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INSULIN THERAPY IN TYPE 2 DIABETES

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Type 2 **diabetes** is a chronic disease characterized by hyperglycemia and numerous other metabolic abnormalities. This chronic and disabling disease affects more than 16 million people in the United States[29] and 200 million people worldwide.[71] Microvascular and macrovascular complications are the major causes of morbidity and mortality in this disease. The microvascular complications of retinopathy, nephropathy, and neuropathy cause major disability and suffering in the lives of patients with type 2 **diabetes**. Nearly 80% of these patients, however, die of macrovascular cardiovascular disease caused by accelerated atherosclerosis. There is now clear evidence from the United Kingdom Prospective **Diabetes** Study (UKPDS) and the Kumamoto study that improved glycemic control through intensive **diabetes** management delays the onset and significantly retards the progression of microvascular complications in patients with type 2 **diabetes mellitus**.[51] [67] Unfortunately, despite an average follow-up of 10 years in nearly 5000 patients, the UKPDS did not definitely prove that intensive insulin therapy with lowered blood glucose levels reduced the risk of cardiovascular complications compared with conventional therapy. Results from the UKPDS were reassuring, however, because although intensive treatment with insulin was associated with increased weight gain and hypoglycemia, there was no evidence of any harmful effect of insulin on cardiovascular outcomes. Also, an epidemiologic analysis of the UKPDS data showed a continuous association between the risk of cardiovascular complications and glycemia: for every percentage point decrease in HbA_{1C} (e.g., from 9% to 8%), there was a 25% reduction in diabetes-related deaths, a 7% reduction in all-cause mortality, and an 18% reduction in combined fatal and nonfatal myocardial infarction.

To achieve glycemic goals in patients with type 2 **diabetes**, multiple pharmacologic agents, including sulfonylureas, meglitinides, metformin, alpha-glucosidase inhibitors, thiazolidinediones, and insulin, are available. Unlike patients with type 1 **diabetes** who have no significant insulin secretion and hence require insulin therapy from the onset of their disease, in patients with type 2 **diabetes** insulin resistance with hyperinsulinemia is a prominent feature in the early stages of the disease. Thus, type 2 diabetics benefit from measures to improve insulin sensitivity such as caloric restriction, exercise, and weight management early in their disease. When these measures fail,

glycemic goals can often be achieved with oral agents such as insulin sensitizers and insulin secretagogues. With progression of type 2 **diabetes**, there is ultimately progressive loss of pancreatic beta-cell function and endogenous insulin secretion. At this stage, most patients require exogenous insulin therapy to achieve optimal glucose control. This article discusses the rationale and indications for insulin treatment therapy in patients with type 2 **diabetes mellitus**, the goals of treatment, the different insulin therapeutic regimens available to achieve glycemic goals, the practical application of these regimens, their possible benefits and adverse effects, newer insulin analogues, and alternative methods of insulin delivery.

RATIONALE FOR INSULIN THERAPY IN TYPE 2 DIABETES

Three major pathophysiologic abnormalities contribute to hyperglycemia in type 2 **diabetes**: excessive hepatic glucose production, impaired pancreatic insulin secretion, and peripheral resistance to insulin action occurring principally in liver and muscle tissue.[16] Of these, peripheral resistance to insulin action and impaired pancreatic beta-cell secretion are early and primary abnormalities, whereas increased hepatic glucose production is a late and secondary manifestation. Early in their disease, patients with type 2 **diabetes** compensate for increased insulin resistance at the tissue level by increasing pancreatic beta-cell insulin secretion.[64] When this compensation is no longer adequate to overcome the insulin resistance, blood glucose levels begin to rise. Over the course of the disease, however, insulin levels slowly begin to decrease, and eventually most patients with type 2 **diabetes** are unable to achieve optimal glycemic control with oral agents. This process was well exemplified in the UKPDS in which all treatment groups showed progressive hyperglycemia along with an associated decrease in beta-cell function (Fig. 1 (Figure Not Available) *A*, *B*). Although only newly diagnosed type 2 diabetics were enrolled in the UKPDS, nearly 20% already had evidence of retinopathy. Also in this study, beta-cell function as measured by the Homeostasis Model Assessment method deteriorated significantly in the diet-treated group, from 53% at year 1 to 26% at year 6 of the study. In the same period, those receiving sulfonylurea therapy demonstrated an early increase in beta-cell function from 45% to 78% in year 1 of the study (consistent with a secretagogue effect of the sulfonylurea agent), but beta-cell function subsequently decreased to 52%. This inevitable decline in beta-cell function occurred even in the metformin group, in which beta-cell function declined from 66% to 38% at year 6 (after a brief increase in the first year similar to that in the sulfonylurea group). Concomitant with this inexorable decline in endogenous insulin secretion in the UKPDS was a progressive increase in hyperglycemia, and HbA_{1C} levels progressively increased regardless of treatment. Thus, over the course of 15 years, the proportion of patients using oral agents declines, and most will require exogenous insulin treatment.[4]

Figure 1. (Figure Not Available) *A*, Progressive decline of beta-cell function as measured by the HOMA model in the United Kingdom Prospective **Diabetes** Study. At the time of diagnosis, there was already an approximate 50% decrease in beta-cell function in the study population as a whole. *B*, In all treatment arms of the obese subgroup in the UKPDS (n = 548) there was a progressive decline in beta-cell function through the study. In the sulfonylurea group, there was an initial increase in beta-cell secretion in keeping with the secretagogue effects of the sulfonylureas, followed by a gradual decline. This decline in beta-cell function was also present in the metformin group. Circle = conventional; triangle = metformin; square = sulfonylurea. *(Adapted from the UKPDS Study Group 16. **Diabetes** 44:1249-1258, 1995; with permission.)*

Although all patients with type 2 **diabetes** become relatively insulinopenic late in the course of their disease, some patients with type 2 **diabetes** may have insufficient insulin secretion early on. This difference arises from the heterogeneity in the metabolic expression of the diabetic state and the difference in the extent to which different abnormalities contribute to the hyperglycemic state. In lean patients with type 2 **diabetes**, impaired insulin secretion is a predominant defect, and insulin resistance tends to be less severe than in obese patients with type 2 **diabetes**.[11] It is possible that some patients with the diagnosis of type 2 **diabetes** may actually have a condition more closely related to insulin-dependent or type 1 **diabetes** with severe insulinopenia. Many of these patients have been shown to have islet-cell antibody positivity or antibodies to glutamic acid decarboxylase,

with a decreased C-peptide response to glucagon stimulation and a propensity for primary oral medication failure.[59] Geographic and racial differences may also influence the need for insulin therapy. Lean patients require the initiation of insulin therapy early in the course of their disease, and metabolic control can usually be achieved with smaller doses of insulin than in obese patients, in whom insulin resistance and hyperinsulinemia are major abnormalities. In obese patients, oral insulin sensitizers are often effective early in the course of disease, and insulin therapy is only required late in the disease, when endogenous insulin secretion begins to fail.[11] Also, because of severe insulin resistance, obese patients require large doses of exogenous insulin to achieve euglycemia.[25]

Besides insulin secretion and insulin resistance, increased hepatic glucose production (HGP) is also important in the genesis of hyperglycemia in type 2 **diabetes** because the basal rate of hepatic glucose production is the primary determinant of the fasting plasma glucose concentration in type 2 **diabetes**.[50] In addition, postprandial hyperglycemia is determined both by peripheral (muscle) glucose utilization and the severity of insulin resistance and also by the postprandial suppression of HGP.

BENEFITS OF INSULIN THERAPY IN TYPE 2 DIABETES

Improvement in Insulin Sensitivity

As already discussed, insulin resistance is a major pathophysiologic abnormality in type 2 **diabetes**. Because insulin therapy frequently leads to weight gain, it would be expected that this increase in weight would further increase insulin resistance in obese patients with type 2 **diabetes**. Several studies, however, have documented that, in the short term, intensive insulin therapy for up to 4 weeks actually improves insulin sensitivity as measured by the glucose-insulin clamp method, the standard for measuring peripheral insulin sensitivity (Fig. 2) .[7] [24] [55] The mechanism for this improvement in insulin sensitivity is presumably reduced glucose toxicity accompanying improved glucose control in these studies. Prolonged hyperglycemia is known to cause impairment both at the level of the pancreatic beta-cells and at peripheral tissues such as skeletal muscle.[51] Whether this improvement in insulin sensitivity with insulin therapy persists long term has not been studied, but at least in the short term intensive insulin therapy with improved glucose control improves, rather than worsens, insulin resistance.

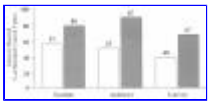

Figure 2. Improvement in insulin sensitivity as measured by the glucose clamp technique, at baseline, and after intensive insulin treatment. Solid bars = after insulin; open bars = baseline. (Data from references [7] [24] [25])

Reduction in Cardiovascular Mortality

A major concern in using insulin therapy to achieve tight glucose control in type 2 **diabetes** is the well-recognized association of hyperinsulinemia with accelerated atherosclerosis. In this context, results from the UKPDS were reassuring: although intensive treatment with insulin was associated with weight gain, there was no evidence of any harmful effect of insulin on cardiovascular outcomes. Moreover, in a recent Swedish study with 620 patients, intensive insulin therapy with acute administration of insulin and glucose followed by intensive treatment with multidose subcutaneous insulin at the time of a myocardial infarction was actually associated with a 30% reduction in mortality at 1 year (Fig. 3) (Figure Not Available) .[37] At follow-up, there was a 28% relative risk reduction after a mean period of 3.5 years (range: 1.6-5.6 years). Most of the survival benefit was apparent in the first month of treatment and may have resulted from the immediate intravenous use of insulin in the intensively treated group. The survival curves tended to separate further over time,

suggesting an ongoing benefit from insulin treatment. In this study the beneficial effects were most apparent in patients who had not previously received insulin treatment. Thus, insulin therapy seems to be appropriate therapy in patients with type 2 **diabetes** at high risk for cardiovascular disease, especially at the time of a myocardial infarction. In a recent follow-up, intensive insulin therapy has also been demonstrated to be cost effective.[3] The only study to suggest a possible association between intensive insulin therapy and increased cardiovascular events is the Department of Veterans Affairs (VA) Cooperative Study. In this study (discussed in detail later), there was a small but nonsignificant increase in cardiovascular events in the insulin-treated group.[2]

Figure 3. (Figure Not Available) *A:* All subjects (N = 620), *B:* Low Risk and not Previously on Insulin (N = 272). Reduction in cardiovascular mortality in those patients treated with insulin therapy as compared with those treated with standard therapy in the **Diabetes Mellitus**, Insulin Glucose Infusion in Acute Myocardial Infarction study. Solid line = standard treatment; dotted line = IV insulin 48 hours, then four injections daily. *(From Malmberg, K and the **Diabetes Mellitus**, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study Group: Prospective randomized study of intensive insulin treatment on long-term survival after acute myocardial infarction in patients with **diabetes mellitus**. BMJ 314:1512-1515, 1997; with permission.)*

