(Indian), but infrequently in the United States or Europe. Whether this reflects an underlying difference in the disease or physician preference is not clear.

Treatment with insulin becomes necessary as type 2 DM enters the phase of relative insulin deficiency (as seen in long-standing DM) and is signaled by inadequate glycemic control with one or two oral glucose-lowering agents. Insulin alone or in combination should be used in patients who fail to reach the glycemic target. For example, a single dose of long-acting insulin at bedtime is often effective in combination with metformin. In contrast, insulin secretagogues have little utility once insulin therapy is started. Experience using incretin therapies and insulin is limited. As endogenous insulin production falls further, multiple injections of long-acting and short-acting insulin regimens are necessary to control postprandial glucose excursions. These insulin regimens are identical to the long-acting and short-acting combination regimens discussed above for type 1 DM. Because the hyperglycemia of type 2 DM tends to be more "stable," these regimens can be increased in 10% increments every 2–3 days using the fasting blood glucose results. Weight gain and hypoglycemia are the major adverse effects of insulin therapy. The daily insulin dose required can become quite large (1–2 units/kg per day) as endogenous insulin production falls and insulin resistance persists. Individuals who require >1 unit/kg per day of long-acting insulin should be considered for combination therapy with metformin or a thiazolidinedione. The addition of metformin or a thiazolidinedione can reduce insulin requirements in some individuals with type 2 DM, while maintaining or even improving glycemic control. Insulin plus a thiazolidinedione promotes weight gain and is associated with peripheral edema. Addition of a thiazolidinedione to a patient's insulin regimen may necessitate a reduction in the insulin dose to avoid hypoglycemia. Patients requiring large doses of insulin (>200 units/day) can be treated with a more concentrated form of insulin, U-500.

EMERGING THERAPIES

Whole pancreas transplantation (performed concomitantly with a renal transplant) may normalize glucose tolerance and is an important therapeutic option in type 1 DM with end-stage renal disease, although it requires substantial expertise and is associated with the side effects of immunosuppression. Pancreatic islet transplantation has been plagued by limitations in pancreatic islet supply and graft survival and remains an area of clinical investigation. Many individuals with long-standing type 1 DM still produce very small amounts of insulin or have insulin-positive cells within the pancreas. This suggests that beta cells may slowly regenerate but are quickly destroyed by the autoimmune process. Thus, efforts to suppress the autoimmune process and to stimulate beta cell regeneration are being tested both at the time of diagnosis and in years after the diagnosis of type 1 DM. Closed-loop pumps that infuse the appropriate amount of insulin in response to changing glucose levels are potentially feasible now that CGM technology has been developed. Bi-hormonal pumps that deliver both insulin and glucagon are under development. New therapies under development for type 2 DM include activators of glucokinase, inhibitors of 11 β-hydroxysteroid dehydrogenase-1, GPR40 agonists, monoclonal antibodies to reduce inflammation, and salsalate.

Bariatric surgery for obese individuals with type 2 DM has shown considerable promise, sometimes with dramatic resolution of the diabetes or major reductions in the needed dose of glucose-lowering therapies **(Chap. 416)**. Several large, unblinded clinical trials have demonstrated a much greater efficacy of bariatric surgery compared to medical management in the treatment of type 2 DM; the durability of the diabetes reversal or improvement is uncertain. The ADA clinical guidelines state that bariatric surgery should be considered in individuals with DM and a body mass index >35 kg/m^2.

ADVERSE EFFECTS OF THERAPY FOR DIABETES MELLITUS

As with any therapy, the benefits of efforts directed toward glycemic control must be balanced against the risks of treatment (Table 418-5). Side effects of intensive treatment include an increased frequency of serious hypoglycemia, weight gain, increased economic costs, and greater demands on the patient. In the DCCT, quality of life was very similar in the intensive and standard therapy groups. The most serious complication of therapy for DM is hypoglycemia, and its treatment with oral glucose or glucagon injection is discussed in **Chap. 420.** Severe, recurrent hypoglycemia warrants examination of treatment regimen and glycemic goal for the individual patient. Weight gain occurs with most (insulin, insulin secretagogues, thiazolidinediones) but not all (metformin, α-glucosidase inhibitors, GLP-1 receptor agonists, DPP-IV inhibitors) therapies. The weight gain is partially due to the anabolic effects of insulin and the reduction in glucosuria. As a result of recent controversies about the optimal glycemic goal and concerns about safety, the FDA now requires information about the cardiovascular safety profile as part of its evaluation of new treatments for type 2 DM.

ACUTE DISORDERS RELATED TO SEVERE HYPERGLYCEMIA

Individuals with type 1 or type 2 DM and severe hyperglycemia (>16.7 mmol/L [300 mg/dL]) should be assessed for clinical stability, including mentation and hydration. Depending on the patient and the rapidity and duration of the severe hyperglycemia, an individual may require more intense and rapid therapy to lower the blood glucose. However, many patients with poorly controlled diabetes and hyperglycemia have few symptoms. The physician should assess if the patient is stable or if diabetic ketoacidosis or a hyperglycemic hyperosmolar state should be considered. Ketones, an indicator of diabetic ketoacidosis, should be measured in individuals with type 1 DM when the plasma glucose is >16.7 mmol/L (300 mg/dL), during a concurrent illness, or with symptoms such as nausea, vomiting, or abdominal pain. Blood measurement of β-hydroxybutyrate is preferred over urine testing with nitroprusside-based assays that measure only acetoacetate and acetone.

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute, severe disorders directly related to diabetes. DKA was formerly considered a hallmark of type 1 DM, but also occurs in individuals who lack immunologic features of type 1 DM and who can sometimes subsequently be treated with oral glucose-lowering agents (these obese individuals with type 2 DM are often of Hispanic or African-American descent). HHS is primarily seen in individuals with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and acid-base abnormalities. DKA and HHS exist along a continuum of hyperglycemia, with or without ketosis. The metabolic similarities and differences in DKA and HHS are highlighted in **Table 418-6**. Both

TABLE 418-6 LABORATORY VALUES IN DIABETIC KETOACIDOSIS (DKA) AND HYPERGLYCEMIC HYPEROSMOLAR STATE (HHS) (REPRESENTATIVE RANGES AT PRESENTATION)

	DKA	HHS
Glucose,[a] mmol/L (mg/dL)	13.9–33.3 (250–600)	33.3–66.6 (600–1200)
Sodium, meq/L	125–135	135–145
Potassium[a,b]	Normal to ↑	Normal
Magnesium[a]	Normal	Normal
Chloride[a]	Normal	Normal
Phosphate[a,b]	Normal	Normal
Creatinine	Slightly ↑	Moderately ↑
Osmolality (mOsm/mL)	300–320	330–380
Plasma ketones[a]	++++	+/–
Serum bicarbonate,[a] meq/L	<15	Normal to slightly ↓
Arterial pH	6.8–7.3	>7.3
Arterial Pco_2,[a] mmHg	20–30	Normal
Anion gap[a](Na – [Cl + HCO_3])	↑	Normal to slightly ↑

[a]Large changes occur during treatment of DKA. [b]Although plasma levels may be normal or high at presentation, total-body stores are usually depleted.