blood glucose is the cornerstone of disease management. The goal for every patient is to normalize A1C levels to less than 7% within 3 months while avoiding hypoglycemia, particularly severe hypoglycemia.[3]

Type 2 DM is a well-recognized consequence of insulin resistance and its resultant syndrome, with other components that include hypertension, hyperlipidemia, and obesity. Clearly, it is of vital importance to address a patient's weight, BP, LDL-C, HDL-C, and triglycerides.

Importance of glycemic control

Issues of glycemic control dictate future treatment and outcomes for every patient with diabetes.

TABLE 1

Summary of ADA Recommendations for Glycemic Control

A1C	<7%*
Preprandial capillary plasma glucose	90 to 130 mg/dL
Peak postprandial capillary plasma glucose	<180 mg/dL

A1C, glycosylated hemoglobin.
*As close to 6% as possible is preferred as long as hypoglycemia is avoided.

From Diabetes Care.® 2007;30(suppl 1):S4-S41.

TABLE 2

The Impact of Type 2 Diabetes

- Affects 10% of the US adult population
- Accounts for >27 million office visits and >72,000 deaths annually
- Represents the sixth leading cause of death in the United States
- Presents a projected lifetime risk for disease development of 33% to 38% for Americans born in 2000
- Continues to increase in impact, despite advances in treatment. The National Health and Nutrition Examination Surveys showed that the average A1C level in patients with type 2 DM rose from 7.8% between 1988 and 1994 to 8.1% between 1999 and 2000

DM, diabetes mellitus.
Source: Ziemer DC, et al. Arch Intern Med. 2006;166:507-513.
Centers for Disease Control and Prevention. www.cdc.gov/nchs/fastats/diabetes.htm. Accessed June 22, 2007.

An FG level greater than 140 mg/dL (7.8 mmol/L) increases the risk for complications such as diabetic retinopathy.[4] Strict glycemic control reduces risk for microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (myocardial infarction [MI] and stroke) complications.[5,6]

Current American Diabetes Association (ADA) recommendations **(TABLE 1)** for glycemic control feature an A1C goal of less than 7% for patients in general and an A1C as close to normal (less than 6%) for the individual patient.[7] In the United Kingdom Prospective Diabetes Study

(UKPDS), each 1% reduction in A1C level was associated with a decreased risk of 37% for microvascular disease, 14% for MI, 21% for diabetes-related deaths, and 14% for all-cause mortality.[6] The current and growing impact of type 2 DM in the United States is summarized in **TABLE 2.**

Glycemic control: A long-term challenge

Lifestyle modification remains the mainstay of diabetes treatment and prevention, although diet and exercise alone often do not succeed long-term. The UKPDS showed that, despite an intensive 3-month dietary program, excellent glycemic control (FG, ≤108 mg/dL) was achieved by only 16% of participants.[8]

Additional interventions will likely be required over time; normoglycemia may be achievable only with early use of pharmacologic agents. The ADA recommends initiating treatment with lifestyle management and metformin.[7] The American Association of Clinical Endocrinologists (AACE) recommends lifestyle management and combination pharmacologic treatment when a patient has an A1C level of 7% to 8%.[3]

Even at an early stage, the progressive nature of the disease means that each treatment's efficacy will diminish over time. Given the potentially devastating effects of hyperglycemia, physicians must favor proactive diabetes management and appropriate intensification of treatment to delay or prevent complications. Approximately 50% of patients using antihyperglycemic medication need to advance from monotherapy to combination therapy by year 3 of treatment.[9] Currently available treatment options appear in **ADDENDUM 1 AND ADDENDUM 2.**

PATIENT CASE

Dr Moore diagnoses new-onset type 2 DM. The diagnosis surprises and upsets Eric. Dr Moore is sympathetic, noting that the signs and symptoms of type 2 DM progress slowly; most people are unaware they have the disease. He advises Eric that both type 2 DM and cardiovascular problems can be managed effectively, provided Eric adheres to the treatment plan that they develop together.

Dr Moore outlines the issues that must be addressed; however, given Eric's state of mind, he focuses on management of hyperglycemia. He tells Eric that other health issues need to be discussed at his next visit. Eric agrees.

