CHAPTER 17

ACUTE METABOLIC COMPLICATIONS IN DIABETES

Arleta Rewers, MD, PhD

Dr. Arleta Rewers is Associate Professor, Department of Pediatrics at University of Colorado Denver School of Medicine, Aurora, CO.

SUMMARY

Diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar state (HHS), lactic acidosis (LA), and hypoglycemia are acute and potentially life-threatening complications of diabetes. DKA and severe hypoglycemia are more common in type 1 diabetes, while HHS without ketoacidosis is associated more frequently with type 2 diabetes. In the United States, the SEARCH for Diabetes in Youth study reported that 29% of patients age <20 years with type 1 diabetes and 10% with type 2 diabetes presented in DKA at diagnosis. The frequency of DKA among adult patients at diagnosis is unknown. A small group of high-risk patients accounts for most recurring DKA in longstanding type 1 diabetes, but the incidence remains high—approximately 1–12 episodes per 100 patient-years. Deaths in the United States with DKA listed as the underlying cause during 2000–2009 decreased 35%, from an annual rate of 12.9 per 100,000 people with diabetes in 2000 and 2001 to 8.4 per 100,000 people with diabetes in 2009. Estimated rates of hospital admissions for HHS are lower compared to DKA. HHS accounted for <1% of all admissions related to diabetes. HHS remains uncommon, but recognition of the state has increased, partially because of high case fatality, exceeding 20% in some patient groups. In 2001–2010, LA accounted for 1.2% of all hospitalizations in diabetic patients. Also in 2001–2010, hypoglycemia was listed as an underlying cause in nearly 288,000 hospitalizations, which represented 5.4% of total hospitalizations due to diabetes. Severe hypoglycemia, i.e., coma or seizure secondary to diabetes treatment, remains high (up to five episodes per 10 patient-years) and has increased among patients who aim for lower glycosylated hemoglobin (A1c) targets without appropriate initial education and ongoing support. All four acute complications are theoretically preventable; unfortunately, they still account for enormous morbidity, hospitalizations, and mortality among diabetic patients and contribute significantly to the high costs of diabetes care.

DIABETIC KETOACIDOSIS

PATHOGENESIS

Diabetic ketoacidosis (DKA) is a common and life-threatening complication of type 1 diabetes, particularly at the time of diagnosis. DKA is less common at diagnosis and during the course of type 2 diabetes.

DKA is caused by very low levels of effective circulating insulin and a concomitant increase in counterregulatory hormones levels, such as glucagon, catecholamines, cortisol, and growth hormone. This combination leads to catabolic changes in the metabolism of carbohydrates, fat, and protein. Impaired glucose utilization and increased glucose production by the liver and kidneys result in hyperglycemia. Lipolysis leads to increased production of ketones, especially beta-hydroxybutyrate (β-OHB), ketonemia, and metabolic acidosis, which is exaggerated by ongoing fluid and electrolyte losses. At the time of diagnosis, DKA is caused by underlying progressive beta cell failure in previously undiagnosed type 1 diabetes patients. In established patients, insulin omission, inadequate insulin dosing during infection, gastrointestinal illness, trauma and stress, or pump failure can precipitate DKA. In type 2 diabetes patients, DKA occurs during concomitant acute illness or during transition to insulin dependency.

DEFINITION

The American Diabetes Association (1,2), the International Society for Pediatric and Adolescent Diabetes (3), and jointly the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society (4) agreed to define DKA as a triad of:

- hyperglycemia, i.e., plasma glucose >250 mg/dL (>13.88 mmol/L)
- venous pH <7.3 and/or bicarbonate <15 mmol/L
- moderate or large ketone levels in urine or blood

In addition, pediatric experts agree that a lower level of hyperglycemia (>200 mg/dL [>11.10 mmol/L]) also meets criteria for DKA. Combination of near-normal glucose levels and ketoacidosis ("euglycemic ketoacidosis") has been reported in pregnant adolescents, very young or partially treated children (5), and children fasting during a period of insulin deficiency (6).

Administrative data sets use International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10), codes to categorize diabetes and diabetic complications. The ICD-9 code for DKA is 250.1x (250.10–250.13). However, the code 250.3 (diabetes with other coma) is used for DKA coma, as well as for coma caused by severe hypoglycemia. In the ICD-10 categories for diabetes (E10–E14), subdivision E1x.1 denotes DKA, while E1x.0 denotes coma with or without ketoacidosis, hyperosmolar or hypoglycemic (x digit is used to define type of diabetes).

Received in final form March 12, 2016.

The incidence of DKA varies with the definition; therefore, it is important to standardize criteria for comparative epidemiologic studies.

PREVALENCE OF DIABETIC KETOACIDOSIS AT THE DIAGNOSIS OF DIABETES

In the United States, the large, population-based SEARCH for Diabetes in Youth study reported that 29% of patients with type 1 diabetes age <20 years presented in DKA at diagnosis (7). The Pediatric Diabetes Consortium reported slightly higher rates, but these data are not population based (8). These estimates are lower than prevalences reported from hospital series (9,10). Data from SEARCH showed that DKA prevalences are stable over time and high (11). Steady, high prevalences of DKA at diagnosis have been observed also in Australia, Germany, and Austria (12,13,14). In contrast, the prevalence of DKA at diagnosis decreased in Finnish children from 30% in 1982–1991 to 19% in 1992–2002 (15). Studies from some developing countries also show a significant decrease in the prevalences of DKA at diagnosis of type 1 diabetes (16,17,18).

Population-based epidemiologic data concerning the prevalence of DKA at the time of presentation of type 2 diabetes are sparse. In youth with type 2 diabetes, the frequency of DKA at presentation is less common than for youth with type 1 diabetes—about 10%—and has decreased over time from 11.7% in 2002–2003 to 6.3% in 2004–2005 and 5.7% in 2008–2010 (7,11).

DKA is a less common initial presentation of diabetes in adults. In the United States, among adults presenting with DKA at diagnosis, an estimated 20%–50% are initially diagnosed as having type 2 diabetes (19,20). However, the later clinical course suggests higher cumulative incidence of type 2 diabetes among these patients, reaching 39%–60% (21,22). A similar proportion (42%–64%) of ketosis-prone cases among type 2 diabetes patients has been reported among African Americans (23). In older studies conducted between 1945 and 1980, DKA was found less frequently as the initial manifestation of diabetes. DKA was present at diagnosis in 20% of patients in the Rhode Island Hospital Study, which was population based (24). A community-based Rochester, Minnesota, study found that 23% of diabetes patients presented with DKA as the initial manifestation. DKA was more frequent in patients diagnosed before age 30 years, reaching 26%, and was present in only 15% of those diagnosed at or after age 30 years (25).

INCIDENCE OF DIABETIC KETOACIDOSIS IN ESTABLISHED DIABETES

The incidence of DKA in children and adolescents with established type 1 diabetes ranges from 1 to 12 episodes per 100 person-years (26,27,28). The incidence of DKA among children and adolescents increases significantly with age in females, but not in males (26). There are no comparable population-based data for adults. In Rochester, the incidence rate was 8 per 1,000 person-years for DKA at all ages and was higher, reaching 13.4 per 1,000 person-years, among diabetic persons who were diagnosed before age 30 years (25). In the Rhode Island Hospital Study, the incidence of DKA among diabetic patients of all ages was 4.6 per 1,000 person-years (24). The rate was higher in women than men with diabetes.

PREDICTORS AND PRECIPITATING FACTORS OF DIABETIC KETOACIDOSIS

The most important risk factor for presence of DKA at diagnosis is younger age (7,27,29), with children age <2 years having three times higher risk of DKA compared to older children (8,30). Lower socioeconomic status, low family income, lack of private health insurance, and lower parental education are also risk factors for the presence of DKA at diagnosis (7,9,31,32). The frequency of DKA is also higher among ethnic minority groups (7,26). Low societal awareness of diabetes symptoms in areas with low incidence of type 1 diabetes is associated with higher risk of DKA. Family history of diabetes, particularly the presence of a first-degree relative with type 1 diabetes, shows a protective effect. A similar protective effect is observed among children involved in longitudinal etiological studies. In addition, medications (glucocorticoids, atypical antipsychotics, and diazoxide) can contribute to precipitation of DKA in individuals without a previous diabetes diagnosis (33,34).

Most episodes of DKA beyond diagnosis are associated with insulin omission, pump failure, or treatment error (35,36). Parental supervision of insulin treatment in children decreases the frequency of DKA (28). Lack of adequate adjustment of insulin therapy during illness or surgery may also lead to the development of DKA (27,28,37). Socioeconomic status and insufficient access to outpatient diabetes care are often the primary precipitating factors for DKA; however, major psychiatric disorders also play a significant role (26).

Continuous subcutaneous insulin infusion (CSII) is effective and safe in both adults and adolescents with type 1 diabetes (38); however, CSII interruption can quickly lead to DKA (39). The incidence of DKA appears to be unchanged during long-term (4 years) follow-up after introduction of CSII in children and youth (40).

Similar to children, for adults with type 1 diabetes, the main precipitating factors are noncompliance with treatment and infections (41,42). Lack of money to buy insulin is a significant cause of stopping insulin in an adult inner city population (43). DKA may also be associated with drug abuse and cigarette smoking (44). Patients with type 2 diabetes may develop DKA when hospitalized for other medical or surgical conditions (45). The risk of DKA is higher in patients with a history of previous episodes (24,26).

HOSPITAL DISCHARGE DATA

New analyses of data from the U.S. National Hospital Discharge Survey, a study conducted by the National Center for Health Statistics, were performed for *Diabetes in America, 3rd edition*. The proportion of hospitalizations due

to acute complications among diabetic patients between 2001 and 2010 (Table 17.1) decreased compared to the time period 1981–1991 (46), except for an increase in hospitalizations due to acidosis. This finding may reflect an increase in the rates of lactic acidosis (LA) among patients with underlying diabetes and better recognition of this condition. DKA was an underlying cause of more than 43% of hospitalizations among diabetic patients age <18 years, but it decreased dramatically with increasing age, and it was unlikely to present in diabetic patients age ≥65 years. DKA rates were highest among blacks and lowest among Asians (Table 17.2). During 2001–2010, there were 157,700 hospitalizations in which DKA was listed as an underlying cause and 7,900 in which diabetic coma was listed. DKA-related hospitalizations represent 3.0% of all hospitalizations among diabetic patients.

TABLE 17.1. Hospitalizations for Acute Complications of Diabetes, by Age, U.S., 2001–2010

ACUTE COMPLICATIONS (ICD-9-CM), BY AGE (YEARS)	AVERAGE ANNUAL NUMBER OF DISCHARGES (THOUSANDS)	PERCENT (SE) OF TOTAL* DIABETES DISCHARGES
Diabetic ketoacidosis (250.1)		
All	157.7	3.0 (0.05)
<18	22.2	43.2 (1.38)
18–44	81.9	14.5 (0.32)
45–64	37.8	2.1 (0.07)
≥65	15.9	0.6 (0.03)
Diabetic with other coma (250.3)		
All	7.9	0.2 (0.01)
<18	0.3	0.5 (0.31)[2]
18–44	2.1	0.4 (0.06)
45–64	2.3	0.1 (0.02)
≥65	3.2	0.1 (0.01)
Diabetic hyperosmolar coma (250.2)		
All	23.9	0.5 (0.02)
<18	0.2	0.3 (0.13)[1]
18–44	4.6	0.8 (0.08)
45–64	10.3	0.6 (0.04)
≥65	8.8	0.3 (0.02)
Acidosis (276.2)		
All	65.2	1.2 (0.03)
<18	0.8	1.6 (0.34)
18–44	8.3	1.5 (0.10)
45–64	24.2	1.3 (0.06)
≥65	32.0	1.1 (0.05)
Hypoglycemia (250.8, 251.2)		
All	287.6	5.4 (0.07)
<18	1.8	3.6 (0.37)
18–44	28.9	5.1 (0.19)
45–64	100.8	5.5 (0.11)
≥65	156.1	5.5 (0.09)

Diabetes hospitalizations are defined as ICD-9-CM codes 250, 357.2, 362.0, 366.41, 648.0, and 775.10, as any diagnosis listed on the hospital discharge record. Standard errors (SE) were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design. There were only 11 patients with hypoglycemia coma among people with diabetes, and none of the estimates were reliable enough to present (all relative standard errors >50%). ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

* Average annual number of discharges (thousands) with any diabetes diagnosis: 5,180 discharges among all ages, 51 discharges <18 years, 558 discharges 18–44 years, 1,800 discharges 45–64 years, and 2,772 discharges ≥65 years.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

SOURCE: National Hospital Discharge Surveys 2001–2010

MORBIDITY AND MORTALITY

DKA-related mortality among patients with diabetes was estimated for *Diabetes in America* using data from the National Vital Statistics System. Deaths in the United States with DKA listed as the underlying cause during 2000–2009 decreased 35%, from an annual rate of 12.9 per 100,000 people with diabetes in 2000 and 2001 to 8.4 per 100,000 people with diabetes in 2009 (Figure 17.1). Mortality rates due to DKA were 2.5 times higher in those age <18 years compared to those age ≥65 years. Another new analysis showed that the rates during this period varied among youth with diabetes, reaching 42.5 per 100,000 people with diabetes in 2002 and decreasing to 18.6 per 100,000 people with diabetes in 2009 (Figure 17.2). The decrease in mortality rates during this time period was greater among youths age <10 years (78%) than among youths age 10–19 years (52%) (47).