DISADVANTAGES OF INSULIN THERAPY IN TYPE 2 DIABETES

Hypoglycemia

Intensive insulin therapy is invariably associated with an increased risk of hypoglycemic reactions. Severe hypoglycemia is usually defined as the inability to self-treat, with a need for assistance from others to administer therapy properly.[14] Neuroglycopenia can masquerade as a neurologic or cardiovascular event and thus can be unrecognized and underreported.[32] Several factors affect the development of severe hypoglycemia. The duration of **diabetes** and insulin therapy, the degree of glycemic control, and a history of prior severe hypoglycemic reactions have been associated with a higher incidence of severe hypoglycemic reactions.[14] Additional causal factors in hypoglycemia include overinsulinization, underfeeding, strenuous unplanned exercise, excessive alcohol intake, and unawareness of hypoglycemia. The risk of severe hypoglycemia in insulin-requiring patients with type 2 **diabetes** has consistently been reported to be significantly reduced compared with the risk in type 1 diabetic patients undergoing intensive insulin therapy.[14] The **Diabetes** Control and Complications Trial (DCCT) and the Stockholm **Diabetes** Intervention Study respectively reported rates of 0.62 and 1.10 severe reactions per patient year in intensively treated type 1 diabetic subjects.[18A] [46A] In the intensive insulin trial of type 2 **diabetes** reported by Henry et al, there were no severe reactions and a low incidence of mild, self-treated hypoglycemic reactions that actually decreased as the 6-month study progressed.[32] Similarly, the Veterans Affairs Cooperative Study of type 2 **diabetes** reported a very low rate (0.0156 and 0.0096) of severe hypoglycemic events per patient after 1 year of intensive treatment with multiple daily injections and intraperitoneal insulin pumps, respectively.[18] Recently, in the UKPDS, only 1.8% of patients treated with insulin experienced hypoglycemic episodes, compared with 1% to 1.4% of patients treated with sulfonylureas.[61] Thus, all these studies of intensive insulin therapy confirm that the risk of severe hypoglycemic reactions in type 2 **diabetes** is low and is significantly less than in patients with type 1 **diabetes**. The lower incidence of severe hypoglycemia in type 2 **diabetes** may result from insulin resistance, which is often quite severe.[39]

Weight Gain

Although insulin therapy is successful in patients with type 2 **diabetes** who are unable to achieve glycemic control through diet, exercise, and oral antidiabetic agents, the lowering of blood glucose concentrations to normal usually requires large doses of exogenous insulin. These dosages result in hyperinsulinemia and weight gain which is closely related to the mean day-long plasma insulin level

and daily insulin dose.[32] It has been estimated that approximately two thirds of this weight gain consists of adipose tissue and one third is lean body mass.[28] Several studies have demonstrated that treating type 2 **diabetes** with exogenous insulin results in an average increase of 3% to 9% over pretreatment body weight, depending on the length of the study and the intensity of glucose control.[25] [32] [50] [67] In addition to exogenous insulin therapy, many other variables may indirectly influence the degree of weight gain in type 2 **diabetes**. These variables include increased appetite and reduced thermogenesis[10] [22] induced by insulin, the retention of calories previously lost as glycosuria, and excessive caloric consumption as a response to, or a fear of, hypoglycemia that may also contribute to excessive weight gain. In the UKPDS, insulin-treated obese patients with type 2 **diabetes** gained an average of 4.0 kg more after 10 years than patients assigned to diet therapy.[61] Patients assigned to sulfonylurea therapy (chlorpropamide or glibenclamide) gained an average of 2.2 kg more than the diet group, whereas those assigned to metformin therapy gained weight in an amount similar to that in patients assigned to diet therapy.[61] [62] Nonetheless, weight gain is an undesirable effect of any therapy, because obesity is a known cause of insulin resistance[17] [68] and represents an independent risk factor for coronary artery disease, hypertension, and dyslipidemia.[33] [42] Excessive weight gain in insulin-treated patients can be minimized by using the lowest possible dose of insulin to achieve the desired glycemic goals and by educating the patient regarding diet, exercise, and the proper caloric response to hypoglycemia. Also, the addition of metformin to insulin therapy in some studies has been shown to ameliorate weight gain.

Patient Compliance and Inconvenience

One of the main reasons for resistance to insulin therapy on the part of patients with type 2 **diabetes** has been the pain and inconvenience associated with multiple insulin injections. The development of insulin pens with smaller and finer needles and more discrete modes of administration has helped remove these obstacles. The prospect of the future availability of inhaled insulin is also encouraging. Another impediment to intensive insulin therapy has been the need for frequent monitoring of blood glucose with fingerstick pricks. Less invasive glucose monitoring systems like the Glucowatch (Cygnus Inc., Redwood City, California) and the MiniMed Continuous Monitoring (MiniMed Technologies, Sylmar, California) system may reduce the inconvenience of monitoring.

GOALS OF THERAPY

The UKPDS conclusively demonstrated that improved glycemic control reduces the risk of overall microvascular complications by 25% and the combined risk of fatal and nonfatal myocardial infarctions by 16% ($P = 0.052$). The American **Diabetes** Association has therefore recommended the following therapeutic objectives:[5]

- Approach or maintain ideal body weight
- Fasting blood glucose (FPG) concentration between 80 and 120 mg/dL
- Bedtime blood glucose concentration between 100 and 140 mg/dL
- Glycosylated hemoglobin (HbA_{1C}) below 7%
- Systolic/diastolic blood pressure below 130/80 mm Hg
- Lipoprotein goals
  - Total cholesterol below 200 mg/dL
  - Triglycerides below 200 mg/dL
  - High-density lipoprotein (HDL) cholesterol above 35 mg/dL

Low-density lipoprotein (LDL) cholesterol below 100 mg/dL

The goals of therapy should be individually tailored. Caution is advised in patients who are aged or who have hypoglycemic unawareness. Other limitations to achieving normoglycemia may include high titers of insulin antibodies, especially in patients with a prior history of intermittent use of insulin of animal origin. Also, patients with type 2 **diabetes** often have hypertension and dyslipidemia.

INDICATIONS FOR INSULIN THERAPY IN TYPE 2 DIABETES

Insulin therapy is indicated for

1. Patients with type 2 **diabetes** with a persistently elevated FPG level of 300 mg/dL or higher and ketonuria or ketonemia.
2. Patients with type 2 **diabetes** with persistent elevations of the FPG level of 300 mg/dL or higher and symptoms of polyuria, polydipsia, and weight loss. Intensive insulin therapy with tight glycemic control helps reverse glucose toxicity.[51] Therapy improves both insulin sensitivity and insulin secretion[51] ; after 6 to 8 weeks of good glycemic control, these patients can be switched to an oral agent or can continue insulin therapy.
3. Patients with type 2 **diabetes** who, after discussing the options with the primary care physician, wish to receive insulin as initial therapy.
4. All women with gestational **diabetes mellitus** whose disease is not controlled with diet alone and women with type 2 **diabetes** who become pregnant should be treated with insulin therapy alone. All oral agents are contraindicated during pregnancy.

INSULIN PREPARATIONS

Several insulin preparations are available to control blood glucose in patients with type 2 **diabetes**. These preparations include rapid-acting insulin (Lispro), short-acting preparations (regular insulin), long-acting insulins (neutral protamine hagedorn [NPH], Lente insulins) and ultra-long-acting insulins (Ultralente, Glargine [Aventis Pharmaceuticals, Parsipanny, NJ]) insulins (Table 1) . Both short- and rapid-acting insulins and long-acting insulin preparations are needed to mimic the pattern of insulin delivery that normally controls blood glucose in nondiabetic individuals. Basal insulin therapy with long-acting insulin analogues is required to suppress hepatic glucose production overnight and between meals, whereas short- or rapid-acting insulin preparations are needed as bolus insulin to prevent hyperglycemia after meals. Insulin injections are usually given subcutaneously into the periumbilical area because of the rapid and consistent absorption kinetics observed at this location.[63] The site of insulin injection should be kept constant, because changing sites can change the pharmacokinetics; also, absorption can be highly variable, especially if lipohypertrophy is present. Before starting insulin therapy, the patient should be well educated in the techniques of home glucose monitoring (HGM), proper insulin administration, and self-adjustment of the insulin dose, if appropriate, as well as knowledgeable about dietary and exercise strategies. The patient and family members also should be informed about preventing, recognizing, and treating hypoglycemia. Initial and ongoing education by a **diabetes** management team is crucial for long-term success and safety of insulin treatment.

TABLE 1 -- COMPARISON OF HUMAN INSULINS AND INSULIN ANALOGUES

Insulin Preparations	Onset of Action	Peak Action	Duration of Action*
Lispro/Aspart	5-15 minutes	1-2 hours	4-6 hours
Human Regular	30-60 minutes	2-4 hours	6-10 hours
Human NPH/Lente	1-2 hours	4-8 hours	10-20 hours
Ultralente	2-4 hours	Unpredictable	16-20 hours
Glargine	1-2 hours	Flat	~ 24 hours

*The time course of action of any insulin may vary in different individuals, or at different times in the same individual. Because of this variation, time periods indicated are considered general guidelines only.

MONITORING INSULIN THERAPY

Home glucose monitoring using any of the commercially available glucose monitors is an essential component of any insulin therapy regimen and is useful both to monitor glycemic control and to adjust insulin doses. An educated patient can use HGM values to help recognize abnormal excursions in glucose values, apply insulin algorithms to make short-term insulin adjustments, avoid the development of severe hypoglycemia, and adjust dietary and exercise regimens appropriately on a day-to-day basis. Home glucose monitoring should be tailored according to the timing of insulin injections and the pharmacokinetics of the insulin sed. Monitoring should normally coincide with the peak action of a particular type of insulin (e.g., 1-3 hours after regular insulin and 6-8 hours after NPH or Lente insulin) to evaluate the efficacy of the dose and to avoid hypoglycemia. One must also pay close attention to the amount and timing of meals and periods of exercise when advising the best times to test blood glucose during the day. Initially, checking blood glucose levels before meals, 2 hours after meals at bedtime, and occasionally at 3:00 AM (the approximate time of the early-morning glucose nadir) will enable the physician to monitor glycemic control adequately in most patients. Once a patient is stabilized on a particular insulin regimen, the frequency of monitoring may be reduced, with intermittent periods of more intensive monitoring.

It is essential that patients know how to evaluate their HGM results and understand that daily variations in eating and exercise habits, as well as inexplicable changes in insulin sensitivity over both long- and short-term periods, affect glucose control. Although the feasibility of self-adjustment of insulin doses using algorithms has been a subject of considerable debate,[15] when patients are properly educated on how to perform and evaluate HGM results and how to use an insulin algorithm, daily glycemic control tends to improve because the patient has a better sense of self-control by participating in his or her own care.[23]

In addition to adjusting the dose of insulin by using an algorithm (as discussed later), a number of nonpharmacologic tools can be used to control excessive glucose levels. For example, the interval between the insulin injection and mealtime can be increased to allow sufficient time for insulin to become active before a meal challenge. Consuming fewer calories, eliminating foods that cause rapid increases in blood glucose, spreading the calories over an extended period of time, and exercising lightly after meals are additional effective nonpharmacologic methods than can be used in concert with HGM values to reduce daily glycemic excursions. If the blood glucose concentration is consistently elevated at a particular time, prospective long-term adjustments must be made to avoid the need to chase high blood glucose concentrations with extra insulin on a regular basis. Figure 4

demonstrates one of the insulin algorithm forms the authors use that exemplifies these pharmacologic and nonpharmacologic tools.

Figure 4. Algorithm form used for patients receiving intensive insulin therapy. As the premeal blood glucose value rises, the amount of regular insulin recommended also increases and is adjusted based on postprandial glucose values. The time between the insulin injection and the meal should also be increased as the premeal blood glucose value rises, thus improving postprandial glucose values. Regular insulin can be given at lunch and at bedtime for extreme hyperglycemia. If the patient consistently (3 days in a row) requires higher regular insulin doses at a particular time, the appropriate long-term adjustments should be made. (Courtesy of VA Endocrinology Clinic, VA Hospital, UCSD, La Jolla, CA.)

The success of any insulin therapeutic regimen depends on frequent self-monitored blood glucose readings. Home glucose monitoring is painful and may not be appealing to many patients with type 2 **diabetes**. In the near future, the availability of minimally invasive, ambulatory, reliable, and continuous real-time glucose sensors may greatly increase the ability to manage diabetics requiring insulin therapy (Fig. 5) (Figure Not Available) .