They decide on a strict diet and exercise plan. Although the 2007 AACE guidelines recommend combination pharmacologic therapy when a patient has an A1C level between 7% and 8%,[3] Dr Moore recommends initiation of metformin monotherapy, as recommended by the ADA.[7]

Eric exhibits no evidence of microvascular damage. Dr Moore does not discuss these aspects of the disease because he does not want to overwhelm Eric, potentially risking Eric's adherence to follow-up. A dose of metformin, 500 mg BID after meals, is chosen. They also discuss proper initiation of self-monitoring blood glucose (SMBG). Eric receives influenza and pneumonia immunizations and schedules meetings with a diabetes educator. Dr Moore establishes a timeline in which to reduce Eric's A1C level to under 7% within 3 months.

Initiating and intensifying therapy

Dr Moore recognized that applying guidelines to the management of a specific patient often requires careful consideration and flexibility. Rather than initiate multiple therapies to treat the various problems Eric is experiencing, Dr Moore determined that initially focusing on one problem (hyperglycemia), while reaching agreement with Eric about the need for more comprehensive long-term management, was a better approach for Eric. Dr Moore initiated lifestyle

management and metformin monotherapy, as recommended by the ADA. This plan is somewhat more aggressive than lifestyle management alone, which has typically been done in the past. For most patients, progressive initiation of therapy, guided by SMBG, will be needed to maintain glycemic control.

PATIENT CASE

Eric presents 3 months after initiating metformin and lifestyle management. He has met with the diabetes educator several times and feels less anxious about his diagnosis. His FG level is 138 mg/dL, and his A1C level is 7.6%. His glucose diary shows postprandial levels of 140 to 160 mg/dL. Eric has lost 6 lb. His metformin dose is increased to 850 mg TID after meals. Dr Moore and Eric review cardiovascular issues; they agree to start aspirin and an angiotensin-converting enzyme (ACE) inhibitor; a statin will be added at the next visit.

At a follow-up visit 3 months later, Eric's A1C level is 7.5%. Dr Moore adds glyburide 10 mg BID. This agent is selected because of cost. The statin is added.

Additional agent to meet glycemic goal

If a patient is unable to meet glycemic goals with metformin monotherapy, adding a second oral agent should be considered. Patients also must be aware of the progressive nature of diabetes. Future needs will likely include insulin, which can be described as a "natural" treatment to replace the deficit inherent in patients with diabetes. Both patients and physicians need to understand that insulin can effectively produce good glycemic control. If insulin use is avoided, suboptimal glycemic control and long-term complications may result.

PATIENT CASE

Three months later, Eric's A1C level is 6.9%. He has lost an additional 4 lb. His BP has decreased to 134/84 mm Hg, and his lipid profile has improved: HDL-C is 50 mg/dL; LDL-C, 102 mg/dL; TC, 178 mg/dL; and TG, 160 mg/dL. No change is made to his metformin/glyburide regimen. Dr Moore increases the dosage of Eric's ACE inhibitor and statin. Over the next year, Eric's BP and lipid profile improve to a level within the target range for a patient with type 2 DM.

One year later, Eric's A1C level has risen to 8.2%, despite a stable weight and claims of an unchanged diet. Eric does note that his work and home life have prevented him from exercising for 6 months. Eric's A1C level correlates with his FG level of 152 mg/dL. Postprandial glucose levels have ranged from 165 to 195 mg/dL. Dr Moore considers administration of exenatide but rules out this agent, which typically reduces A1C levels by less than 1%. Eric requires a reduction of at least 1.2%; therefore, a long-acting insulin analog is needed.

Because Eric's weight has been an issue, Dr Moore chooses insulin detemir, 10 units once a day. Eric will administer the detemir at bedtime; Dr Moore instructs Eric to increase the dose slowly.

Dr Moore encourages Eric to continue to work with the diabetes educator to address his concerns regarding the initiation of insulin, particularly any concerns he may have about needles and hypoglycemia.[10]

After 3 months' use, the detemir dose has been titrated to 36 units once a day. Eric's A1C level is 7.2%. At 6 months, the detemir dose of 46 units once a day yields an A1C level of 6.6%.