The most common cause of death in youth with type 1 diabetes is cerebral edema in the course of DKA (48,49). The reported incidence of clinically overt cerebral edema varies between 0.3% and 1.0% (50,51,52). However, asymptomatic or subclinical cerebral edema in the course of DKA is present in >50% of pediatric patients (53). Hypokalemia, hyperkalemia, thrombosis (42), other neurological complications (54,55), stroke (56,57), sepsis and other infections, such as rhinocerebral mucormycosis (58,59), aspiration pneumonia, and pulmonary edema (60,61) are less frequent complications of DKA.

COST

Direct medical care charges attributed to DKA episodes are high, reaching 28% of the direct medical care charges for all diabetic patients and 56% for those with recurrent DKA (62). In a study among youth with type 1 diabetes who had DKA, predicted mean annual total medical expenditures were $5,837 higher than

TABLE 17.2. Annual Hospitalizations for Diabetic Ketoacidosis and Diabetic Coma, by Age, Sex, and Race, U.S., 2001–2010

CHARACTERISTICS	DIABETES DISCHARGES (NUMBER IN THOUSANDS)	ALL DISCHARGES* (NUMBER IN THOUSANDS)	DIABETIC KETOACIDOSIS			DIABETIC COMA NEC		
				Percent (SE)			Percent (SE)	
			Number (Thousands)	Among All Diabetes Discharges	Among All Discharges	Number (Thousands)	Among All Diabetes Discharges	Among All Discharges
Total	5,180	38,619	157.7	3.0 (0.05)	0.4 (0.01)	7.9	0.2 (0.01)	0.02 (0.002)
Age (years)								
<18	51	6,787	22.2	43.2 (1.38)	0.3 (0.01)	0.3	0.5 (0.31)[2]	[3]
18–44	558	10,040	81.9	14.5 (0.32)	0.8 (0.02)	2.1	0.4 (0.06)	0.02 (0.003)
45–64	1,800	8,569	37.8	2.1 (0.07)	0.4 (0.01)	2.3	0.1 (0.02)	0.03 (0.004)
≥65	2,772	13,223	15.9	0.6 (0.03)	0.1 (0.01)	3.2	0.1 (0.01)	0.02 (0.003)
Sex								
Male	2,355	15,928	75.6	3.1 (0.07)	0.5 (0.01)	3.6	0.2 (0.02)	0.02 (0.003)
Female	2,825	22,691	82.1	2.8 (0.07)	0.4 (0.01)	4.2	0.2 (0.02)	0.02 (0.002)
Race†								
White	3,047	23,312	83.4	2.7 (0.06)	0.4 (0.01)	4.3	0.1 (0.02)	0.02 (0.002)
Black	820	4,806	35.4	4.2 (0.14)	0.7 (0.02)	1.2	0.1 (0.03)	0.02 (0.004)
AI/AN	29	166	1.0	3.3 (0.85)	0.6 (0.16)	0.1	0.2 (0.14)[2]	0.04 (0.025)[2]
Asian	66	612	1.3	1.9 (0.40)	0.2 (0.05)	0.1	0.1 (0.06)[2]	0.01 (0.007)
Other	135	1,027	4.0	2.9 (0.25)	0.4 (0.03)	0.1	0.1 (0.03)[1]	0.01 (0.004)

Diabetic ketoacidosis and diabetic coma are defined as ICD-9-CM codes 250.1 and 250.3, respectively. Diabetes hospitalizations are defined as ICD-9-CM codes 250, 357.2, 362.0, 366.41, 648.0, and 775.10, as any diagnosis listed on the hospital discharge record. Standard errors (SE) were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design. AI/AN, American Indian/Alaska Native; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NEC, not elsewhere classifiable.

* All discharges include patients with diabetes and those without diabetes.

† Twenty-three percent of participants were missing race data.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Hospital Discharge Surveys 2001–2010

among those without DKA. As DKA is treated primarily in hospital settings, the inpatient expenditures attributed to DKA accounted for >90% of the total excess medical expenditures attributed to DKA (63). Among adults with type 1 diabetes, reported medical expenditures are twice as high ($13,046 [2007 dollars]), most likely due to coexisting comorbidities (62). Tieder *et al.* examined a retrospective cohort of children age 2–18 years with a diagnosis of DKA between 2004 and 2009. The mean hospital-level total standardized cost of DKA treatment was $7,142 (64).

According to National Hospital Ambulatory Medical Care Surveys between 1993 and 2003, DKA accounted for approximately 753,000 visits or an average 68,000 visits per year. The majority of DKA patients (87%) were admitted, with most admissions to a non-intensive care unit setting. The rate of emergency department visits for DKA was 64 per 10,000 U.S. diabetic patients, and the number of visits increased between 1993–1998 (315,000) and 1999–2003 (438,000) (65).

During 2004, there were 120,000 admissions due to DKA, 15,000 due to hyperosmolar hyperglycemic state (HHS), and an additional 5,000 due to "diabetic coma" (66). Based on the Diagnostic Related Group codes in the inpatient records, the total hospital cost for DKA was estimated at $1.4–$1.8 billion. An independent analysis by Kitabchi *et al.* estimated the annual hospital cost of DKA in the United States in excess of $1 billion (67). Approximately 25% of the cost is related to DKA at diabetes diagnosis (68).

PREVENTION

Prevention of DKA should be one of the main goals of diabetes education. Knowledge of the signs and symptoms of diabetes, such as the classic triad of polydipsia, polyuria, and polyphagia with weight loss, is the best strategy for early detection of type 1 diabetes and prevention of DKA at the time of diagnosis. Both public and health professional education should make people aware of those symptoms, as patients admitted with severe DKA are often seen hours or days earlier by health care providers who missed the diagnosis, particularly in the youngest children (69,70). The Diabetes Autoimmunity Study in the Young, an observational study following children at genetically high risk for type 1 diabetes by periodic testing for diabetes autoantibodies, glycosylated hemoglobin (A1c), and random blood glucose, demonstrated that prevention of DKA in newly diagnosed children is possible. The prevalence of DKA at the time of diagnosis among children enrolled in this study was significantly lower compared to the community level (71). Similar findings came from the Diabetes Prevention

Trial (72). A community intervention to raise awareness of the signs and symptoms of childhood diabetes in the Parma region of Italy reduced the prevalence of DKA at diagnosis of type 1 diabetes from 83% to 13% (73). The effect persisted 8 years later, but there was an indication that the campaign should be periodically renewed (74).

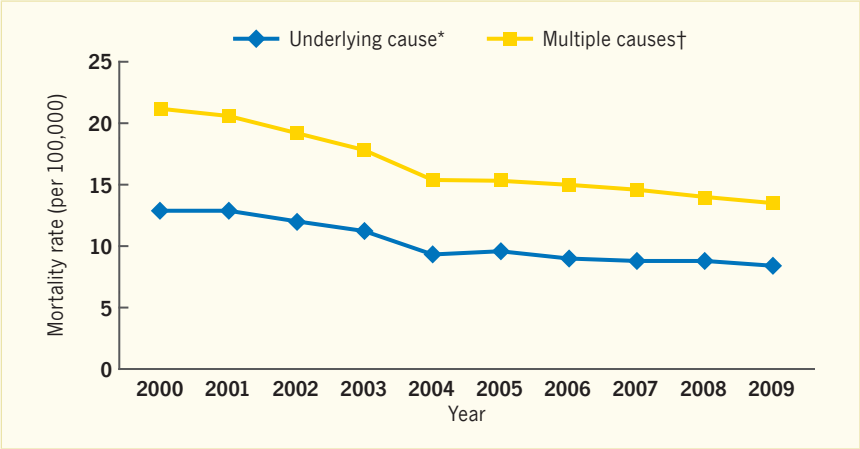
Most studies have shown that most episodes of DKA beyond disease diagnosis are preventable by identification of at-risk patients and use of targeted interventions. Comprehensive diabetes programs and telephone help lines reduced the rates of DKA from 15–60 to 5–6 per 100 patient-years (75,76,77). In the adolescent cohort of the Diabetes Control and Complications Trial (DCCT), intensive diabetes management was associated with less DKA (conventional and intensive treatment groups: 4.7 and 2.8 episodes per 100 patient-years, respectively) (78). In patients treated with insulin pumps, episodes of DKA can be reduced with introduction of treatment algorithms (79). The extent to which home measurement of whole blood or urine β-OHB concentration may assist in the prevention of hospitalization should be further assessed (80).

TREATMENT

The goal of therapy is to correct dehydration by restoring extracellular and intracellular fluid volume and correcting electrolytes imbalances, hyperglycemia, and acidosis. The recommended therapy differs between adults and children given the higher risk of development of cerebral edema in children. The pediatric recommendation for initial volume expansion is slow intravenous infusion of 10–20 mL/kg of normal saline (0.9%) over the first 1–2 hours. Subsequent fluid replacement should be done with 0.45%–0.9% normal saline. To correct ketoacidosis, a "low dose" continuous IV insulin administration is needed as a regular insulin drip at a dose of 0.1 units/kg per hour (1) or even lower doses, such as 0.05 units/kg per hour (81). Pediatric DKA should be treated in a facility with appropriate pediatric expertise.

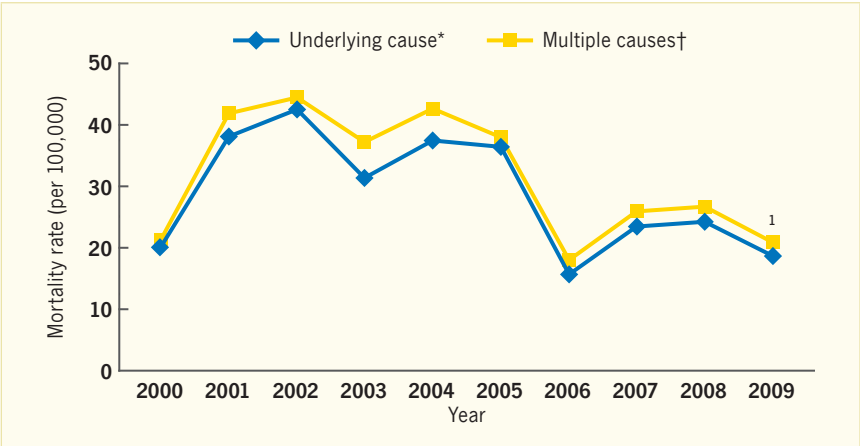
In adults, in the absence of cardiac compromise, isotonic saline is given at a rate of 15–20 mL/kg per hour or 1–1.5 L during the first hour. Subsequent fluid replacement depends on hemodynamic status, serum electrolyte levels, and urinary output. Treatment algorithms recommend the administration of an initial intravenous dose of regular insulin (0.1 units/kg) followed by the infusion of 0.1 units/kg per hour. A prospective randomized study reported that a bolus dose of insulin is not necessary, if patients receive an hourly insulin infusion of 0.14 units/kg body weight (82).