Figure 5. (Figure Not Available) The Glucowatch is a minimally invasive, continuous glucose monitor approved by the FDA and provides glucose readings every 20 minutes for up to 12 hours. *(Courtesy of Cygnus, Inc., Redwood City, CA.)*

INSULIN TREATMENT STRATEGIES

Addition of Insulin to Oral Agents

Combining a sulfonylurea with bedtime insulin is an effective strategy to improve glucose control and to overcome secondary sulfonylurea failure. The rationale of combination therapy with sulfonylureas and insulin is based on the assumption that, if evening insulin lowers the fasting glucose concentration to normal, then daytime sulfonylureas will be more effective in controlling postprandial hyperglycemia and maintaining euglycemia throughout the day. Metabolic profiles of type 2 diabetics have clearly demonstrated that fasting blood glucose contributes more to daytime hyperglycemia than do postprandial changes.[48] In addition, the fasting blood glucose concentration is highly correlated with the degree of hepatic glucose production during the early morning hours.[25] Hepatic glucose output is directly decreased by insulin[60] and is indirectly inhibited by the ability of insulin to reduce adipose tissue lipolysis, with lower concentrations of free fatty acids and gluconeogenesis.[36] The peak action of intermediate-acting insulin taken at bedtime also coincides with the onset of the dawn phenomenon (early morning resistance to insulin caused by diurnal variations in growth hormone and possibly by norepinephrine levels), which usually occurs between 3 and 7 AM. In addition, bedtime insulin increases the morning serum insulin concentration and thus may help reduce the postbreakfast glucose in addition to the fasting value. Several studies have demonstrated the success of a combination sulfonylurea and insulin regimen in patients with type 2 **diabetes** who do not respond to maximal sulfonylurea therapy.

Sulfonylurea Plus Evening NPH

One of the earliest studies to evaluate the additive clinical effects of combined sulfonylurea/insulin therapy (the bedtime insulin, daytime sulfonylurea [BI-DS] regimen) was conducted by Riddle et al.[47] In this study, 20 moderately obese patients with type 2 **diabetes** of less than 15 years' duration and with poor glycemic control on maximal sulfonylurea therapy (glyburide, 10 mg two times/day) were randomly allocated in a 4-month, double-blind, placebo-controlled, crossover study. In one arm of the study, participants received a single injection of NPH insulin in the evening plus glyburide, 10 mg, in the morning. In the other arm, participants received insulin plus placebo. Insulin dose was

adjusted by experienced endocrinologists to ensure the best glycemic control consistent with safety. At the end of the study, combined therapy with glyburide and evening insulin was superior to evening insulin alone (HbA_{1C} : 9.8 ± 0.1% versus 10.6 ± 0.2%) but was associated with greater weight gain (possibly attributable to reduced glucosuria). Despite this weight gain, blood pressure and plasma lipid concentrations were the same on the two regimens. Results from this study were among the first to suggest that in patients who do not respond to maximal sulfonylurea therapy, the addition of a single dose of NPH insulin in the evening, rather than multiple injections of insulin or a single injection of insulin alone, may represent a simple option to achieve glycemic control.

Sulfonylurea Plus Bedtime NPH

DeFronzo and colleagues were among the first to demonstrate the long-term efficacy of the BI-DS regimen.[56] In this well-designed study, 30 patients with type 2 **diabetes** who did not respond to treatment with an oral sulfonylurea agent were switched to glipizide for 2 months (phase I) to confirm lack of response and were then randomly assigned into three groups: BI-DS, BI-no DS, and DS-no BI. During phase II (3 months), the BI dose was fixed at a low dose (20 U/1.73 m^2). During the next 3 months, in phase III, BI was titrated up (high-dose = 40 U/1.73 m^2) to achieve good control or until hypoglycemic symptoms prevented further dose increases. In phase IV (6 months), 25 of the 30 original participants received open-labeled, high-dose BI-DS. At the end of phase II, low-dose BI-DS significantly reduced FPG from 244 ± 14 to 144 ± 11 mg/dL, HbA_{1C} from 8.9 ± 0.7% to 7.6 ± 0.3%, and basal HGP. There was a strong positive correlation ($r = 0.69$, $P < 0.05$) between the declines in FPG and HGP. In contrast, neither low-dose BI alone nor DS alone reduced FPG, HbA_{1C} , or basal HGP. In phase III, high-dose (40 ± 5 U/day) BI plus DS further significantly reduced the FPG to 113 ± 11 mg/dL, HbA_{1C} to 7.1 ± 0.3%, and basal HGP. On the other hand, although high-dose BI alone (38 ± 4 U/day) improved FPG, HbA_{1C} , and basal HGP to a degree similar to low-dose BI-DS, the improvement was less than with high-dose BI-DS. During phase IV, regardless of prior treatment, FPG and HbA_{1C} were controlled in all participants. As in other studies, participants in this study gained weight during BI-DS therapy. The weight gain was largely attributed to reduced glucosuria. The authors concluded that although both BI-DS and high-dose BI (40 U/1.73 m^2) improve glycemia in patients who have not responded to sulfonylurea therapy, BI-DS is superior to both low- and high-dose BI given alone. Moreover, this study demonstrated that good long-term glycemic control (up to 12 months) can be achieved with combined BI-DS therapy.

Sulfonylurea Plus Evening 70/30 Insulin

In contrast to the study by DeFronzo et al in which bedtime insulin was used to improve glucose control, Riddle et al conducted a 6-month study to test whether a simple algorithm using suppertime 70/30 insulin plus continued sulfonylurea therapy with glimepiride would improve glycemic control in obese patients with type 2 **diabetes** after sulfonylurea failure.[49] In this study, 145 type 2 diabetics with uncontrolled hyperglycemia (FPG: 180-300 mg/dL), receiving maximal sulfonylurea therapy (glimiperide, 8 mg two times/day) were randomly allocated to receive placebo plus insulin or glimeperide plus insulin for 6 months. The dose of 70/30 insulin at dinnertime was titrated to keep fasting fingerstick capillary blood glucose (FBG) levels below 120 mg/dL. At 24 weeks, although HbA_{1C} levels decreased similarly in both groups (9.9%-7.6%), the combination group needed nearly 35% less insulin than the insulin-alone group (49 versus 78 units) and also achieved glycemic control faster, with fewer dropouts (3% versus 15%, $P < 0.01$). Surprisingly, weight gain was similar (average: ~ 4.0 kg) in both groups (Fig. 6) (Figure Not Available) . Thus, this study demonstrates

that, for obese patients not responding to full doses of glimepiride, slowly titrating suppertime 70/30 insulin based on patient-measured FBG safely restores acceptable glycemic control either alone or in combination with continued glimepiride. Combined therapy restored glycemic control more rapidly and with lower doses of insulin.

Figure 6. (Figure Not Available) Mean fasting plasma glucose (FPG) *(A)* and daily insulin dosage *(B)* for all subjects in the two groups treated with 70/30 insulin. At 24 weeks, although HbA_{1C} levels decreased similarly in both groups (9.9% to 7.6%), the glimepiride combination group needed nearly 35% less insulin than the insulin group (49 versus 78 units) and also achieved glycemic control faster, with fewer dropouts (3% versus 15%, $P < 0.01$). Surprisingly, weight gain was similar (~ 4.0 kg) in both groups. *$P < 0.001$; † $P < 0.05$; n = 132; circle = placebo and insulin; triangle = glimepiride and insulin titrated to FPG < 140 mg/dL. *(From Riddle MC, Schneider J: Beginning insulin treatment of obese patients with evening 70/30 insulin plus glimepiride versus insulin alone. Glimepiride Combination Group. **Diabetes** Care 21:1052-1057, 1998; with permission.)*

Sulfonylurea Plus Various Insulin Regimes

To evaluate the optimal regimen of insulin treatment in patients with type 2 **diabetes** who do not respond to oral agents, Yki-Jarvinen et al [67] conducted a large study in Finland with 153 patients who had had type 2 **diabetes** for more than 3 years, with a body-mass index (BMI) above 35 kg/m^2, serum C-peptide levels above 0.33 nmol/L, and who had not responded to maximum-dose sulfonylurea alone or with metformin. These patients were randomly allocated to one of five groups. The morning-NPH group continued oral hypoglycemic (usual) therapy and received NPH insulin before breakfast. The evening-NPH group continued usual therapy and received NPH insulin at 2100 hours. The two-insulin-injection group discontinued usual therapy and took insulin (NPH and regular insulin in a ratio of 70/30 two times/day). The multiple-injection group took NPH insulin at 2100 hours and regular insulin before all meals. Control patients continued usual medications. Insulin doses were adjusted to maintain normoglycemia. After 3 months, all treatment groups had similar reductions in mean diurnal glucose concentrations and HbA_{1C} levels (1.6%-1.9%) compared with the control group that received oral agents alone. The group treated with combination oral agents and bedtime NPH insulin had the least weight gain of any group (1.2 ± 0.5 kg versus 1.8-2.9 ± 0.5 kg) and also a 50% to 65% lower increment in mean diurnal serum free insulin concentrations. There was no evidence of severe hypoglycemia with combination therapy, and patient acceptance was excellent. Thus, in patients with type 2 **diabetes** who do not respond to oral hypoglycemic drug therapy, the addition of NPH insulin in the evening improves glycemic control in a manner similar to combination therapy with NPH insulin in the morning, a two-insulin-injection regimen, or a multiple-insulin-injection regimen but induces less weight gain and hyperinsulinemia.

Sulfonylurea Plus Lispro Insulin

Most of the early studies evaluating insulin treatment strategies used NPH insulin in combination with sulfonylureas and focused mainly on reducing overnight hepatic glucose production and fasting blood glucose with long-acting insulin. In contrast, Bastyr et al published a recent study in which they used Lispro insulin (a rapidly acting insulin) to target postprandial glucose, which is being increasingly implicated in diabetic cardiovascular disease. In an elegant study, they compared the overall safety and efficacy of combination therapies focused on fasting or postprandial blood glucose in patients with type 2 **diabetes** not adequately controlled with oral sulfonylurea agents alone. [9] A total of 135 patients were randomly assigned for 3 months to one to three combination regimens. All participants received glyburide (G) and in addition received Lispro (L) insulin to address postprandial blood glucose (the L+G group); bedtime NPH insulin to target FPG (the NPH+G group); or metformin, to target mainly overnight FBG (the M+G group). At the end of 3 months (Fig.

7) (Figure Not Available) , as expected, FBG was significantly lower for the NPH+G group (153 ± 41 mg/dL) than for either the L+G group (190 ± 36 mg/dL) or the M+G group (175 ± 52 mg/dL), and the mean 2-hour postprandial glucose level after a test meal was significantly lower for the L+G group (195 ± 52 mg/dL) than for the NPH+G group (220 ± 56 mg/dL) or the M+G group (228 ± 59 mg/dL). The HbA_{1C} , however, was significantly lower for the L+G group (7.68 ± 0.88%) than for either the NPH+G group (8.51 ± 1.38%, $P = 0.003$) or the M+G group (8.31 ± 1.31%, $P = 0.025$). The overall rate of hypoglycemia was low, and the difference among groups was not statistically significant, but, as expected, all the insulin-treatment groups had weight gain. Thus, antihyperglycemic therapy with Lispro insulin, focusing on postprandial glucose control, has a greater impact on overall metabolic control than do the more traditional approaches of NPH insulin at bedtime or metformin. Lispro insulin remains a treatment option in this patient population.