Maintaining glycemic control

Well-established basal-bolus insulin regimens combine long-acting basal insulin and short-acting

prandial insulin before meals. The older combination, featuring short-acting regular insulin and longer-acting neutral protamine Hagedorn (NPH) insulin, was not optimal for 2 reasons: regular insulin does not work fast enough, and NPH insulin lacks an appropriately prolonged duration of action.[11] Insulin analogs address these shortcomings; faster action provides more immediate postprandial control and longer action creates less serum peaks and hypoglycemia. Physiologic insulin patterns are initiated by basal-bolus regimens incorporating the insulin analogs, thus potentially offering important benefits in controlling hyperglycemia.

PATIENT CASE

While using insulin detemir, Eric's A1C level is stable. His cardiac profile remains within acceptable levels (no change to his ACE inhibitor and statin). At his most recent office visit, Eric's A1C level has increased to 7.8%; FG is normal, at 110-120 mg/dL. Dr Moore is concerned that postprandial hyperglycemia is causing the elevated A1C level; he asks Eric to record 2-hour postprandial glucose levels for 2 weeks. Levels range from 190 to 220 mg/dL and are especially high following dinner. Recent studies suggest the significant contribution of postprandial glucose levels to A1C.[12] Dr Moore adds a rapid-acting analog, to be taken prior to dinner, in addition to nightly basal insulin. He encourages Eric to continue checking postprandial glucose levels. Eventually, the administration of the rapid-acting analog is increased to 3 times a day prior to meals, because of higher postprandial sugars after breakfast and dinner, coupled with an A1C level of 7.4%. Eric's glycemic control is significantly improved, and his A1C level falls to 6.7% within 6 months.

Conclusion

Diabetes is as multifaceted as the treatment options available to manage it. Glycemic control represents the critical factor in diabetes management and provides the greatest opportunity for preventing complications of diabetes in newly diagnosed patients. As this case shows, the progressive nature of type 2 DM makes long-term glycemic control a challenge. Timely modification and intensification of therapy, guided by ongoing monitoring of glycemic endpoints, is of utmost importance. The central role of the patient in the self-management of type 2 DM mandates ongoing patient education. As patient and clinician effectively utilize available treatment options and work together as a team, they can reduce the morbidity and mortality of diabetes and its associated comorbidities. n

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Addendum 1 Available Agents for Glycemic Control

Oral antihyperglycemic agents

z **SULFONYLUREAS** can reduce fasting glucose levels by 50 to 70 mg/dL, but they have little influence on postprandial levels. Also known as beta cell stimulants, they are most effective in patients whose beta cells still create a considerable amount of insulin. Glimepiride and glipizide can reduce glycosylated hemoglobin (A1C) levels by 1% to 2%. The glinides, repaglinide, and nateglinide are administered close to a meal, thus increasing effectiveness in reducing postprandial glucose levels. They have less effect on fasting blood glucose levels.[1]

z **ALPHA-GLUCOSIDASE INHIBITORS**, acarbose and miglitol, can reduce postprandial glucose levels by 30 to 50 mg/dL, fasting glucose levels by 15 to 20 mg/dL, and A1C levels by 0.5% to 0.8%. They delay glucose absorption in the gut and must be taken at the beginning of a meal. They are best used as monotherapy in patients for whom postprandial hyperglycemia is the main concern. These agents are associated with gastrointestinal (GI) side effects (eg, flatulence, abdominal cramping, and diarrhea).[1]

z **METFORMIN** can lower fasting glucose levels by 50 to 70 mg/dL and A1C levels by 1% to 2%. It reduces insulin levels and hepatic glucose production, with the added benefit of reducing plasma triglycerides and low-density lipoprotein cholesterol levels, and possibly increasing high-density lipoprotein cholesterol levels.[1] Lactic acidosis is a rare adverse event (AE) associated with the use of metformin. Dependent on renal clearance, it should not be used in patients with or at risk for renal insufficiency.[1]

z **THIAZOLIDINEDIONES (TZDs),** pioglitazone and rosiglitazone, can reduce fasting glucose levels by 40 to 60 mg/dL and A1C levels by .5% to 1.4%. A recent meta-analysis of 42 clinical trials noted that rosiglitazone was associated with risk of myocardial infarction (MI) (significant risk) and with death from cardiovascular causes (borderline significance).[3] Similar findings were observed in a recent meta-analysis of studies in which rosiglitazone was used for a minimum of 12 months.[4] A meta-analysis of pioglitazone reported a significantly lower risk of death, MI, and stroke. The incidence of serious heart failure was increased but was not associated with an increase in mortality.[5]