FIGURE 17.1. Trends in Age-Standardized Mortality Rate Coded to Diabetic Ketoacidosis Per 100,000 People With Diabetes, U.S., 2000–2009



Ketoacidosis is defined as International Classification of Diseases, Tenth Revision (ICD-10), codes E10.1, E11.1, E12.1, E13.1, or E14.1. Data are standardized to the National Health Interview Survey 2010 diabetes population using age categories <18, 18–44, 45–64, and ≥65 years.
* The disease or injury that initiated the train of events leading directly to death
† In addition to the underlying cause, death certificates list up to 20 additional "multiple" causes of death.
SOURCE: Number of deaths are derived from the National Vital Statistics System 2000–2009; number of people with diabetes are derived from the National Health Interview Surveys 2000–2009.

FIGURE 17.2. Trends in Age-Standardized Mortality Rate Coded to Diabetic Ketoacidosis Per 100,000 People With Diabetes Age <18 Years, U.S., 2000–2009



Ketoacidosis is defined as International Classification of Diseases, Tenth Revision (ICD-10), codes E10.1, E11.1, E12.1, E13.1, or E14.1.
* The disease or injury that initiated the train of events leading directly to death
† In addition to the underlying cause, death certificates list up to 20 additional "multiple" causes of death.
[1] Relative standard error >30%–40% for the 2009 estimates
SOURCE: Number of deaths are derived from the National Vital Statistics System 2000–2009; number of people with diabetes are derived from the National Health Interview Surveys 2000–2009.

HYPERGLYCEMIC HYPEROSMOLAR STATE

PATHOGENESIS

Decrease in the effective action of circulating insulin coupled with a concomitant elevation of counterregulatory hormones is the underlying mechanism for both HHS and DKA. These alterations lead to increased hepatic and renal glucose production and impaired glucose utilization in peripheral tissues, which result in hyperglycemia and parallel changes in osmolality of the extracellular space (83). HHS is associated with glycosuria, leading to osmotic diuresis, with loss of water, sodium, potassium, and other electrolytes. In HHS, insulin levels are inadequate for glucose utilization by insulin sensitive tissues but sufficient (as determined by residual C-peptide) to prevent lipolysis and ketogenesis (83).

DEFINITION

HHS is defined as extreme elevation in blood glucose >600 mg/dL (>33.30 mmol/L) and serum osmolality >320 mOsm/kg in the absence of significant ketosis and acidosis. Small amounts of ketones may be present in blood and urine (84).

In the ICD-9, the HHS code is 250.2: diabetes with hyperosmolarity or hyperosmolar (nonketotic) coma. The ICD-10 does not have a specific code for HHS; E1x.0 denotes coma with or without ketoacidosis, hyperosmolar or hypoglycemic (x digit is used to define type of diabetes).

INCIDENCE AND PREVALENCE

The incidence of HHS is unknown because of the lack of population-based studies and multiple comorbidities often found in these patients. Estimated rates of hospital admissions for HHS are lower compared to DKA. HHS accounts for <1% of all admissions related to diabetes but may affect up to 4% of new type 2 diabetes patients (83).

The prevalence of isolated HHS in adult patients with acute, significant hyperglycemia varies from 15% to 45% (85,86). HHS occurs at any age, but it is more prevalent in elderly patients who have additional comorbidities. Presence of other conditions, such as infection, cardiovascular disease, and cancer, seems to be responsible for the higher mortality associated with HHS compared to DKA (86).

The incidence of HHS is most likely underestimated in children, as the presenting clinical picture in many patients has elements of both HHS and DKA (87,88).

Several studies of pediatric and adolescent diabetic patients, mostly case series or single-institution reviews, have described more than 50 cases of HHS (7,89,90,91,92). Most patients were adolescents with newly diagnosed type 2 diabetes, and many were of African American descent. A study based on data from the Kid's Inpatient Database provided the first national estimate of hospitalizations due to HHS among U.S. children between 1997 and 2009. The estimated population rate for HHS diagnoses for children age 0–18 years was 2.1 per 1,000,000 children in 1997, rising to 3.2 in 2009. The majority (70.5%) of HHS hospitalizations occurred among children with type 1 diabetes (93).

RISK FACTORS

The majority of HHS episodes are precipitated by an infectious process; other precipitants include cerebrovascular accident, alcohol abuse, pancreatitis, myocardial infarction, trauma, and drugs. In a case series of 119 patients with HHS, nearly 60% of the patients had an infection, and 42% had a stroke (94). Medications affecting carbohydrate metabolism, such as corticosteroids, thiazides, and sympathomimetic agents (e.g., dobutamine and terbutaline), may also precipitate the development of HHS. Elderly individuals, particularly those with new-onset diabetes are at risk for HHS. A comparison of 135 patients with hyperosmolar syndrome with 135 age-matched, randomly selected diabetic controls hospitalized in the same time period found female sex (71% in HHS cases vs. 53% in diabetic controls), newly diagnosed diabetes (36% per 100 HHS hospitalizations vs. 7% in diabetic controls), and presence of acute infection (39% per 100 HHS hospitalizations vs. 19% in diabetic controls) to be independently associated with the presence of HHS (95). Among 200 HHS patients in Rhode Island, nursing home residents accounted for 18% of the cases (85).

MORBIDITY AND MORTALITY

Hospitalization data from the National Hospital Discharge Surveys 2001–2010 were analyzed for *Diabetes in America*, confirming that HHS occurs rarely (Tables 17.1 and 17.3). The 18–44 years age group had the highest percentage of hospitalizations listing HHS. The average annual number of hospital discharges listing HHS as a cause doubled to 23,900 during 2001–2010 compared to 10,800 in 1989–1991.

In adults, mortality rates attributed to HHS range from 5% to 25% (82,85,86, 94,96). The mortality increases sharply with age from none in patients age <35 years to 1.2% in those age 35–55 years and 15.0% in patients age >55 years. A U.S. study of 613 adult patients hospitalized for hyperglycemic crises reported similar findings (85). Fatality rates for DKA, mixed DKA-HHS, and isolated HHS alone were, respectively, 4%, 9%, and 12%. In both studies, older age and the degree of hyperosmolarity were the most powerful predictors of a fatal outcome. Deaths due to hyperglycemic crisis in adults with diabetes dropped from 2,989 in 1985 to 2,459 in 2002, according to data from the National Vital Statistics System. During the time period, age-adjusted death rates decreased from 42 to 24 per 100,000 adults with diabetes (97); the decrease was found in all age groups (Figure 17.3) (97). During the period between 1997 and 2009, the mortality rate among children was reported at 2.7 per 100 HHS hospitalizations compared to previously described rates of 33 and 72 per 100 HHS hospitalizations of children dying in the course of HHS (98,99).

COST

Data concerning the cost of HHS are limited, due to the lack of exact incidence data. However, on an individual basis, the cost per event is several times higher than that for uncomplicated DKA (66).

TABLE 17.3. Annual Hospitalizations for Diabetic Hyperosmolar Nonketotic Coma, by Age, Sex, and Race, U.S., 2001–2010

CHARACTERISTICS	DIABETIC HYPEROSMOLAR NONKETOTIC COMA (NUMBER IN THOUSANDS)	PERCENT (STANDARD ERROR)	
		Among Diabetes Discharges	Among All Discharges*
Total	23.9	0.5 (0.02)	0.06 (0.003)
Age (years)			
<18	0.2	0.3 (0.13)[1]	[3]
18–44	4.6	0.8 (0.08)	0.05 (0.004)
45–64	10.3	0.6 (0.04)	0.12 (0.009)
≥65	8.8	0.3 (0.02)	0.07 (0.005)
Sex			
Male	11.7	0.5 (0.03)	0.07 (0.004)
Female	12.2	0.4 (0.03)	0.05 (0.003)
Race†			
White	10.6	0.3 (0.02)	0.05 (0.003)
Black	8.1	1.0 (0.08)	0.17 (0.013)
AI/AN	<0.1	0.1 (0.10)[2]	0.03 (0.018)[2]
Asian	0.3	0.4 (0.17)[2]	0.04 (0.019)
Other	0.9	0.6 (0.15)	0.08 (0.021)

Hyperosmotic nonketotic coma is defined as ICD-9 code 250.2. Diabetes hospitalizations are defined as ICD-9-CM codes 250, 357.2, 362.0, 366.41, 648.0, and 775.10, as any diagnosis listed on the hospital discharge record. Standard errors were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design. AI/AN, American Indian/Alaska Native; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

* All discharges include patients with diabetes and those without diabetes.

† Twenty-three percent of participants were missing race data.

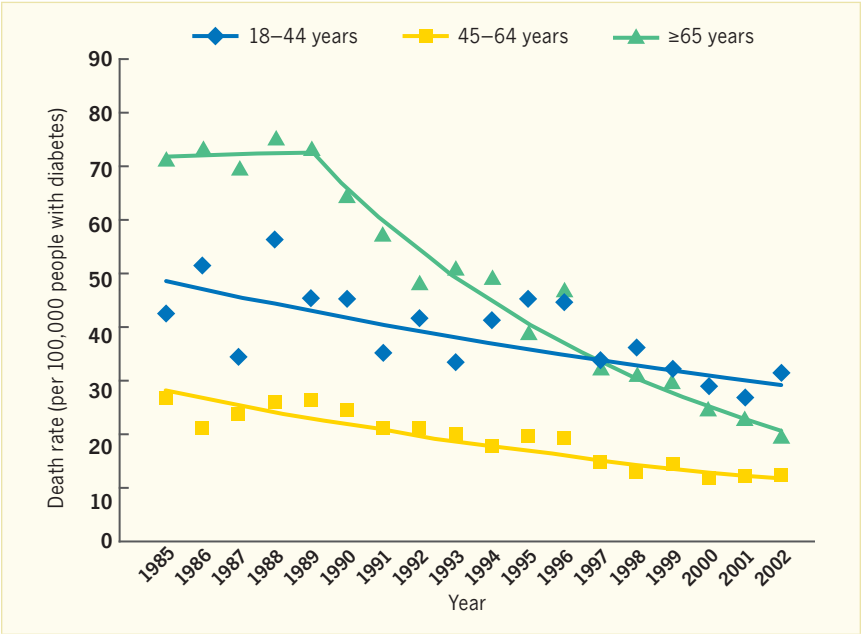
[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

[3] Estimate is too unreliable to present; ≤1 case or relative standard error >50%.

SOURCE: National Hospital Discharge Surveys 2001–2010

FIGURE 17.3. Age-Specific Death Rates for Hyperglycemic Crisis Among Persons With Diabetes Age ≥18 Years, by Age, U.S., 1985–2002



Data are based on the National Vital Statistics System 1985–2002. Denominators are based on National Health Interview Surveys 1985–2002 data.

SOURCE: Reference 97, copyright © 2006 American Diabetes Association, reprinted with permission from The American Diabetes Association

PREVENTION AND TREATMENT

Appropriate diabetes education, adequate treatment, and frequent self-monitoring of blood glucose help to prevent HHS in patients with known diabetes. HHS can be precipitated by dehydration and medications, such as corticosteroids, thiazides, and sympathomimetic agents. Careful use of these medications is indicated in vulnerable patients, e.g., elderly cared for in nursing homes at risk of dehydration and unable to promptly communicate their medical problems. Patients with HHS require hospitalization, which can be prolonged due to underlying conditions. In cases not complicated by underlying conditions, treatment modalities are similar to DKA (82,100). Intravenous rehydration and insulin to correct hyperglycemia lead to prompt resolution of HHS.