Figure 7. (Figure Not Available) In patients with type 2 **diabetes** who fail sulfonylurea therapy, the addition of any second antihyperglycemic agent--Lispro insulin, Neutral Protamine Hagedorn Insulin or glyburide--lowers glucose and HbA_{1C} . Therapy with Lispro insulin focused on lowering postprandial glucose, however, has a greater impact on HbA_{1C} . Metformin therapy is associated with the least weight gain. Solid bar = baseline HbA_{1C} ; shaded bar = follow-up HbA_{1C} ; open bar = follow-up weight gain. *(From Bastyr EJ III, Stuart CA, Brodows RG, et al for the IOEZ Study Group: Therapy focused on lowering postprandial glucose, not fasting glucose may be superior for lowering HbA_{1C} . **Diabetes** Care 23:1236-1241, 2000; with permission.)*

Sulfonylurea Plus Metformin Plus Insulin

Although insulin therapy in combination with sulfonylureas has potent effects in lowering blood glucose and improving overall glycemia, weight gain is a constant occurrence in most clinical trials in which insulin is used to treat type 2 **diabetes**. Weight gain can exacerbate insulin resistance and hyperinsulinemia. The use of metformin in this situation may prove advantageous, because its use is not associated with weight gain. The safety and efficacy of metformin in combination with insulin was well demonstrated in a multicenter study by Yki-Jarvinen et al.[69] In this placebo-controlled study, 96 type 2 diabetics poorly controlled with oral sulfonylurea therapy (mean HbA_{1C} : 9.9% ± 0.2%) were randomly assigned to 1 year of treatment with bedtime intermediate-acting insulin plus either glyburide (10.5 mg), metformin (2 g), glyburide and metformin, or a second injection of intermediate-acting insulin in the morning. Patients were taught to adjust the bedtime insulin dose on the basis of fasting glucose measurements. At 1 year, body weight remained essentially unchanged in patients receiving bedtime insulin plus metformin (mean change: 0.9 ± 1.2 kg) but increased by 3.9 ± 0.7 kg, 3.6 ± 1.2 kg, and 4.6 ± 1.0 kg in patients receiving bedtime insulin plus glyburide, those receiving bedtime insulin plus both oral drugs, and those receiving bedtime and morning insulin, respectively (Fig. 8) . In addition, the greatest decrease in the HbA_{1C} value at 1 year was observed in the group receiving bedtime insulin and metformin (from 9.7% ± 0.4% to 7.2% ± 0.2%). This group also had significantly fewer symptomatic and biochemical cases of hypoglycemia ($P < 0.05$) than the other groups. Thus, this study demonstrated that combination therapy with bedtime insulin plus metformin in patients not adequately controlled with sulfonylurea therapy prevents weight gain and also seems superior to other bedtime insulin regimens in improving glycemic control and reducing the frequency of hypoglycemia.

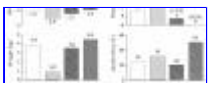

Figure 8. Combination therapy with bedtime NPH insulin plus metformin in patients failing sulfonylurea therapy not only prevents weight gain but also seems superior to other bedtime insulin

regimens like NPH insulin plus glyburide, NPH insulin plus glyburide and metformin, and bedtime NPH insulin plus AM NPH insulin, with respect to improvement in glycemic control and frequency of hypoglycemia. Open bar = glyburide; shaded bar = metformin; hatched bar = glyburide and metformin; solid bar = NPH in the morning. (*Data from* Yki-Jarvinen, H, Ryysy L, Nikkila K, et al: Comparison of bedtime insulin regimens in patients with type 2 **diabetes mellitus**: A randomized, controlled trial. Ann Intern Med 1:389-396, 1999.)

Thus, combination therapy with sulfonylureas, metformin, and insulin (NPH, 70/30, or Lispro) can be a simple and effective means of normalizing glycemia and HbA_{1C} concentrations in selected patients with type 2 **diabetes mellitus** who do not respond to oral antidiabetic agents. In addition to physiologic reasons, there are a number of practical reasons why combination therapy may be beneficial.

Benefits of Combination Therapy

Metabolic benefits of bedtime intermediate-acting insulin

- Reduces the fasting and postprandial blood glucose values
- Directly suppresses hepatic glucose production directly
- Reduces free fatty acid levels, thereby indirectly suppressing hepatic glucose output
- Counteracts the dawn phenomenon

Practical benefits

- Minimal education needed
- No need to know how to mix different insulins
- Easily started on an outpatient basis
- Compliance may be better with one injection than with two or more
- Psychologic acceptance of the needle is good
- Less total exogenous insulin needed than with a two- or three-shot/day regimen, often with less weight gain and peripheral hyperinsulemia

Practical Strategy to Implement a Combination Regimen of an Oral Agent Plus Insulin

Selection of Patients

The type of patient in whom combination therapy can most commonly succeed is one who does not achieve adequate glycemic control with sulfonylurea or metformin therapy but who has some evidence of responsiveness to oral agents. Patients have a higher likelihood of success using daytime sulfonylureas and bedtime insulin if they are obese, have had overt **diabetes** for less than 10 to 15 years, are diagnosed with type 2 **diabetes** after the age of 35 years, do not have fasting blood glucose values consistently over 250 to 300 mg/dL, and have evidence of endogenous insulin secretory ability. Although standard measurement conditions and C-peptide concentrations have not been established for this clinical situation, a fasting ($\geq$ 0.2 nmol/L) or glucagon-stimulated ($\geq$ 0.40 nmol/L) C-peptide value indicates some degree of endogenous insulin secretory ability.[27] [44] Patients with type 2 **diabetes** diagnosed before the age of 35 years more often have atypical forms of **diabetes**. Patients who have had **diabetes** for more than 10 to 15 years tend to have a greater chance of beta-cell exhaustion and thus to be less responsive to oral hypoglycemic agents. Thin patients are more likely to be hypoinsulinemic and often respond inadequately to oral sulfonylureas, which leads to combination therapy failure. In addition, a markedly elevated fasting glucose concentration is often associated with a concomitant decrease in endogenous insulin secretory ability, rendering oral agents ineffective (glucose toxicity). Studies demonstrating the most favorable outcome from combination therapy have involved patients who still had some response to sulfonylureas or had evidence of significant endogenous secretory ability. The actual number of patients who might fit into this category, and possibly respond to combination therapy, is unknown but is estimated to be between 20% and 40% of all patients not achieving adequate glycemic control with maximal doses of sulfonylureas as the sole therapy.

Dose Calculation

Calculation of the initial bedtime dose of intermediate-acting insulin can be based on clinical judgment or various formulas based on the fasting blood glucose concentration or body weight. For example, one can divide the average fasting blood glucose (mg/dL) by 18 or divide the body weight in kilograms by 10 to calculate the initial dose of NPH or Lente insulin to be given at bedtime.[60] One can also safely start 5 to 10 units of intermediate-acting insulin for thin patients and 10 to 15 units for obese patients at bedtime as an initial estimated dose. In either case, the dose is increased in 2- to 4-unit increments every 3 to 4 days until the morning fasting blood glucose concentration is consistently in the range of 80 to 120 mg/dL.

Practical Strategy to Start Insulin Therapy inPatients Failing Oral Agents

- Continue oral agent(s) at same dosage (eventually reduce)
- Add single evening insulin dose

  For thin patients (BMI <25 kg/m^2)--5 to 10 units NPH (bedtime)

  For obese patients (BMI >25 kg/m^2)--10 to 15 units NPH (bedtime) **OR** 70/30 (before dinner)

- Adjust dose by fasting self-monitored blood glucose (goal: 80-120 mg/dL)
- Increase insulin dose weekly as needed

  Increase by 4 units if FBG >140 mg/dL

  Increase by 2 units if FBG = 120 to 140 mg/dL

The best time to give the evening injection of intermediate-acting insulin is between 10 PM and midnight. Many reliable patients can make their own adjustments using HGM. Figure 9 is a patient self-instruction sheet for bedtime insulin adjustments. Based on the results of HGM, combination therapy can be altered to reduce hyperglycemia at identified times during the day. For example, a common situation seen with daytime sulfonylurea and bedtime intermediate-acting insulin therapy is an improvement in the fasting, prelunch, and predinner blood sugar values, although the postdinner blood glucose concentration remains excessively high (>200 mg/dL). In this clinical situation, an injection of premixed regular and intermediate-acting insulin (i.e., 70/30 insulin) before dinner may be more efficacious than a bedtime dose of intermediate-acting insulin. In this regimen the rapidly acting regular insulin component often improves the postdinner blood glucose values, and the NPH component improves overnight blood glucose. With this regimen, however, one must be more cautious about early morning hypoglycemia, because the intermediate-acting insulin given before dinner will exert its peak effect earlier.

Figure 9. Patient self-adjustment form for evening insulin regime.

Dose Adjustment

Once the fasting blood glucose concentrations are consistently in a desirable range, the prelunch, predinner, and bedtime blood sugar values must be monitored to determine if the oral hypoglycemic agents are maintaining daylong euglycemia. It is recommended that, after the addition of evening insulin, patients continue to take the maximal dose of the oral sulfonylurea agent. If the daytime

blood glucose concentrations start to become excessively low, the dose of oral medication must be reduced. This situation is common because glucose toxicity may be reduced by improved glucose control, leading to enhanced sensitivity to both oral agents and insulin. If the prelunch and predinner blood glucose concentrations remain excessively high with combination therapy, the oral sulfonylurea agent is probably not contributing significantly to glycemic control throughout the day. In this situation, in the past, a more conventional two-injection/day insulin regimen has been used, discontinuing therapy with the oral antidiabetic agent. Now, however, the use of insulin-sensitizing agents (metformin and the glitazones) may obviate the need for multiple doses of exogenous insulin and the associated peripheral hyperinsulinemia.

Multiple-Injection Insulin Regimens

With the availability of premixed insulins, one of the most common insulin regimens used to treat obese patients with type 2 **diabetes** who have not achieved adequate glycemic control with oral agents is the split-mixed regimen consisting of a prebreakfast and predinner dose of 70/30 insulin. This combination of an intermediate- and a fast-acting insulin in a two-injection/day regimen is often successful in these patients (unlike type 1 diabetics, in whom this regimen results in persistent early morning hypoglycemia and fasting hyperglycemia). These problems do not seem to occur as frequently in type 2 **diabetes**, probably because of pathophysiologic differences in endogenous insulin secretory ability, insulin resistance, and counterregulatory mechanisms. Despite the widespread use of a multiple-injection insulin regimen to achieve glucose control in patients with type 1 **diabetes**, evidence is still lacking that this regimen has a beneficial effect on macrovascular or atherosclerotic disease in the long term. Two long-term studies, the UKPDS and the Kumamoto study, have shown that although tight glycemic control with multiple insulin injections delays the onset and retards the progression of microvascular complications in patients with type 2 **diabetes**, the effects on macrovascular disease is not clear. Two other studies, a 3-month study by Yki-Jarvinen and the 2-year VA Cooperative Study, found that, compared with a multiple-injection insulin regimen, the combination of a sulfonylurea and evening NPH insulin resulted in equal glycemic control with far less weight gain and peripheral hyperinsulinemia.

One of the first studies to demonstrate the utility and efficacy of the two times/day split-mixed regimen was conducted by Henry et al.[32] The purpose of this 6-month study was to determine whether tight glycemic control could be obtained using intensive conventional split-dose insulin therapy in the outpatient management of type 2 **diabetes** without development of unacceptable side effects. Fourteen obese (BMI: 31 $\pm$ 2 kg/m^2) type 2 diabetics were treated with an intensive program of conventional insulin (subcutaneous NPH and regular insulin before breakfast and supper) for 6 months. Patients were monitored biweekly as outpatients, and insulin dose adjustments were determined using an algorithm based on frequent capillary blood glucose (CBG) measurements (4-6 times/day). Glycemic control was achieved by 1 month (mean plasma glucose fell from 315 ± 16 to 139 ± 13 mg/dL, $P < 0.001$) and remained in this range thereafter. Hypoglycemic events in this study were mild and infrequent at 1 month and decreased progressively throughout the study. Most of the improvement in glycemic control in this study resulted from the suppression of basal hepatic glucose production by 44% (from 628 $\pm$ 44 to 350 $\pm$ 17 mumol/m^2/min, $P < 0.001$), with a more modest but significant improvement in peripheral glucose uptake (from 1418 ± 156 to 1657 ± 128 mumol/m^2/min, $P < 0.05$), as determined by the glucose clamp technique. The total dose of exogenous insulin required was 100 ± 24 U at 6 months. As expected, mean serum insulin levels increased from 308 ± 80 to 510 ± 102 pmol/L ($P < 0.05$), and body weight increased from 93.5 ± 5.8 to 102.2 ± 6.8 kg ($P < 0.001$). Weight gain was directly correlated with both mean daylong serum insulin level ($r = 0.67$, $P < 0.01$) and total exogenous insulin dose ($r = 0.62$, $P < 0.02$). The authors concluded that intensive insulin treatment, when combined with frequent blood glucose

measurements, can be used to improve glycemic control rapidly in type 2 **diabetes** without development of unacceptable hypoglycemia. Interestingly, in this study, approximately 50% of the total insulin dose was required before breakfast and 50% before dinner, and the ratio of NPH to regular was 75/25. This ratio approximates that used in the 70/30 premixed insulin.