In August 2007, the US Food and Drug Administration (FDA) updated its precautions and contraindications on the use of TZDs. Trials on both agents suggest an increased risk of AEs including worsening edema and increased dyspnea, and heightened use of heart failure medications. Because of these post-marketing reports, new boxed warnings have been added to both agents' prescribing information. The FDA requests that clinicians incorporate this recent information when determining whether to prescribe these agents.[6]

TABLE 1A

Treatment Options: Monotherapy

Intervention	Expected decrease in A1C (%)
Lifestyle to decrease weight/increase activity	1.0-2.0
Sulfonylureas	1.5
Alpha-glucosidase inhibitors	0.5-0.8
Metformin	1.5
Thiazolidines	0.5-1.4
Insulin	1.5-2.5
Exenatide	0.5-1.0
Glinides	1.0-1.5
Pramlintide	0.5-1.0

A1C, glycosylated hemoglobiin.

TABLE 2A

Treatment Options: Combination

Intervention	Expected decrease in A1C (%)
Sulfonylurea + metformin	1.7
Sulfonylurea + rosiglitazone	1.4
Sulfonylurea + pioglitazone	1.2
Sulfonylurea + acarbose	1.3
Repaglinide + metformin	0.14
Pioglitazone + metformin	0.7
Rosiglitazone + metformin	0.8
Dipeptidyl-peptidase 4 inhibitor + metformin	0.7
Dipeptidyl-peptidase 4 inhibitor + pioglitazone	0.7

A1C, glycosylated hemoglobiin.
Reprinted with permission: AACE Diabetes Mellitus Clinical Practice Guideline Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocr Pract.* **2007;13(suppl 1):1-68.**

Insulin treatment options

z **HUMAN INSULIN** is injected subcutaneously at least 30 minutes prior to meals. It peaks at 2 to 4 hours. Considered a short-acting insulin, duration of action is 8 to 10 hours and is, therefore, unsuitable for postprandial glucose management.

z **NEUTRAL PROTAMINE HAGEDORN (NPH)** insulin, created by adding a protamine molecule to regular insulin,[7] offers slow absorption and a duration of action of 10 to 20 hours, peaking at 4 to 8 hours. This increases the risk of hypoglycemia, especially when administered at bedtime.

z **INSULIN ANALOGS** are synthetic alternatives that feature a modified insulin molecule structure that more closely mimics physiologic insulin secretion. Both long-acting (basal) and rapid-acting (prandial or bolus) insulin analogs are available. Available long-acting analogs are insulin glargine and insulin detemir. Both have an onset of action of 1 to 2 hours, a steady activity plateau, and a relatively flat peak over 24 hours. Consequently, both are often administered once daily.[8]

Compared with NPH insulin, insulin detemir has a more predictable dosing profile. It produces less within-subject variability in fasting glucose levels, a lower incidence of hypoglycemic events, and a reduced incidence of weight gain than do NPH insulin or insulin glargine.[9]

z **RAPID-ACTING ANALOGS**—insulin aspart, insulin lispro, and insulin glulisine—are injected within 15 minutes of a meal. They can be used alone or as part of a basal-bolus regimen.[10]

Insulin aspart is approved for use in adults with type 1 or type 2 DM by subcutaneous injection or an external infusion pump.[11] Compared with regular insulin, insulin aspart demonstrates improved plasma glucose excursion determined by postprandial glucose levels.[12] One study demonstrated a 20% reduction in postprandial glucose with insulin aspart versus regular insulin.[10] Insulin aspart has been shown to improve A1C levels and quality-of-life measures versus regular insulin, with similar incidence of hypoglycemic events.[12]

Insulin lispro has been shown to produce a postprandial glucose level 53% lower than that seen with regular insulin.[10] Hypoglycemic episodes are also reduced with this agent.[12]