LACTIC ACIDOSIS

DEFINITION

LA consists of elevation of lactic acid above 5.0 mEq/L with acidosis (pH <7.3) and without ketoacidosis. There may be low levels of ketones present (1:4 on serum dilution or β-OHB >0.4–<0.6 mmol/L). The ICD-9 code 276.2 describes acidosis, primarily LA.

INCIDENCE

Data on incidence rates for LA are sparse. It is a rare, but important, adverse event in patients with diabetes. National Hospital Discharge Survey data on hospitalizations in 2001–2010 with an LA code in patients with and without a concomitant diagnosis of diabetes were analyzed for *Diabetes in America* (Tables 17.1 and 17.4). Whereas the highest absolute number of LA cases occurred in patients age >45 years, in women, in whites, and in patients for whom diabetes was not listed on the hospital discharge summary, the percentage of diabetes discharges with LA was greater in younger people.

The frequency of hospitalizations due to LA increased from 0.6% to 1.2% among patients with diabetes and from 0.3% to 1.0% among those without diabetes in comparison to previous data from 1989–1991 (46).

PRECIPITATING FACTORS

The usual precipitating factors for LA are conditions of impaired oxygenation, such as hypoxemia, shock, sepsis, carbon monoxide poisoning, and some medications, including phenformin and metformin, particularly when used in patients with renal failure. Phenformin, a biguanide, increases the risk of life-threatening LA and is no longer available in the United States. Also, metformin is thought to increase the risk of LA in patients with diabetes and is contraindicated in conditions associated with LA, such as cardiovascular, renal, hepatic, and pulmonary diseases, and advanced age. However, a Cochrane Database review of prospective comparative trials and observational cohort studies showed no difference in the incidence of LA during metformin treatment compared to other antihyperglycemic treatments. In this review, the incidence of metformin-associated LA was 8.4 cases per 100,000 patient-years, and in the non-metformin group, it was 9 cases per 100,000 patient-years (101). In other studies, the reported incidence of metformin-associated LA in type 2 diabetes patients ranged from 10 to 47 cases per 100,000 patient-years (102,103). Most studies have found no significant difference in the incidence of LA during treatment with metformin in patients with and without renal impairment defined as a reduced glomerular filtration rate (102).

MORBIDITY AND MORTALITY

LA leads to neurologic impairment. Rapid correction of the acid-base and electrolyte disturbances may induce cerebral edema. The mechanism of cerebral

TABLE 17.4. Annual Hospitalizations for Lactic Acidosis, by Diabetes Status, Age, Sex, and Race, U.S., 2001–2010

CHARACTERISTICS	DIABETES			NO DIABETES	
	Lactic Acidosis and Diabetes (Number in Thousands)	Percent (SE)		Lactic Acidosis and No Diabetes (Number in Thousands)	Percent (SE)
		Among Diabetes Discharges	Among All Discharges*		Among All Discharges
Total	65.2	1.2 (0.03)	0.17 (0.005)	340.3	1.02 (0.012)
Age (years)					
<18	0.8	1.6 (0.34)	0.01 (0.003)	42.5	0.63 (0.020)
18–44	8.3	1.5 (0.10)	0.08 (0.006)	45.5	0.48 (0.015)
45–64	24.2	1.3 (0.06)	0.28 (0.013)	88.8	1.32 (0.030)
≥65	32.0	1.1 (0.05)	0.24 (0.010)	163.4	1.58 (0.027)
Sex					
Male	31.6	1.3 (0.05)	0.20 (0.008)	158.9	1.18 (0.020)
Female	33.6	1.2 (0.04)	0.15 (0.006)	181.4	0.92 (0.015)
Race†					
White	35.7	1.1 (0.05)	0.15 (0.006)	205.0	1.02 (0.016)
Black	13.8	1.6 (0.09)	0.29 (0.016)	49.4	1.25 (0.036)
AI/AN	0.5	1.7 (0.65)[1]	0.31 (0.119)	1.7	1.24 (0.227)
Asian	1.1	1.6 (0.39)	0.18 (0.043)	5.5	1.01 (0.115)
Other	2.4	1.7 (0.18)	0.24 (0.025)	10.4	1.17 (0.069)

Lactic acidosis is defined as ICD-9 code 276.2. Diabetes hospitalizations are defined as ICD-9-CM codes 250, 357.2, 362.0, 366.41, 648.0, and 775.10, as any diagnosis listed on the hospital discharge record. Standard errors (SE) were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design. AI/AN, American Indian/Alaska Native; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

* All discharges include patients with diabetes and those without diabetes.

† Twenty-three percent of participants were missing race data.

[1] Relative standard error >30%–40%

SOURCE: National Hospital Discharge Surveys 2001–2010

edema in the course of LA is unclear. The mortality rates from LA are high and associated with higher lactic acid levels. Based on data from National Hospital Discharge Surveys 2001–2010, LA accounts for 1.2% of all hospitalizations in diabetic patients (Table 17.4).

PREVENTION AND TREATMENT

LA is usually associated with unexpected and catastrophic hypoxic events and is therefore less likely to be amenable to preventive measures. Long-term prevention of cardiovascular disease or sepsis among diabetic patients through improved glucose control and alteration of other risk factors could decrease the incidence of LA.

The only effective treatment for LA is cessation of lactic acid production by the improvement of tissue oxygenation. Treatment of underlying conditions, such as shock or myocardial infarction, includes restoration of the fluid volume, improvement of cardiac function, amelioration of sepsis, and correction of hyperglycemia (104).

HYPOGLYCEMIA

PATHOGENESIS

Hypoglycemia is the most common, life-threatening acute complication of diabetes treatment. It is characterized by multiple risk factors and complex pathophysiology (105). The brain depends on a continuous supply of glucose for energy, although it can also utilize ketone bodies. Young children and adolescents are at higher risk for hypoglycemia, and the spectrum of outcomes ranges from mild cognitive impairment to coma, seizure, and sudden death.

Missed meals, inadvertent insulin dosing error, and rapid insulin absorption due to intramuscular injection or hot shower/bath shortly after injection are common causes of hypoglycemia in insulin-treated patients. Rarely, secondary gain or suicide attempt may lead to insulin overdose. In all these situations, insulin overdose reduces hepatic glucose output. Physical activity increases glucose utilization and may lead to hypoglycemia, if not matched by lowering of insulin dose and increased carbohydrate intake. Oral hypoglycemic agents may lead to hypoglycemia by either decreasing hepatic glucose output or increasing insulin levels. In contrast, enhancers of peripheral glucose utilization (thiazolidinediones) do not cause hypoglycemia in patients with residual insulin and glucagon secretion. Release of glucagon—the major counterregulatory response to hypoglycemia in nondiabetic persons—is progressively lost within a few years after diagnosis of type 1 diabetes. Catecholamine release, the other powerful counterregulatory mechanism, is also impaired in diabetic patients, especially in those with type 1 diabetes and those on beta blocker treatment (106).

DEFINITION

Various definitions of hypoglycemia are in use; for comparative epidemiologic studies, it is important to standardize criteria. The American Diabetes Association Workgroup on Hypoglycemia defined hypoglycemia broadly as all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm (107,108). According to the Workgroup, a hypoglycemic episode could be:

- *Severe hypoglycemia*: an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. The episode may lead to a significant neuroglycopenia and seizure or coma. Plasma glucose measurements may be missing during an event, but neurological recovery is sufficient evidence that the event was induced by a low plasma glucose concentration.
- *Documented symptomatic hypoglycemia*: an event with typical symptoms of hypoglycemia and a measured plasma glucose concentration ≤70 mg/dL (≤3.89 mmol/L).
- *Asymptomatic hypoglycemia*: an event with a measured plasma glucose concentration ≤70 mg/dL, but without typical symptoms of hypoglycemia.
- *Probable symptomatic hypoglycemia*: an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination.
- *Relative hypoglycemia*: an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, with a measured plasma glucose concentration >70 mg/dL.

The DCCT defined severe hypoglycemia as an episode in which the patient required assistance with treatment from another person to recover; blood glucose level had to be documented as <50 mg/dL (<2.78 mmol/L) and/or the clinical manifestations had to be reversed by oral carbohydrate, subcutaneous glucagon, or intravenous glucose (109). This definition is of limited value in children, particularly the youngest, as they require assistance even for mild episodes of hypoglycemia. There is lack of a uniform definition of hypoglycemia for children and adolescents with diabetes. Most experts agree that blood glucose values <60–70 mg/dL (<3.33–3.89 mmol/L) put the patient at risk for severe hypoglycemia. Those blood glucose levels lead to alterations in the counterregulatory hormones essential to the spontaneous reversal of hypoglycemia. For clinical use, the value of <65 mg/dL (<3.61 mmol/L) has been most often used as the level for defining hypoglycemia in the pediatric population. Other studies have limited the definition of severe hypoglycemia in children to episodes leading to unconsciousness or seizure (110,111).

In the ICD-9, hypoglycemic coma secondary to diabetes treatment is coded 250.3; however, this code is also used for coma with DKA. Other forms of diabetic hypoglycemia are coded 250.8. Hypoglycemia not associated with diabetes is coded 251.2. An additional E code is recommended to identify the drug that induced hypoglycemia. In the ICD-10, E1x.0 denotes coma with or without ketoacidosis, hyperosmolarity or hypoglycemia (with the x digit used to define type of diabetes), while E16.0 denotes diabetic drug-induced hypoglycemia without coma.

INCIDENCE IN TYPE 1 DIABETES PATIENTS

The incidence of moderate or mild hypoglycemia is unknown; those events are frequent among patients treated with insulin and are often unrecognized or underreported. Severe hypoglycemia is more likely to be recognized. Pre-DCCT incidence rates of severe hypoglycemia varied from 3 to 86 per 100 patient-years depending on definition, age, duration of diabetes, and treatment modality (112,113,114,115,116).

Among adolescents participating in the DCCT, the incidences of hypoglycemia were 86 per 100 patient-years in intensively treated and 28 per 100 patient-years in conventionally treated participants (78). The incidences of coma and seizure in the adolescents were 27 per 100 patient-years and 10 per 100 patient-years, respectively. In all DCCT participants, intensive treatment of type 1 diabetes increased the frequency of severe hypoglycemia from two to six times that observed with conventional treatment (117).

Several studies examined the incidence rates of severe hypoglycemia in youth during the post-DCCT era. Few used a prospective design or were population based. The incidence of severe hypoglycemia of 19 per 100 patient-years was reported from a large cohort of type 1 diabetic children age 0–19 years followed by the Barbara Davis Center for Childhood Diabetes (26). A Joslin Clinic study with a similar definition found a lower rate of 8 per 100 patient-years in a cohort of older children age 7–16 years. However, this study excluded children with psychiatric disorders and difficult social situations (118). Similar rates were reported from other European, American, and Australian studies (119,120,121,122,123), with an exception of very low incidence (<4 per 100 person-years) in a study from Finland (124).

INCIDENCE IN TYPE 2 DIABETES PATIENTS

Patients with type 2 diabetes treated with diet and exercise do not suffer from severe hypoglycemia. It occurs rarely in patients treated with oral hypoglycemic agents. However, the risk of hypoglycemia increases with transition to insulin-dependence. In the United Kingdom Prospective Diabetes Study (UKPDS), the risk of severe hypoglycemia was 1.0 per 100 patient-years in those intensively treated with chlorpropamide, 1.4 per 100 patient-years with glibenclamide, and 1.8 per 100 patient-years with insulin (125). Long-acting sulfonylureas confer higher risk compared to shorter-acting ones (126), particularly in older patients and those with a longer duration of diabetes, polypharmacy, and a recent hospitalization (127). One study suggested an increase in risk of hypoglycemia in patients treated with sulfonylurea and angiotensin-converting enzyme (ACE) inhibitors (128), but that finding was not confirmed in a large trial (129). Hospital admission rates for hypoglycemia in U.S. have declined since 2007; however, rates among black Medicare beneficiaries and those older than 75 years remain high (130).