The study by Henry et al emphasizes several important aspects of insulin therapy in obese patients with type 2 **diabetes**: (1) The average daily dose of insulin needed to control such patients may approximate 1 U/kg of body weight. (2) The total daily insulin requirement can be split equally between the prebreakfast and predinner injections. (3) The split-mixed regimen in patients with type 2 **diabetes** is usually devoid of the problems commonly seen with this regimen in type 1 **diabetes**, particularly early morning hypoglycemia and fasting (preprandial) hyperglycemia. (4) Both severe and mild hypoglycemic events are much less frequent in patients with type 2 **diabetes mellitus** than in patients with type 1 **diabetes** undergoing intensive insulin therapy. (5) Metabolic improvement requires large doses of exogenous insulin to overcome peripheral insulin resistance, which leads to greater hyperinsulinemia with progressive weight gain.

In the longer term, both the UKPD and the Kumamoto study have documented the efficacy of multiple insulin injections.[57] [61] The UKPDS was a landmark study that conclusively proved that intensive blood-glucose control by either insulin or sulphonylureas substantially decreases the risk of microvascular complications in patients with type 2 **diabetes**. This study enrolled 3867 newly diagnosed patients with type 2 **diabetes** (median age, 54 years), who after 3 months' diet treatment had a mean of two FPG concentrations of 110 to 270 mg/dL. These persons were randomly assigned to an intensive regimen with a sulphonylurea (chlorpropamide, glibenclamide, or glipizide) or with insulin or to a conventional regimen with diet. The aim of the intensively treated group was an FPG below 108 mg/dL. In the conventionally treated group, the aim was the best FPG that could be achieved with diet alone; drugs were added only if there were hyperglycemic symptoms or an FPG level above 270 mg/dL. In this study, 1156 patients assigned to insulin therapy initially received Ultralente or isophane insulin one time/day. If the daily dose of insulin was more than 14 U or premeal glucose measurements were above 126 mg/dL, regular insulin was added. Over 10 years, the median HbA_{1C} was 7.0% in the insulin group (7.0% in the intensively treated group as a whole) compared with 7.9% in the conventionally treated group. There was no difference in HbA_{1C} among agents in the intensively treated group. In the UKPDS, intensive glycemic control with sulfonylureas or insulin significantly reduced microvascular complications, but the beneficial effects on cardiovascular events was of borderline significance ($P = 0.52$). On the other hand, although the study did not demonstrate any beneficial effect of intensive control on macrovascular disease, it was reassuring that none of the sulfonylureas or insulin had an adverse effect on cardiovascular outcomes. As expected, intensive treatment with insulin increased the risk of hypoglycemia, with a 1.8% incidence of major hypoglycemic episodes and a 28% incidence of any hypoglycemic episodes (compared with 0.7% and 10%, respectively, in the diet group). There was also a significant increase in weight in the insulin group (4.0 kg compared with the conventional group). In comparison, patients receiving chlorpropamide and glibenclamide gained 2.6 kg and 1.7 kg, respectively. Fasting plasma insulin levels in participants assigned to insulin therapy also increased more than in those in the conventional group because higher insulin doses were given. The median insulin doses at 3 years, 6 years, 9 years, and 12 years in patients assigned intensive treatment with insulin were 22 U, 28 U, 34U, and 36U, respectively. Median doses of insulin for patients with BMIs below 25 kg/m^2 and above 35 kg/m^2 were 16 U (10-24 U) and 36 U (23-50 U), respectively, at 3 years and 24 U (14-36 U) and 60 U (40-82 U) at 12 years. The maximum insulin dose was 400 U/day.

Like the UKBS, the Kumamoto study [57] also documented beneficial effects on microvascular complications in Japanese patients with type 2 **diabetes**. In this study, however, the patients with type 2 **diabetes** were lean (BMI: ~ 21 kg/m^2) and also insulinopenic when compared with the obese, hyperinsulinemic patients with type 2 **diabetes** in the United States and in European countries. In the Kumamoto study, a total of 110 patients with type 2 **diabetes** (55 with no

retinopathy [the primary prevention cohort] and 55 with simple retinopathy [the secondary intervention cohort]) were randomly assigned to multiple-injection insulin therapy (MIT) groups who received three or more insulin injections/day or to conventional insulin injection therapy (CIT) groups and who received one or two injections of intermediate-acting insulin/day. After 8 years, in both primary prevention and secondary intervention cohorts, the cumulative percentages of worsening in retinopathy, neuropathy, and nephropathy were significantly lower in the MIT group than in the CIT group. In regard to cardiovascular events, there were only four events in the MIT group and seven events in the CIT group.

In contrast to the UKPDS and the Kumamoto studies documenting the beneficial effects of multiple insulin injections, other studies suggest that a multiple-injection regimen may be inferior in some aspects to combination therapy with insulin and sulfonylureas. In one 3-month study, Yki-Jarvinen et al compared four insulin-treatment regimens with continued oral hypoglycemic drug therapy in patients with type 2 **diabetes**.[69] Despite similar improvements in HbA_{1C} in all the insulin-treatment groups (1.6%-1.9%), weight gain was significantly less (1.2 ± 0.5 kg) in the evening-NPH group than in the other insulin-treatment groups (2.2 ± 0.5 kg in the morning-NPH group, 1.8 ± 0.5 kg in the two-injection group, and 2.9 ± 0.5 kg in the multiple-injection group; $P < 0.05$). The latter two multiple-injection groups were also associated with a 39% and 36% increase in mean diurnal serum free insulin levels and a total daily insulin dose of 43 U and 45 U, respectively. The overall lower weight gain and insulin requirements in this study (as compared with the study by Henry et al)[32] probably result primarily from differences in patient characteristics. Patients in this study were leaner (BMI: 29 versus 31 kg/m^2) and had lower baseline FBG values (225 versus 283 mg/dL).

Similar beneficial effects of combination sulfonylurea plus insulin therapy as compared with a multiple-injection insulin regimen were obtained in the VA Cooperative Study on Glycemic Control and Complications in Type 2 **Diabetes** (VA CSDM), which prospectively studied 153 insulin-requiring type 2 **diabetes** patients (BMI: 30.7 ± 4 kg/m^2, HbA_{1C}: 9.3 ± 1.8%).[2] Patients were randomly allocated between an intensively treated arm and a standard-treatment arm with a mean follow-up of 27 months. A four-step management technique was used, with patients moving to the next step if the glycemic goals were not met. In phase I, evening intermediate- or long-acting insulin was used; in phase II, daytime glipizide was added; in phase III, patients were switched to two injections of insulin alone; and in phase IV, multiple daily insulin injections were used. Home glucose monitoring measurements were made two times/day and at 3:00 AM one time/week. In phase I, fasting serum glucose fell from 205 ± 59 mg/dL to nearly normal and remained so in the other treatment phases. The intensively treated arm achieved HbA_{1C} levels below 7.3%, and an HbA_{1C} separation of 2.1% with the standard arm was maintained through the course of the study. In this study (Fig. 10) (Figure Not Available) , most of the decrease in HbA_{1C} occurred in phase I with one injection of insulin alone (-1.4%) or by adding daytime glipizide in phase II (-1.9% compared with baseline). In phase III, after the substitution of two injections of insulin alone with no glipizide, HbA_{1C} did not decrease further, despite a doubling of the insulin dose. In phase IV, multiple daily injections resulted in an additional HbA_{1C} decrease of 0.5% (-2.4% compared with baseline). Two thirds of the patients, however, were still receiving one or two injections/day at the end of the study. Changes in HGM levels paralleled those of the HbA_{1C}, as did the increments in number of reported hypoglycemic reactions (virtually all either mild or moderate in character). For the combination of

glipizide and insulin (phase II), the only significant effect was obtained with doses up to 10 mg/day; there were no significant additional benefits with up to fourfold higher daily doses, and HbA_{1C} levels had an upward trend with doses above 20 mg/day. Surprisingly, in the VA CSDM trial, weight changes in the intensively treated arm did not differ significantly from those in the standard-treatment arm, probably because of the gradual incorporation of progressive treatment steps and the relatively low daily insulin doses in phases I (61 ± 38 U) and II (64 ± 41 U).

Figure 10. (Figure Not Available) Maximal effects of each treatment phase in the VA Study. Data represent means ± SE HbA_{1C} and insulin daily dose, as the last values recorded at each step-treatment phase, including patients who remained in the phase at the end of the study and those who progressed to higher treatment phases. *Significant difference from the values reported in the preceding phase; Ins × 1 = evening insulin injection; Ins + Glip = evening injection and daytime glipizide; Ins BID = two daily injections of insulin; MDI = multiple daily injections of insulin. *(From Abraira C, Henderson WG, Colwell JA, et al: Response to intensive therapy steps and to glipizide dose in combination with insulin in type 2 **diabetes**: VA feasibility study on glycemic control and complications (VA CSDM). **Diabetes** Care 21:574-579, 1998; with permission.)*

Although the VA Cooperative Study was only a feasibility study, the authors did report on micro- and macrovascular events.[1] [20] [21] Intensive control did not cause any transient deterioration of retinopathy. Although no improvement was seen in retinopathy, the follow-up was 24 months, an interval shorter than the 3 years or more of intensive therapy before improvement is seen in type 1 diabetic studies. This finding does not rule out the possibility that longer periods of intensive therapy might have improved retinopathy, as was seen in the UKPDS. The effects of intensive therapy on macrovascular complications were inconclusive.[1] There were 61 new cardiovascular events in 24 patients (32%) in the intensive-treatment arm and in 16 patients (20%) in the standard-treatment arm ($P = 0.10$). There was no difference in total and cardiovascular mortality (n = 5 and n = 3 in the intensive- and standard-treatment arms, respectively) or in new events in patients with cardiovascular history (n = 10 in each arm). The effects of intensive therapy on metabolic risk factors for cardiovascular disease were intriguing.[20] Although intensive insulin therapy led to a potentially beneficial reduction in serum triglyceride levels and preservation of HDL cholesterol and apolipoprotein A1 levels, there was a transient elevation in plasma fibrinogen levels, a possible thrombogenic effect. The long-term implications of these effects will be assessed in the recently begun, 7-year VA prospective trial to assess the risk-benefit ratio of intensive insulin therapy in patients with type 2 **diabetes**.

Thus, in the VA CSDM trial, a simple regimen of a single injection of insulin, alone or with glipizide, seemed sufficient to obtain clinically acceptable levels of HbA_{1C} for most obese, insulin-requiring, type 2 **diabetes** patients. Further decrease of HbA_{1C} required multiple daily injections at the expense of doubling the insulin dose and the rate of hypoglycemic events. Also, in combination therapy, doses of glipizide above 20 mg/day offered no additional benefit.

Practical Strategy to Implement a Multiple-Injection Insulin Regimen

Dose Calculation

There are several acceptable methods for initiating insulin therapy in type 2 **diabetes**. A conservative yet effect strategy using a stepwise approach to institute a split-mixed regimen was used successfully and safely by Henry et al.[32] A simple alternative method for initiating a split-mixed regimen in obese patients uses 70/30 premixed insulin with an initial total daily dose (0.4-0.8 U/kg) equally split between the prebreakfast and predinner meals. Adjustments are based on HGM results, which may involve increasing or decreasing the ratio of intermediate- to regular-acting insulin. It is advisable to use lower doses (total daily dose: 0.2-0.5 U/kg) in thin patients with type 2 **diabetes** (BMI < 25 kg/m^2), because premixed insulins contain fixed doses of regular insulin. Thin patients tend to be

more sensitive to the glucose-lowering effects of insulin and thus may be more prone to severe hypoglycemia.