Insulin glulisine is approved for use in adults with type 1 or type 2 DM by subcutaneous injection or an external infusion pump.[13]

z **PREMIXED INSULIN.** Many patients maintain glycemic control with the combined use of a rapid- or short-acting insulin and a long-acting insulin. For example, in patients with type 1 or type 2 DM, insulin aspart premix 70/30 significantly reduced postprandial hyperglycemia without increasing the risk of hypoglycemia compared with human insulin premix 70/30.[14]

z **INHALED INSULIN.** A fine, dry, powdered form of regular insulin is now available for use as an oral inhalant administered before meals. It exhibits an early, quick rise and a duration of action shorter than regular insulin, offering a more physiologic profile during meals. Data suggest that inhaled insulin is well tolerated; however, it is contraindicated in smokers (active or within the previous 6 months) and in patients with asthma or lung disease.[15] Pulmonary function should be assessed prior to initiation and periodically thereafter.[16]

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Addendum 2 Newer Agents for Glycemic Control

The injectable antihyperglycemic agents, pramlintide and exenatide, are gastrointestinal (GI) hormone drugs. These agents can produce a reduction in A1C levels of up to 1%. Pramlintide, a synthetic form, or analog, of the hormone amylin, can be prescribed for patients who have not achieved optimal glycemic control with basal and preprandial insulin. It slows gastric emptying and suppresses glucagon levels, resulting in better postprandial control, reducing A1C levels by approximately 0.5%, and, frequently, reducing food intake and body weight. Exenatide, a peptide derived from Gila monster saliva, is an agonist of glucagon-like peptide 1 (GLP-1) receptors, and can be used in combination with a sulfonylurea, metformin, or both. It is associated with an increase in insulin secretion.

New glucoregulatory agents—amylin agonists, GLP-1 receptor agonists, and dipeptidyl peptidase (DPP)-IV inhibitors—complement currently available agents. In nondiabetic individuals, glucoregulatory hormones such as insulin, amylin, glucagon, and GLP-1 interact to achieve normal glucose homeostasis; however, in patients with diabetes, these hormones are abnormally regulated.[2]

Amylin is a natural glucoregulatory hormone found within pancreatic beta cells along with insulin. It is secreted with insulin as a postprandial response to a glucose load, and it complements the effects of insulin. Patients with type 1 DM have an absolute deficiency of amylin; a relative deficiency of amylin is present in patients with type 2 DM. To increase levels of amylin, the amylin agonist pramlintide can be injected subcutaneously before major meals, resulting in reduced postprandial glucose excursions possibly related to the prevention of a postprandial glucagon rise. The movement of nutrients between the stomach and small intestine is also slowed with pramlintide, prolonging gastric-emptying time by approximately 90 minutes. The addition of pramlintide to insulin therapy has been shown to produce a 0.5% to 1% reduction in A1C levels as well as a reduction in body weight. An average loss of 2.4 kg has been demonstrated in patients with type 2 DM with a BMI greater than 35 kg/m^2 after treatment with pramlintide for 26 weeks.[2]

GLP-1, an incretin hormone, stimulates insulin secretion, controls glucagon secretion, and delays gastric emptying. It has been shown to reduce appetite and produce weight loss. Patients with type 2 DM secrete lower levels of GLP-1 during meals than do nondiabetic individuals. When administered via continuous intravenous infusion, native GLP-1 produces an instant decrease in blood glucose levels in patients for whom sulfonylurea therapy has failed, resulting in significant effects on fasting and 8-hour plasma glucose, A1C levels, and weight loss. However, native GLP-1 is quickly metabolized by DPP-IV. In addition, GLP-1 must be present continuously in the blood stream to be effective.[3] The long-acting GLP-1 analog liraglutide is now being studied and acts as a full agonist to the GLP-1 receptors. Its half-life after single and multiple dosing is approximately 12 hours in both healthy individuals and patients with type 2 DM. It can be administered once daily by injection. DPP-IV inhibitors slow degradation of GLP-1 to boost availability. These drugs decrease blood glucose levels in patients with type 2 DM, when used either independently or in combination with other antihyperglycemic medications. Both of the available DPP-IV inhibitors are associated either with decreased or unchanged body weight.[4] Thus, by potentiating the natural incretins, the DPP-IV inhibitors provide yet another avenue toward glucose control.

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