RISK FACTORS

There is a strong relationship between severe hypoglycemia and tight glycemic control (131), especially in children and older adults (118,120,132,133,134). Age (infancy and adolescence) (120,135), male sex (26), and increased duration of diabetes (136) are the most commonly reported predictors of severe hypoglycemia in patients with type 1 diabetes. The risk of hypoglycemia increases with duration of diabetes, partially due to progressive loss of alpha cell glucagon response to hypoglycemia, and is inversely related to preservation of beta cells (137). In the DCCT, presence of residual endogenous insulin secretion predicted 65% lower risk of severe hypoglycemia (138). Sudden loss of endogenous insulin production is seen more frequently in patients with the human leukocyte antigen (HLA)-DR3/4 genotype (139,140,141) and those with multiple islet autoantibodies (140,142).

In patients with type 2 diabetes, aggressive glycemic control puts them at risk of hypoglycemia. A large, cross-sectional study of older adult patients in the Veterans Health Administration in 2009 identified patients at risk of hypoglycemia based on whether they were receiving insulin and/or sulfonylureas. Instances of overtreatment were defined as using one of these agents in patients with A1c levels below specific thresholds, such as <7.0% (<53 mmol/mol). Among patients age ≥75 years, who had a serum creatinine >2.0 mg/dL or an ICD-9-CM diagnosis of cognitive impairment or dementia (31.5% of patients), rates of overtreatment were 11.3% for those with A1c <6.0% (<42 mmol/mol), 28.6% for A1c <6.5% (<48 mmol/mol), and 50.0% for A1c <7.0%. Among patients with additional comorbidity, similar rates of overtreatment were found by A1c thresholds (134). Additional information about glycemic control and hypoglycemia risk in older adults is provided in Chapter 16 *Diabetes in Older Adults*.

Modifiable predictors of severe hypoglycemia include intensive insulin treatment, marked by lower A1c levels and higher insulin dose (26,119). The relation between severe hypoglycemia and tight glycemic control had been extensively explored, especially in children (118,120,132). Over 60% of the intensively treated adolescents who participated in the DCCT had coma or seizure during the trial compared to 25% of those treated conventionally (78). Intensive treatment, such as the use of insulin pumps, is beneficial in lowering A1c levels without a coincident higher risk of hypoglycemia in pediatric populations (143,144). The addition of continuous glucose monitoring to insulin pump therapy has further lowered the rates of hypoglycemia (145,146,147).

Another risk factor is the presence of hypoglycemia unawareness leading to an inability to recognize symptoms of hypoglycemia. It is present in about 10% of patients and is more common in patients with low average glucose levels (148,149). Even a single hypoglycemic episode can cause significant decrease in neurohormonal counterregulatory responses and worsen unawareness of hypoglycemia (150).

The main effect of exercise on glucose metabolism is blood glucose lowering via insulin-independent skeletal muscle

uptake, which may result in hypoglycemia without modification of insulin dose and intake of carbohydrates (151).

Alcohol consumption is a significant risk factor for development of severe hypoglycemia. Alcohol suppresses gluconeogenesis and glycogenolysis and acutely improves insulin sensitivity (152,153) and may induce hypoglycemia unawareness (154). In combination with exercise, drinking alcohol can lead to severe hypoglycemia with a delay of symptoms up to 10–12 hours after alcohol consumption (155).

Family dynamics, behavioral factors, and psychiatric factors are important risk factors, particularly in the pediatric population. The DCCT showed that conventional risk factors explained only 8.5% of the variance in the occurrence of severe hypoglycemia (117). Factors such as inadequate diabetes education, low socioeconomic status, lack of insurance, unstable living conditions, behavioral factors, and psychiatric disorders affecting patients and their families have been shown to have significant influence on glycemic control and the rate of hypoglycemia. Family relationships and personality type have also had a significant effect on adaptation to illness and metabolic control among persons with diabetes (156). Presence of psychiatric disorders has a detrimental effect on metabolic control (157,158) and compliance with treatment (159). Prevalence of psychiatric disorders among patients with type 1 diabetes reached 48% by 10 years of diabetes duration and age 20 years in a small longitudinal cohort (160,161), the most prevalent being major depressive disorder (28%). Prevalence of psychiatric disorders, however, has been shown to be much lower in other studies, as discussed in Chapter 33 *Psychiatric and Psychosocial Issues Among Individuals Living With Diabetes*.

Coexisting autoimmune conditions, such as autoimmune thyroid, celiac, and Addison's diseases, occurring in up to 30% of patients with type 1 diabetes, increase the risk of hypoglycemia (162,163,164,165). In pregnancy with type 1 diabetes, the incidence of mild and severe hypoglycemia is highest in early pregnancy, although metabolic control is usually tighter in the last part of pregnancy. Predictors for severe hypoglycemia are history of severe hypoglycemia and impaired awareness (166). Chronic kidney disease can be found in up to 23% of patients with diabetes. Chronic kidney disease is an independent risk factor for hypoglycemia and augments the risk already present in people with diabetes (167,168).

MORBIDITY AND MORTALITY

A new analysis for *Diabetes in America* of the frequency of hypoglycemia (ICD-9 codes 250.8 and 251.2) as a discharge diagnosis for hospitalizations in the United States in 2001–2010 is shown in Tables 17.1 and 17.5, using data from the National Hospital Discharge Survey. Hypoglycemia was listed as

TABLE 17.5. Annual Hospitalizations for Hypoglycemia, by Diabetes Status, Age, Sex, and Race, U.S., 2001–2010

	DIABETES			NO DIABETES	
		Percent (SE)			Percent (SE)
CHARACTERISTICS	Hypoglycemia and Diabetes (Number in Thousands)	Among All Diabetes Discharges	Among All Discharges*	Hypoglycemia With No Diabetes (Number in Thousands)	Among All Discharges
Total	287.6	5.4 (0.07)	0.74 (0.009)	28.9	0.09 (0.003)
Age (years)					
<18	1.8	3.6 (0.37)	0.03 (0.003)	7.9	0.12 (0.009)
18–44	28.9	5.1 (0.19)	0.29 (0.011)	5.9	0.06 (0.005)
45–64	100.8	5.5 (0.11)	1.18 (0.025)	5.6	0.08 (0.006)
≥65	156.1	5.5 (0.09)	1.18 (0.021)	9.6	0.09 (0.006)
Sex					
Male	140.9	5.8 (0.10)	0.88 (0.016)	12.4	0.09 (0.005)
Female	146.7	5.1 (0.09)	0.65 (0.012)	16.5	0.08 (0.004)
Race†					
White	160.8	5.1 (0.09)	0.69 (0.012)	18.0	0.09 (0.004)
Black	56.9	6.8 (0.17)	1.18 (0.031)	4.5	0.11 (0.010)
AI/AN	1.8	5.9 (0.96)	1.07 (0.180)	0.1	0.09 (0.041)[2]
Asian	4.1	6.0 (0.65)	0.67 (0.074)	0.5	0.09 (0.032)[1]
Other	7.3	5.3 (0.31)	0.71 (0.042)	0.6	0.07 (0.014)

ICD-9-CM codes used to identify hypoglycemia hospitalizations were 250.8 for those with diabetes and 251.2 for those without diabetes. Diabetes hospitalizations are defined as ICD-9-CM codes 250, 357.2, 362.0, 366.41, 648.0, and 775.10, as any diagnosis listed on the hospital discharge record. Standard errors (SE) were most likely underestimated because the National Hospital Discharge Survey sampling variables were not available, and consequently, it was not possible to take into account the complex sampling design. There were only 11 patients with hypoglycemia coma among people with diabetes, and none of the estimates were reliable enough to present (all relative standard errors >50%). AI/AN, American Indian/Alaska Native; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

* All discharges include patients with diabetes and those without diabetes.

† Twenty-three percent of participants were missing race data.

[1] Relative standard error >30%–40%

[2] Relative standard error >40%–50%

SOURCE: National Hospital Discharge Surveys 2001–2010

an underlying cause in about 288,000 hospitalizations, which represented 5.4% of hospitalizations due to diabetes. Hospital discharges for hypoglycemia in diabetic patients occurred least often in patients age <18 years. The total number of hypoglycemic events was higher in females with diabetes compared to males, but the percentage of discharges was higher in males compared to females. The total number of hospitalizations due to hypoglycemia was greatest among whites followed by blacks, while the percentage of discharges was lower in whites than in the other race/ethnicity groups (Table 17.5).

Hypoglycemia is a significant factor in excess mortality in patients with diabetes (169). Despite improvements in therapy, diabetes-related mortality among children did not decline in the time period between 1968 and 1998 (170). Sudden nocturnal death in young persons with type 1 diabetes has been described and is known as the "dead in bed" syndrome (171); it appears to be responsible for about 6% of deaths in diabetic patients age <40 years (172). In these cases, nocturnal hypoglycemia is a likely precipitant, consistent with demonstrated impairment of counter-regulatory hormone response during sleep (173), as well as a high frequency of nocturnal hypoglycemia reported by the DCCT (117) and more recent studies using continuous glucose monitoring.

Hypoglycemic episodes range from mild neurogenic symptoms to coma and seizures. There is an association between hypoglycemia and a decrease in cognitive functioning in children with type 1 diabetes (174,175,176), particularly among the youngest patients (176,177). Hypoglycemic seizures lead to significant declines in verbal abilities (178), memory skills (179), and the ability to organize and recall information (180), even after mild hypoglycemia (181). Severe hypoglycemia in children may lead to persistent electroencephalographic changes (182,183,184,185). On the other hand, intensive insulin treatment in the DCCT cohort (age 13–39 years at baseline), while increasing the incidence of hypoglycemia, did not lead to a significant worsening of neuropsychological or cognitive functioning during the trial (186,187), as well as 18 years after entry into the trial (188). However, risk of hypoglycemia should be balanced by emerging data on a detrimental effect of hyperglycemia on the development of a normal brain (189).

COST

In a study among youth with diabetes, the predicted mean annual total medical expenditures were $12,850 and $8,970 for youth with and without severe hypoglycemia, respectively. The excess of expenditures was greater among those with more than one episode ($5,929) than among those with only one ($2,888) (63). A study from Germany, Spain, and the United Kingdom showed that hospital treatment of severe hypoglycemia was a major contributor to its high cost. Average severe hypoglycemia event treatment costs were higher for patients with type 2 diabetes (Germany, €533; Spain, €691; U.K., €537) than those with type 1 diabetes (€441, €577, and €236, respectively) (190). Reliable data are not available concerning the cost of hypoglycemia in adults with diabetes in the United States.

The personal, family, and societal cost of trauma of loss of consciousness, seizure, long-term disability, and fears are harder to measure. Further studies are needed to update these figures and to estimate, in addition, indirect costs (e.g., lost productivity and diminished quality of life).

PREVENTION

Improved insulin delivery and technological advances provide new opportunities to improve glycemic control with decreased risk of severe hypoglycemia, but they require intensified teaching and compliance (136,191,192). Intensive insulin therapy using insulin pumps, multiple daily injections, and new insulin analogues has been found effective in lowering A1c levels, but there is less evidence for a beneficial effect on the risk of hypoglycemia. Insulin pump treatment may lower A1c levels and improve quality of life compared to multiple daily injections of insulin and, of importance, reduce the rate of severe hypoglycemia (193,194).

The introduction of rapid-acting insulin analogues (e.g., lispro, aspart) has made insulin treatment more efficient and potentially less likely to induce hypoglycemia. An ecologic analysis explored the effects of the DCCT report in 1993 and that of the introduction of a rapid-acting insulin analogue (lispro) in 1996 on the risk of severe hypoglycemia in type 1 diabetic patients (195). A1c levels declined significantly during 1993–1996 ($p<0.001$), following the DCCT report, but the number of severe hypoglycemic events increased ($p<0.001$) during that time frame. A further decline in A1c levels was observed after the introduction of lispro insulin in 1996 ($p<0.001$), however, without a concomitant change in the incidence of severe hypoglycemia. The introduction of long-acting insulin analogues in 2003 also suggests a potential for improving glycemic control without an increased risk of hypoglycemia (196,197,198).

