The goal is to design and implement insulin regimens that mimic physiologic insulin secretion. Because individuals with type 1 DM partially or completely lack endogenous insulin production, administration of basal insulin is essential for regulating glycogen breakdown, gluconeogenesis, lipolysis, and ketogenesis. Likewise, insulin replacement for meals should be appropriate for the carbohydrate intake and promote normal glucose utilization and storage.

Intensive Management Intensive diabetes management has the goal of achieving euglycemia or near-normal glycemia. This approach requires multiple resources, including thorough and continuing patient education, comprehensive recording of plasma glucose measurements and nutrition intake by the patient, and a variable insulin regimen that matches glucose intake and insulin dose. Insulin regimens usually include multiple-component insulin regimens, multiple daily injections (MDIs), or insulin infusion devices (each discussed below).

The benefits of intensive diabetes management and improved glycemic control include a reduction in the microvascular complications of DM and a reduction in diabetes-related complications. From a psychological standpoint, the patient experiences greater control over his or her diabetes and often notes an improved sense of well-being, greater flexibility in the timing and content of meals, and the capability to alter insulin dosing with exercise. In addition, intensive diabetes management prior to and during pregnancy reduces the risk of fetal malformations and morbidity. Intensive diabetes management is encouraged in newly diagnosed patients with type 1 DM because it may prolong the period of C-peptide production, which may result in better glycemic control and a reduced risk of serious hypoglycemia. Although intensive management confers impressive benefits, it is also accompanied by significant personal and financial costs and is therefore not appropriate for all individuals.

Insulin Preparations Current insulin preparations are generated by recombinant DNA technology and consist of the amino acid sequence of human insulin or variations thereof. In the United States, most insulin is formulated as U-100 (100 units/mL). Regular insulin formulated as U-500 (500 units/mL) is available and sometimes useful in patients with severe insulin resistance. Human insulin has been formulated with distinctive pharmacokinetics or genetically modified to more closely mimic physiologic insulin secretion. Insulins can be classified as short-acting or long-acting (Table 418-4). For example, one short-acting insulin formulation, insulin lispro, is an insulin analogue in which the 28th and 29th amino acids (lysine and proline) on the insulin B chain have been reversed by recombinant DNA technology. Insulin aspart and insulin glulisine are genetically modified insulin analogues with properties similar to lispro. All three of the insulin analogues have full biologic activity but less tendency for self-aggregation, resulting in more rapid absorption and onset of action and a shorter duration of action. These characteristics are particularly advantageous for allowing entrainment of insulin injection and action to rising plasma glucose levels following meals. The shorter duration of action also appears to be associated with a decreased number of hypoglycemic episodes, primarily because the decay of insulin action corresponds to the decline in plasma glucose after a meal. Thus, insulin aspart, lispro, or glulisine is preferred over regular insulin for prandial coverage. Insulin glargine is a long-acting biosynthetic human insulin that differs from normal insulin in that asparagine is replaced by glycine at amino acid 21, and two arginine residues are added to the C terminus of the B chain. Compared to neutral protamine Hagedorn (NPH) insulin, the onset of insulin glargine action is later, the duration of action is longer (~24 h), and there is a less pronounced peak. A lower incidence of hypoglycemia, especially at night, has been reported with insulin glargine when compared to NPH insulin. The most recent evidence does not support an association between glargine and increased cancer risk. Insulin detemir has a fatty acid side chain that prolongs its action by slowing absorption and catabolism. Twice-daily injections of glargine or detemir are sometimes required to provide 24-h coverage. Regular and NPH insulin have the native insulin amino acid sequence.

Basal insulin requirements are provided by long-acting (NPH insulin, insulin glargine, or insulin detemir) insulin formulations. These

TABLE 418-4 PROPERTIES OF INSULIN PREPARATIONS[a]

Preparation	Time of Action		
	Onset, h	Peak, h	Effective Duration, h
Short-acting			
Aspart	<0.25	0.5–1.5	2–4
Glulisine	<0.25	0.5–1.5	2–4
Lispro	<0.25	0.5–1.5	2–4
Regular	0.5–1.0	2–3	3–6
Long-acting			
Detemir	1–4	—[b]	12-24[c]
Glargine	2–4	—[b]	20-24
NPH	2–4	4–10	10–16
Insulin combinations[d]			
75/25–75% protamine lispro, 25% lispro	<0.25	Dual[e]	10–16
70/30–70% protamine aspart, 30% aspart	<0.25	Dual[e]	15-18
50/50–50% protamine lispro, 50% lispro	<0.25	Dual[e]	10–16
70/30–70% NPH, 30% regular	0.5–1	Dual[e]	10–16

[a]Insulin preparations available in the United States; others are available in the United Kingdom and Europe. [b]Glargine and detemir have minimal peak activity. [c]Duration is dose-dependent (shorter at lower doses). [d]Other insulin combinations are available [e]Dual: two peaks—one at 2–3 h and the second one several hours later.

Source: Adapted from FR Kaufman: *Medical Management of Type 1 Diabetes,* 6th edition. Alexandria, VA: American Diabetes Association, 2012.

are usually prescribed with short-acting insulin in an attempt to mimic physiologic insulin release with meals. Although mixing of NPH and short-acting insulin formulations is common practice, this mixing may alter the insulin absorption profile (especially the short-acting insulins). For example, lispro absorption is delayed by mixing with NPH. The alteration in insulin absorption when the patient mixes different insulin formulations should not prevent mixing insulins. However, the following guidelines should be followed: (1) mix the different insulin formulations in the syringe immediately before injection (inject within 2 min after mixing); (2) do not store insulin as a mixture; (3) follow the same routine in terms of insulin mixing and administration to standardize the physiologic response to injected insulin; and (4) do not mix insulin glargine or detemir with other insulins. The miscibility of some insulins allows for the production of combination insulins that contain 70% NPH and 30% regular (70/30), or equal mixtures of NPH and regular (50/50). By including the insulin analogue mixed with protamine, several combinations have a short-acting and long-acting profile (Table 418-4). Although more convenient for the patient (only two injections/day), combination insulin formulations do not allow independent adjustment of short-acting and long-acting activity. Several insulin formulations are available as insulin "pens," which may be more convenient for some patients. Insulin delivery by inhalation has recently been approved but is not yet available. Other insulins, such as one with a duration of action of several days, are under development but are not currently available in the United States.

Insulin Regimens Representations of the various insulin regimens that may be used in type 1 DM are illustrated in Fig. 418-1. Although the insulin profiles are depicted as "smooth," symmetric curves, there is considerable patient-to-patient variation in the peak and duration. In all regimens, long-acting insulins (NPH, glargine, or detemir) supply basal insulin, whereas regular, insulin aspart, glulisine, or lispro insulin provides prandial insulin. Short-acting insulin analogues should be injected just before (<10 min) or just after a meal; regular insulin is given 30–45 min prior to a meal. Sometimes short-acting insulin analogues are injected just after a meal (gastroparesis, unpredictable food intake).

A shortcoming of current insulin regimens is that injected insulin immediately enters the systemic circulation, whereas endogenous