Dose Adjustment

Premixed insulins (70/30 insulin) are easy to administer and effective. Insulin adjustments are based on HGM, and the dose is increased by 2- to 4-unit increments every 3 to 4 days until the morning FPG and predinner blood glucose concentration are consistently in the range of 80 to 120 mg/dL. The disadvantages of a multiple-injection insulin regimen are a greater incidence of weight gain and the need for increased insulin doses. These disadvantages may be ameliorated by the addition of an insulin sensitizer such as metformin or a glitazone to any insulin or insulin-plus-sulfonylurea combination regimen. The use of metformin has been frequently shown to restrain weight gain and to reduce insulin requirements when used in combination with insulin, and the use of the glitazones also seems to have insulin-sparing effects, which are discussed later.

Addition of Oral Agents to Insulin

Until recently, the only option for patients not adequately controlled with sulfonylurea agents and insulin was to increase the insulin dose. This practice, however, further increases the chance of hyperinsulinemia and weight gain. Ongoing research indicates that adding oral agents such as metformin, glitazones, or acarbose to insulin therapy, alone or in combination, is a feasible way of improving or normalizing glycemic control in a significant number of patients.

Insulin Plus Metformin

Clinical data suggest that metformin is a useful adjunct in patients poorly controlled with insulin, after sulfonylurea agents have achieved maximal benefit (Fig. 11) . Metformin offers the advantage of not stimulating insulin secretion and exacerbating hyperinsulinemia. The beneficial effect of adjuvant metformin therapy has been demonstrated in a randomized, double-blind, placebo-controlled study involving 43 obese patients with type 2 **diabetes** who were poorly controlled with insulin (Fig. 12) (Figure Not Available) . [8] The addition of metformin to insulin therapy resulted in HbA_{1C} concentrations that were 10% lower than those achieved by insulin therapy alone. Average final HbA_{1C} levels were 6.5% in the metformin group and 7.6% in the placebo group. For patients who received placebo, the insulin dose increased by 22.8 U or 29% more than did the dose for patients who received metformin ($P = 0.002$); for patients receiving metformin, the insulin dose decreased slightly. Patients in the placebo group gained an average of 3.2 kg of body weight (confidence interval [CI]: 1.2 to 5.1 kg); patients in the metformin group gained an average of 0.5 kg of body weight ($P = 0.07$). Similar results were reported in an earlier study by Giugliano et al.[26]

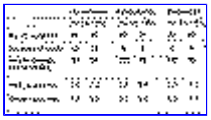

Figure 11. In a number of studies, the addition of metformin to insulin therapy attenuates weight gain. Data from Yki-Jarvinen et al: Comparison of bedtime insulin regimens in patients with type 2 **diabetes mellitus**. A randomized, controlled trial. Ann Intern Med 130:389-396, 1999; Aviles-Santa L, et al: Effects of metformin in patients with poorly controlled, insulin-treated type 2 **diabetes mellitus**: A randomized, double-blind, placebo-controlled trial. Ann Intern Med 131:182-188, 1999; and Bergenstal R et al: Advantages of adding metformin to multiple dose insulin therapy in type 2 **diabetes**. **Diabetes** 47(suppl 1):A89, Astract 347, 1998.

Figure 12. (Figure Not Available) *A* and *B*, The glycemic and insulin-sparing effects achieved by the addition of metformin to insulin therapy. Open bar = metformin/insulin (n = 21); shaded bar = placebo/insulin (n = 22). * $P = 0.02$ versus placebo/insulin; † $P = 0.04$ versus placebo/insulin. *(From Aviles-Santa L, Sinding J, Raskin P: Effects of metformin in patients with poorly controlled, insulin-treated type 2 **diabetes mellitus**: A randomized, double-blind, placebo-controlled trial. Ann Intern Med 131:182-188, 1999; with permission.)*

In head-to-head comparison studies, however, troglitazone seems to be superior to metformin in its insulin-sensitizing and insulin-sparing effects. This superiority was well demonstrated in a study conducted by Yu et al comparing the insulin-sparing actions of these two agents and their effects on insulin sensitivity and insulin secretion in 20 patients with type 2 **diabetes**.[70] To avoid the confounding effect of improved glycemic control on insulin action and secretion, patients were first rendered euglycemic with 4 weeks of continuous subcutaneous insulin infusion (CSII) before being randomly allocated to receive CSII plus troglitazone (n = 10) or CSII plus metformin (n = 10); euglycemia was maintained for another 6 to 7 weeks. Insulin sensitivity was assessed by a hyperinsulinemic-euglycemic clamp at baseline, after 4 weeks of CSII and after CSII plus either troglitazone or metformin. Good glycemic control was achieved with CSII alone and was maintained with CSII plus an oral agent (mean 24-hour glucose: troglitazone, 112 ± 11 mg/dL; metformin, 112 ± 5 mg/dL). Insulin requirements decreased 53% with troglitazone compared with CSII alone (48 ± 4 versus 102 ± 13 U/day, $P < 0.001$), but only 31% with metformin (76 ± 13 versus 110 ± 18 U/day, $P < 0.005$) (Fig. 13) . The 24-hour C-peptide profiles were similar. Normal fasting hepatic glucose output was maintained with both agents although insulin levels were lower than with CSII alone. Insulin sensitivity did not change significantly with CSII alone or with CSII plus metformin but improved 29% with CSII plus troglitazone ($P < 0.005$ versus CSII alone) and was also 45% higher than in the patients receiving CSII plus metformin ($P < 0.005$). The authors concluded that metformin has no effect on insulin-stimulated glucose disposal independent of glycemic control in type 2 **diabetes** and that troglitazone (600 mg/day) had greater insulin-sparing effects than metformin (1700 mg/day) in CSII-treated euglycemic patients, probably because of the peripheral tissue insulin-sensitizing effects of troglitazone.

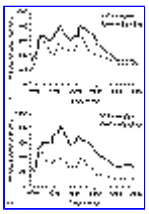

Figure 13. Comparison of the insulin-sparing effects of metformin *(A)* versus troglitazone *(B)* during a euglycemic-hyperinsulinemic clamp, before and after treatment with either of these agents. Troglitazone was the glitazone used in this study, but is no longer FDA-approved for clinical use. Solid line = continuous insulin infusion; dotted line = continuous insulin infusion plus metformin or glitazone. (*Data from* Yu JG, Kruszynska YT, Mulford M, et al: A comparison of troglitazone and metformin on insulin requirements in euglycemic intensively insulin-treatd type 2 diabetic patients. **Diabetes** 48:2414-2421, 1999.)

In a patient achieving suboptimal glycemic control with a full insulin regimen, one can attempt to initiate and titrate metformin up to 500 mg three times/day. If the fasting plasma glucose remains above 140 mg/dL consistently, the dose of metformin can be further increased gradually to a maximum of 850 mg three times/day (or 1000 mg two times/day). If glycemic control is adequate (fasting plasma glucose remains below 140 mg/dL on 2 consecutive days), one can attempt to reduce the dose of insulin by 25% and closely monitor blood glucose values for decompensation. If decompensation occurs or if glycemic control is not adequate with the maximal dose of metformin and lower doses of insulin, there is the option of adding a once-daily sulfonylurea (glipizide extended release or glimepiride), titrating the dose as required.

Insulin Plus Glitazones

The glitazones are potent insulin sensitizers[40] and thus are well suited for use in insulin-resistant patients with type 2 **diabetes**. In several studies, troglitazone was documented to improve glycemic control and to reduce exogenous insulin requirements in obese patients with type 2 **diabetes**.[53] [65] Moreover, as discussed previously, troglitazone probably has greater peripheral insulin-sensitizing and insulin-sparing effects than metformin. Troglitazone was withdrawn from the United States, however, because of an increased risk of severe idiosyncratic liver damage. Of the two glitazones available for clinical use in the United States, rosiglitazone and pioglitazone, only pioglitazone is

currently approved by the Food and Drug Administration (FDA) for use in combination with insulin. Both agents, however, have been shown to improve glycemia in combination with insulin (Fig. 14) . In one 16-week study, Rubin and co-workers[54] demonstrated that the addition of pioglitazone, 15 mg/day and 30 mg/day, to patients receiving a median dose of 60.5 units of insulin resulted in mean FPG reductions of 36 mg/dL and 49 mg/dL and HbA_{1C} reductions of 0.7% and 1.0%, respectively, compared with placebo.[52] The insulin-sparing properties of rosiglitazone were shown in a 6-month study conducted by Raskin et al.[45] They demonstrated that the addition of rosiglitazone (Glaxo, SmithKline, Philadelphia, PA), 2 mg two times/day and 4 mg two times/day, improved glycemic control by 0.6% and 1.2% respectively, as compared with placebo in 312 patients with type 2 **diabetes** uncontrolled on approximately 70 U of insulin/day (baseline HbA_{1C} : 9%). Moreover, insulin requirements were also reduced by approximately 5 and 10 U in the two rosiglitazone treatment groups, in keeping with the insulin-sensitizing effects of the glitazones.[45]

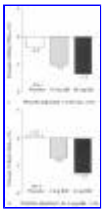

Figure 14. The glycemic effects obtained with the addition of pioglitazone *(A)* and rosiglitazone *(B)* to insulin treatment, when compared with placebo. Data from Rubin C, Egan J, Schneider R: Combination therapy with pioglitazone and insulin in patients with type 2 **diabetes**. **Diabetes** 48 (suppl 1):A110, abstract 474, 1999; and Raskin P, Dole TF, Rappaport EB: Rosiglitazone improves glucose control in poorly controlled, insulin treated patients with type 2 **diabetes mellitus**. **Diabetes** 48(suppl 1):A94, abstract 404, 1999.

When initiating glitazone treatment in type 2 diabetic patients who have suboptimal glucose control using insulin alone, the current insulin dose should be continued, and the lowest dose of the glitazone should be added once daily with a meal. If fasting plasma glucose levels are consistently above 140 mg/dL, the dose of the glitazone should be increased after 2 to 4 weeks, up to the maximal daily dose, until fasting plasma glucose levels are consistently within the target range. When blood glucose is under control, the total daily dose of insulin may be lowered by 10% to 25%.

Insulin Plus Acarbose

The addition of acarbose to insulin therapy may be an option in patients who have pronounced postprandial hyperglycemia. The first long-term, controlled study to demonstrate a beneficial effect of acarbose in patients receiving insulin therapy was reported by Chiasson et al.[13] Of the patients in this study, 91 were receiving insulin and had HbA_{1C} values of 7% or higher. Postprandial plasma glucose levels at 90 minutes were significantly reduced, to 282 mg/dL, with the addition of acarbose, as compared with 331 mg/dL seen with insulin alone. Glycosylated hemoglobin values decreased by 0.4% in the acarbose group, but as expected, no significant decreases in fasting plasma glucose levels were seen. Acarbose treatment may be initiated in patients receiving insulin treatment by starting with a low dose of 25 mg with breakfast and titrating up by 25 mg/week to 50 to 100 mg three times/day with meals (a dose of 100 mg three times/day for patients weighing less than 60 kg), depending on gastrointestinal tolerance and efficacy.

Thus, it is apparent from a review of the available literature that there is no one perfect insulin/combination or multiple-injection insulin regimen that can be used in all patients with type 2 **diabetes**. In a subgroup of patients who do not respond to maximal doses of sulfonylureas, the addition of an evening dose of insulin can be beneficial, cost-effective, and easy to administer and can reduce the need for large doses of exogenous insulin. Once a patient demonstrates unresponsiveness to combination insulin/sulfonylurea therapy, a more conventional insulin regimen should be used. A split-mixed regimen of intermediate- and regular-acting insulin given before breakfast and before dinner is usually preferred. Insulin adjustments are based on HGM, and particular attention should be directed to minimizing the weight gain seen with intensive insulin therapy. Obese patients who fail to respond to combinaregimen that can be used in all patients with type 2 **diabetes**. In a to weight gain, which may make therapeutic success more difficult. The use of metformin in these patients seems to be beneficial and prevents or attenuates the weight gain that is

characteristically associated with insulin therapy. The addition of glitazones is also associated with insulin-sparing effects. It must be understood that normalizing HbA_{1C} levels with a particular regimen depends on numerous variables, including the severity of insulin resistance, the extent and type of obesity, prior failure with oral hypoglycemic agents, endogenous insulin secretory capacity, preceding degree of glucose control, and other complicating medical conditions. Furthermore, the success of a particular insulin regimen is influenced by the severity of glucose toxicity. Prolonged hyperglycemia reduces beta-cell secretory ability and worsens peripheral insulin resistance.[51] Thus, the metabolic success of these different insulin regimens can be highly variable.