Continuous Glucose Monitoring

Frequent self-blood glucose monitoring has been found to be an important factor in attaining better glucose control for the intensively treated participants in the DCCT and the UKPDS. However, many patients do not accept frequent blood glucose monitoring, mainly because of pain and inconvenience. The results also give data valid for only a discrete point in time, without any information on glucose trends before or after the glucose value. In addition, patients infrequently measure blood glucose levels during the night, although >50% of severe hypoglycemic events occur during sleep (113,117).

Continuous glucose monitoring holds great promise for prevention of hypoglycemia. Clinical trials of continuous glucose monitoring have given reason to believe that tighter glycemic control may not necessarily lead to increased risk of hypoglycemia (199,200,201,202,203,204,205). The main goal of research on devices for

diabetes management is the development of automatic glucose sensing and insulin delivery without patient intervention (206). Studies evaluating closed-loop insulin delivery suggest improved glucose control and a decreased risk of hypoglycemia (207,208). Data from the Automation to Simulate Pancreatic Insulin REsponse (ASPIRE) study confirmed that use of sensor-augmented insulin pump therapy with the threshold-suspend feature reduced nocturnal hypoglycemia, without increasing A1c values (209).

Behavioral Interventions

Behavioral interventions, including intensive diabetes education, good access to care, and psychosocial support, including treatment of psychiatric disorders, lower the risk of hypoglycemia (210,211).

TREATMENT

The goal of treatment of hypoglycemia is to immediately increase the blood glucose approximately 3–4 mmol/L (~55–70 mg/dL). This can be accomplished by giving glucose tablets or sweetened fluids, such as juice, glucagon injection in unconscious patients, or dextrose infusion in a hospital setting.

LIST OF ABBREVIATIONS

A1c. . . . . glycosylated hemoglobin
β-OHB . . . . . beta-hydroxybutyrate
CSII . . . . . continuous subcutaneous insulin infusion
DCCT. . . . . Diabetes Control and Complications Trial
DKA. . . . . diabetic ketoacidosis
HHS. . . . . hyperglycemic hyperosmolar state
ICD-9-CM/ICD-10 . . . . . International Classification of Diseases, Ninth Revision, Clinical Modification/Tenth Revision
LA . . . . . lactic acidosis
SEARCH . . . . . SEARCH for Diabetes in Youth study
UKPDS. . . . . United Kingdom Prospective Diabetes Study

CONVERSIONS

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*.

DUALITY OF INTEREST

Dr. Rewers reported no conflicts of interest.

REFERENCES

1. Wolfsdorf J, Glaser N, Sperling MA; American Diabetes Association: Diabetic ketoacidosis in infants, children, and adolescents: a consensus statement from the American Diabetes Association. *Diabetes Care* 29:1150–1159, 2006
2. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA: Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care* 29:2739–2748, 2006
3. Wolfsdorf JI, Allgrove J, Craig ME, Edge J, Glaser N, Jain V, Lee WW, Mungai LN, Rosenbloom AL, Sperling MA, Hanas R; International Society for Pediatric and Adolescent Diabetes: ISPAD Clinical Practice Consensus Guidelines 2014. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatr Diabetes* 15(Suppl 20):154–179, 2014
4. Dunger DB, Sperling MA, Acerini CL, Bohn DJ, Daneman D, Danne TP, Glaser NS, Hanas R, Hintz RL, Levitsky LL, Savage MO, Tasker RC, Wolfsdorf JI; ESPE; LWPES: ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. *Arch Dis Child* 89:188–194, 2004
5. Ireland JT, Thomson WS: Euglycemic diabetic ketoacidosis. *Br Med J* 3:107, 1973
6. Burge MR, Hardy KJ, Schade DS: Short-term fasting is a mechanism for the development of euglycemic ketoacidosis during periods of insulin deficiency. *J Clin Endocrinol Metab* 76:1192–1198, 1993
7. Rewers A, Klingensmith G, Davis C, Petitti DB, Pihoker C, Rodriguez B, Schwartz D, Imperatore G, Williams D, Dolan L, Mayer-Davis E, Dabelea D: Diabetes ketoacidosis at onset of diabetes: the SEARCH for Diabetes in Youth Study (Abstract). *Diabetes* 54(Suppl 1):A63–A64, 2005
8. Klingensmith GJ, Tamborlane WV, Wood J, Haller MJ, Silverstein J, Cengiz E, Shanmugham S, Kollman C, Wong-Jacobson S, Beck RW; Pediatric Diabetes Consortium: Diabetic ketoacidosis at diabetes onset: still an all too common threat in youth. *J Pediatr* 162:330–334.e1, 2013
9. Mallare JT, Cordice CC, Ryan BA, Carey DE, Kreitzer PM, Frank GR: Identifying risk factors for the development of diabetic ketoacidosis in new onset type 1 diabetes mellitus. *Clin Pediatr (Phila)* 42:591–597, 2003
10. Quinn M, Fleischman A, Rosner B, Nigrin DJ, Wolfsdorf JI: Characteristics at diagnosis of type 1 diabetes in children younger than 6 years. *J Pediatr* 148:366–371, 2006
11. Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, Imperatore G, D'Agostino RB, Jr., Mayer-Davis EJ, Pihoker C; SEARCH for Diabetes in Youth Study Group: Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for Diabetes in Youth study. *Pediatrics* 133:e938–e945, 2014

12. Claessen FM, Donaghue K, Craig M: Consistently high incidence of diabetic ketoacidosis in children with newly diagnosed type 1 diabetes. *Med J Aust* 197:216, 2012
13. Neu A, Hofer SE, Karges B, Oeverink R, Rosenbauer J, Holl RW; DPV Initiative and the German BMBF Competency Network for Diabetes Mellitus: Ketoacidosis at diabetes onset is still frequent in children and adolescents: a multicenter analysis of 14,664 patients from 106 institutions. *Diabetes Care* 32:1647–1648, 2009
14. Schober E, Rami B, Waldhoer T; Austrian Diabetes Incidence Study Group: Diabetic ketoacidosis at diagnosis in Austrian children in 1989–2008: a population-based analysis. *Diabetologia* 53:1057–1061, 2010
15. Hekkala A, Knip M, Veijola R: Ketoacidosis at diagnosis of type 1 diabetes in children in northern Finland: temporal changes over 20 years. *Diabetes Care* 30:861–866, 2007
16. Abdul-Rasoul M, Al-Mahdi M, Al-Qattan H, Al-Tarkait N, Alkhouly M, Al-Safi R, Al-Shawaf F, Mahmoud H: Ketoacidosis at presentation of type 1 diabetes in children in Kuwait: frequency and clinical characteristics. *Pediatr Diabetes* 11:351–356, 2010
17. Jesic MD, Jesic MM, Stanisavljevic D, Zdravkovic V, Bojic V, Vranjes M, Trifunovic D, Necic S, Sajic S: Ketoacidosis at presentation of type 1 diabetes mellitus in children: a retrospective 20-year experience from a tertiary care hospital in Serbia. *Eur J Pediatr* 172:1581–1585, 2013
18. Ucar A, Saka N, Bas F, Sukur M, Poyrazoglu S, Darendeliler F, Bundak R: Frequency and severity of ketoacidosis at onset of autoimmune type 1 diabetes over the past decade in children referred to a tertiary paediatric care centre: potential impact of a national programme highlighted. *J Pediatr Endocrinol Metab* 26:1059–1065, 2013
19. Westphal SA: The occurrence of diabetic ketoacidosis in non-insulin-dependent diabetes and newly diagnosed diabetic adults. *Am J Med* 101:19–24, 1996
20. Umpierrez GE, Kelly JP, Navarrete JE, Casals MM, Kitabchi AE: Hyperglycemic crises in urban blacks. *Arch Intern Med* 157:669–675, 1997
21. Balasubramanyam A, Zern JW, Hyman DJ, Pavlik V: New profiles of diabetic ketoacidosis: type 1 vs type 2 diabetes and the effect of ethnicity. *Arch Intern Med* 159:2317–2322, 1999
22. Pinero-Pilona A, Raskin P: Idiopathic type 1 diabetes. *J Diabetes Complications* 15:328–335, 2001
23. Mauvais-Jarvis F, Sobngwi E, Porcher R, Riveline JP, Kevorkian JP, Vaisse C, Charpentier G, Guillausseau PJ, Vexiau P, Gautier JF: Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of beta-cell dysfunction and insulin resistance. *Diabetes* 53:645–653, 2004
24. Faich GA, Fishbein HA, Ellis SE: The epidemiology of diabetic acidosis: a population-based study. *Am J Epidemiol* 117:551–558, 1983
25. Johnson DD, Palumbo PJ, Chu CP: Diabetic ketoacidosis in a community-based population. *Mayo Clin Proc* 55:83–88, 1980
26. Rewers A, Chase HP, Mackenzie T, Walravens P, Roback M, Rewers M, Hamman RF, Klingensmith G: Predictors of acute complications in children with type 1 diabetes. *JAMA* 287:2511–2518, 2002
27. Pinkey JH, Bingley PJ, Sawtell PA, Dunger DB, Gale EA: Presentation and progress of childhood diabetes mellitus: a prospective population-based study. The Bart's-Oxford Study Group. *Diabetologia* 37:70–74, 1994
28. Golden MP, Herrold AJ, Orr DP: An approach to prevention of recurrent diabetic ketoacidosis in the pediatric population. *J Pediatr* 107:195–200, 1985
29. Levy-Marchal C, Papoz L, de Beaufort C, Doutreix J, Froment V, Voirin J, Czernichow P: Clinical and laboratory features of type 1 diabetic children at the time of diagnosis. *Diabet Med* 9:279–284, 1992
30. Smith CP, Firth D, Bennett S, Howard C, Chisholm P: Ketoacidosis occurring in newly diagnosed and established diabetic children. *Acta Paediatr* 87:537–541, 1998
31. Maniatis AK, Goehrig SH, Gao D, Rewers A, Walravens P, Klingensmith GJ: Increased incidence and severity of diabetic ketoacidosis among uninsured children with newly diagnosed type 1 diabetes mellitus. *Pediatr Diabetes* 6:79–83, 2005
32. Neu A, Willasch A, Ehehalt S, Hub R, Ranke MB; DIARY Group Baden-Wuerttemberg: Ketoacidosis at onset of type 1 diabetes mellitus in children—frequency and clinical presentation. *Pediatr Diabetes* 4:77–81, 2003
33. Alavi IA, Sharma BK, Pillay VK: Steroid-induced diabetic ketoacidosis. *Am J Med Sci* 262:15–23, 1971
34. Wilson DR, D'Souza L, Sarkar N, Newton M, Hammond C: New-onset diabetes and ketoacidosis with atypical antipsychotics. *Schizophr Res* 59:1–6, 2003
35. Reda E, Von Reitzenstein A, Dunn P: Metabolic control with insulin pump therapy: the Waikato experience. *N Z Med J* 120:U2401, 2007
36. Mbugua PK, Otieno CF, Kayima JK, Amayo AA, McLigeyo SO: Diabetic ketoacidosis: clinical presentation and precipitating factors at Kenyatta National Hospital, Nairobi. *East Afr Med J* 82(12 Suppl):S191–S196, 2005
37. Flood RG, Chiang VW: Rate and prediction of infection in children with diabetic ketoacidosis. *Am J Emerg Med* 19:270–273, 2001
38. Kaufman FR, Halvorson M, Miller D, Mackenzie M, Fisher LK, Pitukcheewanont P: Insulin pump therapy in type 1 pediatric patients: now and into the year 2000. *Diabetes Metab Res Rev* 15:338–352, 1999
39. Hanas R, Ludvigsson J: Hypoglycemia and ketoacidosis with insulin pump therapy in children and adolescents. *Pediatr Diabetes* 7(Suppl 4):32–38, 2006
40. Sulli N, Shashaj B: Long-term benefits of continuous subcutaneous insulin infusion in children with type 1 diabetes: a 4-year follow-up. *Diabet Med* 23:900–906, 2006
41. Umpierrez GE, Kitabchi AE: Diabetic ketoacidosis: risk factors and management strategies. *Treat Endocrinol* 2:95–108, 2003
42. Gutierrez JA, Bagatell R, Samson MP, Theodorou AA, Berg RA: Femoral central venous catheter-associated deep venous thrombosis in children with diabetic ketoacidosis. *Crit Care Med* 31:80–83, 2003
43. Randall L, Begovic J, Hudson M, Smiley D, Peng L, Pitre N, Umpierrez D, Umpierrez G: Recurrent diabetic ketoacidosis in inner-city minority patients: behavioral, socioeconomic, and psychosocial factors. *Diabetes Care* 34:1891–1896, 2011
44. Nyenwe EA, Loganathan RS, Blum S, Ezuteh DO, Erani DM, Wan JY, Palace MR, Kitabchi AE: Active use of cocaine: an independent risk factor for recurrent diabetic ketoacidosis in a city hospital. *Endocr Pract* 13:22–29, 2007
45. Quinn L: Diabetes emergencies in the patient with type 2 diabetes. *Nurs Clin North Am* 36:341–360, viii, 2001
46. *Diabetes in America*. 2nd ed. Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, Eds. Bethesda, MD, National Institutes of Health, NIH Pub No. 95-1468, 1995
47. Centers for Disease Control and Prevention: Diabetes death rates among youths aged ≤ 19 years—United States, 1968–2009. *MMWR Morb Mortal Wkly Rep* 61:869–872, 2012
48. Edge JA, Ford-Adams ME, Dunger DB: Causes of death in children with insulin dependent diabetes 1990–96. *Arch Dis Child* 81:318–323, 1999

49. Podar T, Solntsev A, Reunanen A, Urbonaite B, Zalinkevicius R, Karvonen M, LaPorte RE, Tuomilehto J: Mortality in patients with childhood-onset type 1 diabetes in Finland, Estonia, and Lithuania: follow-up of nationwide cohorts. *Diabetes Care* 23:290–294, 2000
50. Edge JA, Hawkins MM, Winter DL, Dunger DB: The risk and outcome of cerebral oedema developing during diabetic keto-acidosis. *Arch Dis Child* 85:16–22, 2001
51. Lawrence SE, Cummings EA, Gaboury I, Daneman D: Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis. *J Pediatr* 146:688–692, 2005
52. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, Kaufman F, Quayle K, Roback M, Malley R, Kuppermann N; Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics: Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. *N Engl J Med* 344:264–269, 2001
53. Glaser NS, Wootton-Gorges SL, Buonocore MH, Marcin JP, Rewers A, Strain J, DiCarlo J, Neely EK, Barnes P, Kuppermann N: Frequency of sub-clinical cerebral edema in children with diabetic ketoacidosis. *Pediatr Diabetes* 7:75–80, 2006
54. Roberts MD, Slover RH, Chase HP: Diabetic ketoacidosis with intracerebral complications. *Pediatr Diabetes* 2:109–114, 2001
55. Atluru VL: Spontaneous intracerebral hematomas in juvenile diabetic keto-acidosis. *Pediatr Neurol* 2:167–169, 1986
56. Ho J, Mah JK, Hill MD, Pacaud D: Pediatric stroke associated with new onset type 1 diabetes mellitus: case reports and review of the literature. *Pediatr Diabetes* 7:116–121, 2006
57. Kanter RK, Oliphant M, Zimmerman JJ, Stuart MJ: Arterial thrombosis causing cerebral edema in association with diabetic ketoacidosis. *Crit Care Med* 15:175–176, 1987
58. Kameh DS, Gonzalez OR, Pearl GS, Walsh AF, Gambon T, Kropp TM: Fatal rhino-orbital-cerebral zygomycosis. *South Med J* 90:1133–1135, 1997
59. Gessesse M, Chali D, Wolde-Tensai B, Ergete W: Rhinocerebral mucormycosis in an 11-year-old boy. *Ethiop Med J* 39:341–348, 2001
60. Dixon AN, Jude EB, Banerjee AK, Bain SC: Simultaneous pulmonary and cerebral oedema, and multiple CNS infarctions as complications of diabetic ketoacidosis: a case report. *Diabet Med* 23:571–573, 2006
61. Young MC: Simultaneous acute cerebral and pulmonary edema complicating diabetic ketoacidosis. *Diabetes Care* 18:1288–1290, 1995
62. Javor KA, Kotsanos JG, McDonald RC, Baron AD, Kesterson JG, Tierney WM: Diabetic ketoacidosis charges relative to medical charges of adult patients with type I diabetes. *Diabetes Care* 20:349–354, 1997
63. Shrestha SS, Zhang P, Barker L, Imperatore G: Medical expenditures associated with diabetes acute complications in privately insured U.S. youth. *Diabetes Care* 33:2617–2622, 2010
64. Tieder JS, McLeod L, Keren R, Luan X, Localio R, Mahant S, Malik F, Shah SS, Wilson KM, Srivastava R; Pediatric Research in Inpatient Settings Network: Variation in resource use and readmission for diabetic ketoacidosis in children's hospitals. *Pediatrics* 132:229–236, 2013
65. Ginde AA, Pelletier AJ, Camargo CA, Jr.: National study of U.S. emergency department visits with diabetic ketoacidosis, 1993–2003. *Diabetes Care* 29:2117–2119, 2006
66. Kim S: Burden of hospitalizations primarily due to uncontrolled diabetes: implications of inadequate primary health care in the United States. *Diabetes Care* 30:1281–1282, 2007
67. Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, Wall BM: Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 24:131–153, 2001
68. Maldonado MR, Chong ER, Oehl MA, Balasubramanyam A: Economic impact of diabetic ketoacidosis in a multiethnic indigent population: analysis of costs based on the precipitating cause. *Diabetes Care* 26:1265–1269, 2003
69. Bui H, To T, Stein R, Fung K, Daneman D: Is diabetic ketoacidosis at disease onset a result of missed diagnosis? *J Pediatr* 156:472–477, 2010
70. Lokulo-Sodipe K, Moon RJ, Edge JA, Davies JH: Identifying targets to reduce the incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes in the UK. *Arch Dis Child* 99:438–442, 2014
71. Barker JM, Goehrig SH, Barriga K, Hoffman M, Slover R, Eisenbarth GS, Norris JM, Klingensmith GJ, Rewers M; DAISY study: Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. *Diabetes Care* 27:1399–1404, 2004
72. Diabetes Prevention Trial—Type 1 Diabetes Study Group: Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med* 346:1685–1691, 2002
73. Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F: Effectiveness of a prevention program for diabetic ketoacidosis in children. An 8-year study in schools and private practices. *Diabetes Care* 22:7–9, 1999
74. Vanelli M, Chiari G, Lacava S, Iovane B: Campaign for diabetic ketoacidosis prevention still effective 8 years later. *Diabetes Care* 30:e12, 2007
75. Hoffman WH, O'Neill P, Khoury C, Bernstein SS: Service and education for the insulin-dependent child. *Diabetes Care* 1:285–288, 1978
76. Drozda DJ, Dawson VA, Long DJ, Freson LS, Sperling MA: Assessment of the effect of a comprehensive diabetes management program on hospital admission rates of children with diabetes mellitus. *Diabetes Educ* 16:389–393, 1990
77. Grey M, Boland EA, Davidson M, Li J, Tamborlane WV: Coping skills training for youth with diabetes mellitus has long-lasting effects on metabolic control and quality of life. *J Pediatr* 137:107–113, 2000
78. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. *J Pediatr* 125:177–188, 1994
79. O'Grady MJ, Retterath AJ, Keenan DB, Kurtz N, Cantwell M, Spital G, Kremliovsky MN, Roy A, Davis EA, Jones TW, Ly TT: The use of an automated, portable glucose control system for overnight glucose control in adolescents and young adults with type 1 diabetes. *Diabetes Care* 35:2182–2187, 2012
80. Laffel LM, Wentzell K, Loughlin C, Tovar A, Moltz K, Brink S: Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with T1DM: a randomized clinical trial. *Diabet Med* 23:278–284, 2006
81. Wolfsdorf JI: The International Society of Pediatric and Adolescent Diabetes guidelines for management of diabetic ketoacidosis: do the guidelines need to be modified? *Pediatr Diabetes* 15:277–286, 2014
82. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN: Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 32:1335–1343, 2009
83. American Diabetes Association: Hyperglycemic crises in patients with diabetes mellitus 1988–1996. *Diabetes Care* 24:1988–1996, 2001