Most studies of intensive insulin therapy have been carried out in academic settings, using strict research protocols with specialty teams devoted to patient care. In such settings, one can expect decreases in HbA_{1C} values of about 2% or more. These results may not be replicated in a private-practice setting. Most primary care physicians have neither specialized training in insulin use and management of its complications nor the opportunity to follow up patients at frequent intervals to ensure appropriate adjustment of the insulin dose.[30]

NOVEL METHODS OF INSULIN DELIVERY

External Insulin Pump Therapy

External insulin pump therapy or CSII has been traditionally used mainly in people with type 1 **diabetes**. Insulin pump therapy is extremely valuable, however, in patients with insulin-requiring type 2 **diabetes** who have not achieved glycemic control with subcutaneous injections or who desire a more flexible lifestyle. All the benefits of CSII that are enjoyed by patients with type 1 **diabetes** also apply to people with type 2 **diabetes**. Many experts believe that because of the more physiologic delivery of insulin, glucose control is achieved with less insulin than needed with a subcutaneous-injection insulin regimen. This control may result from a reduction in glucose toxicity and improvement of insulin resistance and beta-cell secretory function because of improved glycemic control with pump therapy. Weight gain is less of an issue because the patient is generally using less insulin than before insulin pump therapy. In addition, with the reduction of hypoglycemic events there is less overeating to compensate for excessive insulin. Lastly, it is possible that pump therapy may result in less strain placed on the pancreatic beta cells of patients with type 2 **diabetes**, and this reduced strain may help with overall glycemic control, because a functioning beta cell can also autoregulate against hyper- and hypoglycemia, as occurs in nondiabetic individuals.

Many older patients with the diagnosis of insulin-requiring type 2 **diabetes** may have true late-onset type 1 **diabetes**. In some studies, tests for antiglutamic acid decarboxylase (GAD) antibodies in patients with insulin-requiring type 2 **diabetes mellitus** revealed a 5% to 8% positivity rate.[59] These individuals are thinner at the time of diagnosis. They generally do not respond well to oral agents and require insulin, although they do not present in severe diabetic ketoacidosis. In general, if a patient with insulin-requiring type 2 **diabetes** cannot achieve glycemic control with an intensive insulin-injection regimen, insulin pump therapy should be considered.

Insulin pump therapy allows increased flexibility in meal timing and amounts, increased flexibility in the time and intensity of exercise, improved glucose control while traveling across time zones or with variable working schedules, and better quality of life in terms of self-reliance and control. For individuals who are hypoglycemically unaware, there is less danger of unconsciousness.

Because pumps use only regular insulin, there is no peaking of injected intermediate- and long-

acting insulins, which cannot provide a constant basal rate because of variable absorption and pharmacokinetics. Variable insulin absorption and pharmacokinetics are probably responsible for up to 50% to 60% of the day-to-day fluctuation in blood glucose values in individuals using multiple-injection regimens with various insulin types. Insulin pump therapy allows a more regular insulin absorption and pharmacokinetic profile, resulting in improved reproducibility in insulin availability and reduced fluctuations in glycemic control.

At present, there is a paucity of clinical trials using CSII in type 2 **diabetes**. Continuous subcutaneous insulin infusion is, however, a viable option in insulin-requiring patients with type 2 **diabetes** who are unable to achieve adequate glycemic control with multiple-injection insulin regimens. Although some studies demonstrate metabolic benefits of pump therapy in type 2 **diabetes**, all are limited by a relatively short period of evaluation and a small number of heterogeneous participants. Interpretation of these studies is further confounded by the random assignment of patients to dissimilar conventional insulin regimens, making comparisons among studies difficult.

Garvey et al[24] studied the effect of intensive insulin therapy on insulin secretion and insulin action before and after 3 weeks of CSII therapy in 14 patients with type 2 **diabetes** (age: 50 ± 3 years, duration of **diabetes**: 7.8 ± 2.1 years, and body weight: 119% of ideal). In 3 weeks of therapy, the mean fasting plasma blood glucose and HbA_{1C} values fell 46% and 38%, respectively. The mean daily insulin dose stabilized at approximately 110 U/day, and there was a 74% increase in the insulin-stimulated glucose disposal rate and a 45% reduction in hepatic glucose output to mean levels similar to those of nondiabetic persons. In addition, there were significant improvements in both endogenous insulin and C-peptide secretion. This study demonstrated that pump therapy is feasible and effective in improving metabolic control and reversing glucose toxicity in these persons with poorly controlled type 2 **diabetes**.

Jennings et al[36] randomly assigned 20 type 2 diabetics (median age: 61 years, duration of **diabetes**: 6 years, and percentage of ideal body weight: 120%) to either CSII or injections of regular and NPH insulin two times/day for 4 months. Glycemic control improved in both groups, although there was a 30% reduction in the HbA_{1C} level in the CSII-treated group and only a 17% reduction in the group treated with twice-daily injections. There were no significant differences between the two groups in median daily insulin requirement (0.58 versus 0.65 U/kg), weight gained (4.5 versus 4.2 kg), prevalence of mild hypoglycemic reactions, or patient acceptance. In addition, in the CSII group, 58% of the total daily insulin requirement was given as a basal infusion, with the remainder as premeal bolus injections using insulin algorithms. This ratio of basal-to-bolus insulin requirements is similar to the ratio commonly used in type 1 **diabetes**; however, there are characteristics of pump therapy that are different in type 2 **diabetes**.

Characteristics of Pump Therapy in Type 2 versus Type 1 Diabetes

1. Type 2 diabetics usually need a higher basal rate.
2. Premeal boluses are greater in type 2 **diabetes**.
3. The time between refills is shorter in type 2 **diabetes**.
4. Battery life may be shorter in type 2 **diabetes**.
5. Pump therapy may improve endogenous insulin secretion and resistance in type 2 **diabetes**.
6. Patient acceptance and satisfaction are similar in type 2 **diabetes**.

In summary, CSII pump therapy has not been fully evaluated in patients with type 2 **diabetes**. From the limited number of studies available, it is apparent that CSII therapy can safely improve glycemic control and beta-cell function in a relatively short period. Continuous subcutaneous insulin infusion may be particularly useful in treating patients with type 2 **diabetes** who do not respond satisfactorily to more conventional insulin treatment strategies.

Intraperitoneal Insulin Delivery System

Implantable, programmable, variable-rate pumps with intraperitoneal insulin delivery are currently being evaluated in patients with type 1 and type 2 **diabetes** (Figs. 15 (Figure Not Available) , 16) (Figure Not Available) . Studies in type 1 diabetics indicate that excellent glucose control can be safely achieved. The degree of control is equal to that seen with CSII therapy but with fewer glycemic excursions and subsequently fewer hypoglycemic reactions.[43] The implantable insulin pump is surgically placed below the subcutaneous fat just above the rectus sheath in the abdominal area. The catheter is placed through the rectus sheath and floats freely in the peritoneal cavity. The major advantage of implantable over subcutaneous infusion pumps is the more physiologic absorption of delivered insulin. Most of the insulin delivered into the peritoneal cavity drains to the liver through the portal vein, where hepatic extraction, similar to the normal situation, occurs before the insulin is delivered to the systemic circulation. This more physiologic form of insulin delivery has distinct advantages. First, intraperitoneal insulin is more rapidly and predictably absorbed than subcutaneous insulin, with direct effects on the liver.[34] Second, because of the effect of hepatic extraction, peritoneal administration may result in lower peripheral insulin concentration than an equivalent subcutaneous dose of insulin.[34]

Figure 15. (Figure Not Available) Implantable programmable insulin pump. The pump is placed under the subcutaneous fat above the rectus sheath, as demonstrated in Figure 16 (Figure Not Available) . The distal half of the catheter is placed freely in the peritoneal cavity. The central inverted cone area is for insulin refills performed through the skin. The inverted cone area at the catheter exit site is for a flush procedure to prevent or correct catheter blockage. The three rubber wings (both sides and bottom) are for anchoring the pump to the rectus sheath to prevent pump migration *(Courtesy of MiniMed Company, Sylmar, CA).*

Figure 16. (Figure Not Available) Implantable programmable insulin pump is inserted into a patient with type 2 **diabetes**. The pump is placed under the subcutaneous fat just above the rectus sheath and is sutured down by way of the rubber wings to prevent pump migration. See text for more details *(Courtesy of MiniMed Company, Sylmar, CA).*

The Department of Veterans Affairs Cooperative Studies Center performed a 1-year randomized feasibility trial (344A) in 113 patients with type 2 **diabetes** who had previously not responded to other insulin regimen.[54] This study compared the effects of intensive metabolic control achieved using the implantable, programmable pump providing intraperitoneal insulin delivery with that achieved using multiple daily subcutaneous insulin injections. The results demonstrate comparable improvement in glycemic control and HbA_{1C} to nearly normal values in both groups. The group using the implantable insulin pump, however, demonstrated greater improvement in daily blood glucose excursions and a reduced incidence of definite and suspected mild and severe hypoglycemic reactions than the group treated with multiple daily injections. Furthermore, the patients randomly assigned to treatment with intraperitoneal insulin did not gain weight despite the improvement in glucose control, in stark contrast with the patients treated with subcutaneous insulin (Fig. 17) (Figure Not Available) .

Figure 17. (Figure Not Available) Change in body weight by month during the VA Cooperative Implantable Insulin Pump Study. The multiple daily insulin injection group *(dashed line)* and the implantable insulin pump group *(solid line)* are shown. The difference between treatment groups is significant ($P = 0.003$). *(From Saudek CD, Duckworth WC, Giobbie-Hurder A, et al: Implantable insulin pump vs multiple-dose insulin for non-insulin-dependent **diabetes mellitus**: A randomized clinical trial. Department of Veterans Affairs Implantable Insulin Pump Study Group. JAMA 276:1322-1327, 1996; with permission.)*

Disetronic (Zurich, Switzerland) has developed a catheter (Disport) that is introduced externally through the subcutaneous fat and rectus sheath to float freely in the intraperitoneum and is connected proximally to an external insulin pump, thus obviating surgery for an implantable device while

providing the benefits of intraperitoneal insulin delivery. The main concern with this type of catheter is peritonitis, which seems to be a rare problem in the ongoing European trials in type 1 diabetics.

The superior pharmacokinetics of intraperitoneal insulin was clearly demonstrated by Kelly et al.[34]

Figure 18 (Figure Not Available) shows the insulin appearance rates in patients who received a bolus of insulin (0.5 U/kg of body weight) by either the intraperitoneal or subcutaneous route on different days. Intraperitoneal insulin administration resulted in a dramatic rise (seven times above baseline) and a rapid clearance within 2 to 3 hours. In contrast, subcutaneous insulin only rose to two times above baseline and remained elevated for the duration of the 5-hour study. The glucose disposal rate was also significantly higher in the group receiving insulin intraperitoneally (Fig. 19) (Figure Not Available) . Intraperitoneal insulin delivery may prove to have several major physiologic advantages over subcutaneous insulin delivery systems, with important implications for the future treatment of type 2 **diabetes**.

Figure 18. (Figure Not Available) Insulin appearance curves when insulin is delivered intraperitoneally *(open circles)* and subcutaneously *(solid circles)* in insulin-requiring subjects with type 2 **diabetes**. Note that the rise in insulin when given intraperitoneally is seven times above baseline, whereas it rises only two times above baseline and remains elevated for the duration of the 5-hour study in the subcutaneous group. *Significant differences between the intraperitoneal and subcutaneous injection group. *(From Kelley DE, Henry RR, Edelman SV: Acute effects of intraperitoneal versus subcutaneous insulin delivery on glucose homeostasis in patients with NIDDM. Veterans Affairs Implantable Insulin Pump Study Group. **Diabetes** Care 19:1237-1242, 1996; with permission.)*

Figure 19. (Figure Not Available) Glucose disposal rate during 5 hours following intraperitoneally *(open circles)* and subcutaneously *(solid circles)* administered insulin in subjects with type 2 **diabetes**. *Significant differences between the intraperitoneal and subcutaneous injection group. *(From Kelley DE, Henry RR, Edelman SV: Acute effects of intraperitoneal versus subcutaneous insulin delivery on glucose homeostasis in patients with NIDDM. Veterans Affairs Implantable Insulin Pump Study Group. **Diabetes** Care 19:1237-1242, 1996; with permission.)*

Inhaled Insulin

Inhaled insulin is currently under development by several pharmaceutical companies (Pfizer, Lilly, Novo Nordisk, and others) for use in people with type 1 and type 2 **diabetes**. The insulin is contained in a pellet which is vaporized in an inhaler, aerosolizing the liquid insulin. Inhaled insulin can also be delivered as a dry powder inhaled through a mouthpiece to be delivered to the pulmonary microvasculature. Inhaled insulin provides the obvious advantage that diabetic patients can use insulin without the need for injections.

Recently, Cefalu et al[12] conducted a randomized, open-label, 3-month study in 26 patients (16 men, 10 women, average age: 51.1 years) with type 2 **diabetes** (average duration of **diabetes**: 11.2 years). Patients received inhaled insulin before each meal plus a bedtime injection of Ultralente insulin, performed HGM, and had a weekly adjustment of insulin dose. The target level for preprandial plasma glucose was 100 to 160 mg/dL. At the end of 3 months, inhaled insulin treatment significantly improved glycemic control compared with baseline, and mean HbA_{1C} levels decreased by 0.07%. Hypoglycemic events were mild, and patients showed no significant weight gain or change in pulmonary function compared with baseline. Thus, in this study, pulmonary delivery of insulin in type 2 diabetic patients who require insulin improved glycemic control, was well tolerated, and demonstrated no adverse pulmonary effects in the short term. Larger-scale and long-term studies are needed to provide long-term efficacy and safety data.[41]

Insulin can also be taken orally through capsules enterocoated with a soybean trypsin inhibitor that prevents insulin degradation. This approach has clinical potential, but large clinical trials have not been conducted. Chemically modified human insulin (Hexyl insulin), using proprietary conjugation technology to improve its stability and oral absorption, has shown promise. Preliminary results reported that in healthy human volunteers, Hexyl insulin caused dose-dependent hypoglycemia, was safe, and was well tolerated.

INSULIN ANALOGUES

DNA technology has allowed the development of several insulin analogues that seem to have favorable pharmacokinetic properties compared with currently available fast-acting insulin preparations. Amino acids can be added to or substituted for human insulin, resulting in monomeric or dimeric analogues. These analogues, when given subcutaneously and immediately before a meal, have more rapid and predictable onset of action and disappearance rates. These characteristics may markedly reduce the development of postprandial hyperglycemia, prolonged hyperinsulinemia, and delayed hypoglycemia. In addition, regional differences in the rate of subcutaneous insulin absorption from various injection sites may be minimized, and the development of insulin antibodies is markedly reduced. With these analogues, the inconvenience of timing injections of currently available insulin preparations to at least 30 minutes before eating may no longer be necessary.

Insulin Lispro

Anderson et al examined the clinical effects of regular versus fast-acting insulin analogue (Lispro) before meals in type 2 **diabetes**.[6] Compared with regular insulin, Lispro reduced the 1- and 2-hour postprandial glucose values by 30% and 53%, respectively ($P < 0.001$) (Fig. 20) (Figure Not Available) . In addition, during Lispro therapy the rate of overall and overnight hypoglycemia was lower and the number of asymptomatic hypoglycemic episodes was smaller than seen with the regular insulin treatment group. Humalog Mix 75/25 (Eli Lilly Co., Indianapolis, IN) is a mixture of neutral insulin Lispro protamine suspension (an intermediate-acting insulin similar to NPH) and Lispro. Humalog Mix 75/25 has been shown to improve the postmeal glucose values in type 2 **diabetes**, especially after breakfast and dinner.[38]

Figure 20. (Figure Not Available) Rises in the postprandial glucose levels after a test meal at study endpoint in the group treated with the human regular insulin *(solid circles)* versus human Lispro *(open circles)*. $P < 0.001$ at both time points. * = $p < 0.001$. *(From Anderson JH, Jr, Brunelle RL, Keohane P, et al: Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non-insulin-dependent **diabetes mellitus**. Multicenter Insulin Lispro Study Group. Arch Intern Med 157:1249-1255, 1997; with permission.)*

Insulin Glargine

Insulin glargine (Lantus, Aventis), also known as HOE-901, seems to be the first true peakless, long-acting, basal insulin analogue (Fig. 21) . By switching one amino acid on the insulin A chain, two amino acids on the B chain, and existing in an acidic environment, glargine seems to last for a full 24 hours without a peak.[31] In studies in patients with type 1 **diabetes**, lower FPG levels with fewer episodes of hypoglycemia were achieved with insulin glargine compared with NPH insulin injected one or two times/day as part of a basal-bolus regimen.[46] Recently, Yki-Jarvinen et al published the results of their study testing the peakless and longer duration of action of insulin glargine as compared with NPH insulin in 426 previously insulin-naive patients. These patients were randomly assigned for 1 year to treatment with bedtime insulin glargine or bedtime NPH while therapy with oral agents was continued. At the end of the study, despite the use of similar insulin doses and similar glycemic control in both groups, the use of insulin glargine was associated with significantly less nocturnal hypoglycemia as compared with NPH.[66]

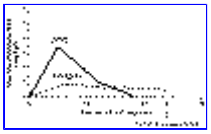

Figure 21. Insulin glargine *(dotted line)* has a smooth peakless profile of action that is required from a basal insulin *(solid line)* injected once daily. Glucose infusion rate required to maintain plasma glucose at 130 mg/dL after an injection of 0.3 U/kg of either NPH or glargine insulin in 20 patients with type 1 **diabetes** in a crossover design, glucose clamp study. The study was discontinued when plasma glucose rose above 200 mg/dL. (*Data from* Lepore M, Kurzhals R, Pampanelli S, et al: Pharmacokinetics dynamics of subcutaneous injection of long-acting human insulin glargine in type 1 **diabetes mellitus**. **Diabetes** 48(suppl):A97, 1999.)

Insulin glargine seems to be a promising alternative for diabetics who require or can benefit from a steady basal level of insulin. Because of its acidic pH, however, insulin glargine cannot be mixed within the insulin bottle or the injection syringe with other forms of insulin.

NOVEL INJECTABLE PEPTIDES THAT COMPLEMENT THE ACTION OF INSULIN

Amylin Analogue

Amylin is a pancreatic beta-cell hormone that is co-packaged and co-secreted with insulin. Pramlintide (Amylin Pharmaceuticals, San Diego, CA) is an analogue of human amylin that has been shown to work by several different mechanisms, including delaying the absorption of carbohydrates along the physiologic section of the gastrointestinal tract and suppressing postprandial glucagon levels. Clinical trials in both type 1 and type 2 **diabetes** have demonstrated significant improvement in glycemic control while inducing weight loss, making this injectable peptide potentially very advantageous.[53] [58]

Pramlintide is currently not available but is fairly advanced in the regulatory process.

Glucagon-like Peptide Analogues

Exendin-4 (Amylin Pharmaceuticals, San Diego, CA) is a peptide first isolated from the oral secretions of the gila monster. Exendin-4 shares many properties of glucagon-like peptide 1 (GLP-1), especially in response to a meal. It has a much longer duration of action than GLP-1 and has many physiologic effects that improve the insulin-resistant state. Synthetic Exendin-4 has been studied in humans and has been shown to lower postprandial glucose and triglyceride values significantly, to suppress glucagon, and to slow gastric emptying. Exendin-4 may also suppress the appetite and lead to weight loss. In a recent report, Exendin-4, a long-acting GLP-1 agonist, was shown to stimulate both the differentiation of beta-cells from ductal progenitor cells (neogenesis) and the proliferation of beta-cells when administered to rats.[65] Glucagon-like peptide 1 analogues have also been shown to improve beta-cell function dramatically. Thus, GLP-1 analogues hold promise as a novel therapy and have the potential to make a major impact on the management of type 2 **diabetes** and the insulin-resistant syndrome.

SUMMARY

Type 2 **diabetes** is a common disorder often accompanied by numerous metabolic abnormalities leading to a high risk of cardiovascular morbidity and mortality. Results from the UKPDS have confirmed that intensive glucose control delays the onset and retards the progression of microvascular disease and possibly of macrovascular disease in patients with type 2 **diabetes**. In the early stages of the disease, insulin resistance plays a major role in the development of hyperglycemia and other metabolic abnormalities, and patients with type 2 **diabetes** often benefit from measures to improve insulin sensitivity such as weight loss, dietary changes, and exercise. Later, the use of oral insulin secretagogues and insulin sensitizers as monotherapy and in combination helps maintain glycemia for varying periods of time. Ultimately, because of the progressive nature of the disease and the progressive decline in pancreatic beta-cell function, insulin therapy is almost always obligatory to achieve optimal glycemic goals. Not all patients are candidates for aggressive insulin management; therefore, the goals of therapy should be modified, especially in elderly individuals and those with co-morbid conditions. Candidates for intensive management should be motivated, compliant, and educable, without other major medical conditions and physical limitations that would

preclude accurate and reliable HGM and insulin administration.

In selected patients, combination therapy with insulin and oral antidiabetic medications can be an effective method for normalizing glycemia without the need for rigorous multiple-injection regimens. The patients for whom combination therapy is most commonly successful are those who do not achieve adequate glycemic control using daytime oral agents but who still show some evidence of responsiveness to the medications. Bedtime intermediate-acting or predinner premixed intermediate- and rapid-acting insulin is administered and progressively increased until the FPG concentration is normalized. If combination therapy is not successful, a split-mixed regimen of intermediate- and rapid-acting insulin equally divided between the prebreakfast and predinner periods is advised for obese patients, and more intensive regimens are advised for thin patients. Insulin therapy is invariably associated with weight gain and hypoglycemia. The use of metformin or glitazones in combination with insulin has been demonstrated to have insulin-sparing properties. Also, metformin use may ameliorate weight gain.

The use of continuous subcutaneous insulin infusion pumps can be particularly beneficial in treating patients with type 2 **diabetes mellitus** who do not respond satisfactorily to more conventional treatment strategies. Intraperitoneal insulin delivery systems hold considerable promise in type 2 **diabetes** because of their more physiologic delivery of insulin and their ability to inhibit hepatic glucose production selectively, with less peripheral insulinemia than with subcutaneous insulin injections. Newer insulin analogues such as the rapidly acting Lispro insulin and the peakless, long-acting glargine insulin are increasingly being used because of their unique physiologic pharmacokinetics. New developments such as inhaled and buccal insulin preparations will also make it easier for many patients to initiate and maintain a proper insulin regimen. Finally, a new generation of gut peptides such as amylin and GLP-1 will add a new dimension to glycemic control through modification of nutrient delivery and other mechanisms; however, the ultimate goal in the management of type 2 **diabetes** is the primary prevention of the disease. The **Diabetes** Prevention Program (DPP) sponsored by the National Institutes of Health has currently randomly assigned more than 3000 persons with impaired glucose tolerance and at high risk of developing **diabetes** into three treatment arms:[19] metformin arm, an intensive lifestyle-modification arm, and a placebo arm. The study will conclude in 2002 after all participants have been followed for 3 to 6 years.

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