84. Kitabchi AE, Nyenwe EA: Hyperglycemic crises in diabetes mellitus: diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Endocrinol Metab Clin North Am* 35:725–751, viii, 2006
85. Wachtel TJ, Tetu-Mouradjian LM, Goldman DL, Ellis SE, O'Sullivan PS: Hyperosmolarity and acidosis in diabetes mellitus: a three-year experience in Rhode Island. *J Gen Intern Med* 6:495–502, 1991
86. MacIsaac RJ, Lee LY, McNeil KJ, Tsalamandris C, Jerums G: Influence of age on the presentation and outcome of acidotic and hyperosmolar diabetic emergencies. *Intern Med J* 32:379–385, 2002
87. Canarie MF, Bogue CW, Banasiak KJ, Weinzimer SA, Tamborlane WV: Decompensated hyperglycemic hyperosmolarity without significant ketoacidosis in the adolescent and young adult population. *J Pediatr Endocrinol Metab* 20:1115–1124, 2007
88. Venkatraman R, Singhi SC: Hyperglycemic hyperosmolar nonketotic syndrome. *Indian J Pediatr* 73:55–60, 2006
89. Morales AE, Rosenbloom AL: Death caused by hyperglycemic hyperosmolar state at the onset of type 2 diabetes. *J Pediatr* 144:270–273, 2004
90. Fourtner SH, Weinzimer SA, Levitt Katz LE: Hyperglycemic hyperosmolar non-ketotic syndrome in children with type 2 diabetes*. *Pediatr Diabetes* 6:129–135, 2005
91. Carchman RM, Dechert-Zeger M, Calikoglu AS, Harris BD: A new challenge in pediatric obesity: pediatric hyperglycemic hyperosmolar syndrome. *Pediatr Crit Care Med* 6:20–24, 2005
92. Kershaw MJ, Newton T, Barrett TG, Berry K, Kirk J: Childhood diabetes presenting with hyperosmolar dehydration but without ketoacidosis: a report of three cases. *Diabet Med* 22:645–647, 2005
93. Bagdure D, Rewers A, Campagna E, Sills MR: Epidemiology of hyperglycemic hyperosmolar syndrome in children hospitalized in USA. *Pediatr Diabetes* 14:18–24, 2013
94. Chu CH, Lee JK, Lam HC, Lu CC: Prognostic factors of hyperglycemic hyperosmolar nonketotic state. *Chang Gung Med J* 24:345–351, 2001
95. Wachtel TJ, Silliman RA, Lamberton P: Predisposing factors for the diabetic hyperosmolar state. *Arch Intern Med* 147:499–501, 1987
96. Pinies JA, Cairo G, Gaztambide S, Vazquez JA: Course and prognosis of 132 patients with diabetic non ketotic hyperosmolar state. *Diabet Metab* 20:43–48, 1994
97. Wang J, Williams DE, Narayan KM, Geiss LS: Declining death rates from hyperglycemic crisis among adults with diabetes, U.S., 1985–2002. *Diabetes Care* 29:2018–2022, 2006
98. Cochran JB, Walters S, Losek JD: Pediatric hyperglycemic hyperosmolar syndrome: diagnostic difficulties and high mortality rate. *Am J Emerg Med* 24:297–301, 2006
99. Rosenbloom AL: Hyperglycemic hyperosmolar state: an emerging pediatric problem. *J Pediatr* 156:180–184, 2010
100. Zeitler P, Haqq A, Rosenbloom A, Glaser N; Drugs and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society: Hyperglycemic hyperosmolar syndrome in children: pathophysiological considerations and suggested guidelines for treatment. *J Pediatr* 158:9–14.e2, 2011
101. Salpeter S, Greyber E, Pasternak G, Salpeter E: Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2:CD002967, 2003
102. Richy FF, Sabido-Espin M, Guedes S, Corvino FA, Gottwald-Hostalek U: Incidence of lactic acidosis in patients with type 2 diabetes with and without renal impairment treated with metformin: a retrospective cohort study. *Diabetes Care* 37:2291–2295, 2014
103. van Berlo-van de Laar IR, Vermeij CG, Doorenbos CJ: Metformin associated lactic acidosis: incidence and clinical correlation with metformin serum concentration measurements. *J Clin Pharm Ther* 36:376–382, 2011
104. Luft FC: Lactic acidosis update for critical care clinicians. *J Am Soc Nephrol* 12(Suppl 17):S15–S19, 2001
105. Cryer PE: Hypoglycemia in diabetes: pathophysiological mechanisms and diurnal variation. *Prog Brain Res* 153:361–365, 2006
106. Kerr D, Macdonald IA, Heller SR, Tattersall RB: Beta-adrenoceptor blockade and hypoglycaemia. A randomised, double-blind, placebo controlled comparison of metoprolol CR, atenolol and propranolol LA in normal subjects. *Br J Clin Pharmacol* 29:685–693, 1990
107. Workgroup on Hypoglycemia, American Diabetes Association: Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 28:1245–1249, 2005
108. Ly TT, Maahs DM, Rewers A, Dunger D, Oduwole A, Jones TW; International Society for Pediatric and Adolescent Diabetes: ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes* 15(Suppl 20):180–192, 2014
109. Adverse events and their association with treatment regimens in the Diabetes Control and Complications Trial. *Diabetes Care* 18:1415–1427, 1995
110. Becker DJ, Ryan CM: Hypoglycemia: a complication of diabetes therapy in children. *Trends Endocrinol Metab* 11:198–202, 2000
111. Davis EA, Keating B, Byrne GC, Russell M, Jones TW: Impact of improved glycaemic control on rates of hypoglycaemia in insulin dependent diabetes mellitus. *Arch Dis Child* 78:111–115, 1998
112. Bhatia V, Wolfsdorf JI: Severe hypoglycemia in youth with insulin-dependent diabetes mellitus: frequency and causative factors. *Pediatrics* 88:1187–1193, 1991
113. Bergada I, Suissa S, Dufresne J, Schiffrin A: Severe hypoglycemia in IDDM children. *Diabetes Care* 12:239–244, 1989
114. Daneman D, Frank M, Perlman K, Tamm J, Ehrlich R: Severe hypoglycemia in children with insulin-dependent diabetes mellitus: frequency and predisposing factors. *J Pediatr* 115:681–685, 1989
115. Aman J, Karlsson I, Wranne L: Symptomatic hypoglycaemia in childhood diabetes: a population-based questionnaire study. *Diabet Med* 6:257–261, 1989
116. Egger M, Gschwend S, Smith GD, Zuppinger K: Increasing incidence of hypoglycemic coma in children with IDDM. *Diabetes Care* 14:1001–1005, 1991
117. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. The DCCT Research Group. *Am J Med* 90:450–459, 1991
118. Levine BS, Anderson BJ, Butler DA, Antisdel JE, Brackett J, Laffel LM: Predictors of glycemic control and short-term adverse outcomes in youth with type 1 diabetes. *J Pediatr* 139:197–203, 2001
119. Nordfeldt S, Ludvigsson J: Severe hypoglycemia in children with IDDM. A prospective population study, 1992–1994. *Diabetes Care* 20:497–503, 1997
120. Mortensen HB, Hougaard P: Comparison of metabolic control in a cross-sectional study of 2,873 children and adolescents with IDDM from 18 countries. The Hvidore Study Group on Childhood Diabetes. *Diabetes Care* 20:714–720, 1997
121. Thomsett M, Shield G, Batch J, Cotterill A: How well are we doing? Metabolic control in patients with diabetes. *J Paediatr Child Health* 35:479–482, 1999
122. Danne T, Mortensen HB, Hougaard P, Lynggaard H, Aanstoot HJ, Chiarelli F, Daneman D, Dorchy H, Garandeau

P, Greene SA, Hoey H, Holl RW, Kaprio EA, Kocova M, Martul P, Matsuura N, Robertson KJ, Schoenle EJ, Sovik O, Swift PG, Tsou RM, Vanelli M, Aman J; Hvidore Study Group on Childhood Diabetes: Persistent differences among centers over 3 years in glycemic control and hypoglycemia in a study of 3,805 children and adolescents with type 1 diabetes from the Hvidore Study Group. *Diabetes Care* 24:1342–1347, 2001

123. Cherubini V, Pintaudi B, Rossi MC, Lucisano G, Pellegrini F, Chiumello G, Frongia AP, Monciotti C, Patera IP, Toni S, Zucchini S, Nicolucci A; SHIP-D Study Group: Severe hypoglycemia and ketoacidosis over one year in Italian pediatric population with type 1 diabetes mellitus: a multicenter retrospective observational study. *Nutr Metab Cardiovasc Dis* 24:538–546, 2014
124. Tupola S, Rajantie J, Maenpaa J: Severe hypoglycaemia in children and adolescents during multiple-dose insulin therapy. *Diabet Med* 15:695–699, 1998
125. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:837–853, 1998
126. Shorr RI, Ray WA, Daugherty JR, Griffin MR: Individual sulfonylureas and serious hypoglycemia in older people. *J Am Geriatr Soc* 44:751–755, 1996
127. Shorr RI, Ray WA, Daugherty JR, Griffin MR: Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med* 157:1681–1686, 1997
128. Shorr RI, Ray WA, Daugherty JR, Griffin MR: Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas. *JAMA* 278:40–43, 1997
129. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 355:253–259, 2000
130. Lipska KJ, Ross JS, Wang Y, Inzucchi SE, Minges K, Karter AJ, Huang ES, Desai MM, Gill TM, Krumholz HM: National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. *JAMA Intern Med* 174:1116–1124, 2014
131. Cryer PE, Fisher JN, Shamoon H: Hypoglycemia. *Diabetes Care* 17:734–755, 1994
132. Nordfeldt S, Ludvigsson J: Adverse events in intensively treated children and adolescents with type 1 diabetes. *Acta Paediatr* 88:1184–1193, 1999
133. Andrews MA, O'Malley PG: Diabetes overtreatment in elderly individuals: risky business in need of better management. *JAMA* 311:2326–2327, 2014
134. Tseng CL, Soroka O, Maney M, Aron DC, Pogach LM: Assessing potential glycemic overtreatment in persons at hypoglycemic risk. *JAMA Intern Med* 174:259–268, 2014
135. Jones TW, Boulware SD, Kraemer DT, Caprio S, Sherwin RS, Tamborlane WV: Independent effects of youth and poor diabetes control on responses to hypoglycemia in children. *Diabetes* 40:358–363, 1991
136. Rosilio M, Cotton JB, Wieliczko MC, Gendrault B, Carel JC, Couvaras O, Ser N, Gillet P, Soskin S, Garandeau P, Stuckens C, Le Luyer B, Jos J, Bony-Trifunovic H, Bertrand AM, Leturcq F, Lafuma A; French Pediatric Diabetes Group, Bougneres PF: Factors associated with glycemic control. A cross-sectional nationwide study in 2,579 French children with type 1 diabetes. The French Pediatric Diabetes Group. *Diabetes Care* 21:1146–1153, 1998
137. Fukuda M, Tanaka A, Tahara Y, Ikegami H, Yamamoto Y, Kumahara Y, Shima K: Correlation between minimal secretory capacity of pancreatic beta-cells and stability of diabetic control. *Diabetes* 37:81–88, 1988
138. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the Diabetes Control and Complications Trial. A randomized, controlled trial. The Diabetes Control and Complications Trial Research Group. *Ann Intern Med* 128:517–523, 1998
139. Knip M, Ilonen J, Mustonen A, Akerblom HK: Evidence of an accelerated B-cell destruction in HLA-Dw3/Dw4 heterozygous children with type I (insulin-dependent) diabetes. *Diabetologia* 29:347–351, 1986
140. Dahlquist G, Blom L, Persson B, Wallensteen M, Wall S: The epidemiology of lost residual beta-cell function in short term diabetic children. *Acta Paediatr Scand* 77:852–859, 1988
141. Petersen JS, Dyrberg T, Karlsen AE, Molvig J, Michelsen B, Nerup J, Mandrup-Poulsen T: Glutamic acid decarboxylase (GAD65) autoantibodies in prediction of beta-cell function and remission in recent-onset IDDM after cyclosporin treatment. The Canadian-European Randomized Control Trial Group. *Diabetes* 43:1291–1296, 1994
142. Lteif AN, Schwenk WF 2nd: Type 1 diabetes mellitus in early childhood: glycemic control and associated risk of hypoglycemic reactions. *Mayo Clin Proc* 74:211–216, 1999
143. Cooper MN, O'Connell SM, Davis EA, Jones TW: A population-based study of risk factors for severe hypoglycaemia in a contemporary cohort of childhood-onset type 1 diabetes. *Diabetologia* 56:2164–2170, 2013
144. Hasselmann C, Bonnemaison E, Faure N, Mercat I, Bouillo Pepin-Donat M, Magontier N, Chantepie A, Labarthe F: [Benefits of continuous subcutaneous insulin infusion in children with type 1 diabetes mellitus]. [Article in French] *Arch Pediatr* 19:593–598, 2012
145. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group; Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, Hirsch IB, Huang ES, Kollman C, Kowalski AJ, Laffel L, Lawrence JM, Lee J, Mauras N, O'Grady M, Ruedy KJ, Tansey M, Tsalikian E, Weinzimer S, Wilson DM, Wolpert H, Wysocki T, Xing D: Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 359:1464–1476, 2008
146. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group; Beck RW, Hirsch IB, Laffel L, Tamborlane WV, Bode BW, Buckingham B, Chase P, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, Huang ES, Kollman C, Kowalski AJ, Lawrence JM, Lee J, Mauras N, O'Grady M, Ruedy KJ, Tansey M, Tsalikian E, Weinzimer SA, Wilson DM, Wolpert H, Wysocki T, Xing D: The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care* 32:1378–1383, 2009
147. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329:977–986, 1993
148. Simonson DC, Tamborlane WV, DeFronzo RA, Sherwin RS: Intensive insulin therapy reduces counterregulatory hormone responses to hypoglycemia in patients with type I diabetes. *Ann Intern Med* 103:184–190, 1985
149. Jones TW, Borg WP, Borg MA, Boulware SD, McCarthy G, Silver D, Tamborlane WV, Sherwin RS: Resistance to neuroglycopenia: an adaptive response during intensive insulin treatment of diabetes. *J Clin Endocrinol Metab* 82:1713–1718, 1997

150. Heller SR, Cryer PE: Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. *Diabetes* 40:223–226, 1991
151. Diabetes Research in Children Network (DirecNet) Study Group; Tsalikian E, Kollman C, Tamborlane WB, Beck RW, Fiallo-Scharer R, Fox L, Janz KF, Ruedy KJ, Wilson D, Xing D, Weinzimer SA: Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. *Diabetes Care* 29:2200–2204, 2006
152. van de Wiel A: Diabetes mellitus and alcohol. *Diabetes Metab Res Rev* 20:263–267, 2004
153. Avogaro A, Watanabe RM, Dall'Arche A, De Kreutzenberg SV, Tiengo A, Pacini G: Acute alcohol consumption improves insulin action without affecting insulin secretion in type 2 diabetic subjects. *Diabetes Care* 27:1369–1374, 2004
154. Kerr D, Macdonald IA, Heller SR, Tattersall RB: Alcohol causes hypoglycaemic unawareness in healthy volunteers and patients with type 1 (insulin-dependent) diabetes. *Diabetologia* 33:216–221, 1990
155. Ismail D, Gebert R, Vuillermin PJ, Fraser L, McDonnell CM, Donath SM, Cameron FJ: Social consumption of alcohol in adolescents with type 1 diabetes is associated with increased glucose lability, but not hypoglycaemia. *Diabet Med* 23:830–833, 2006
156. Bargagna S, Tosi B, Calisti L, Crespin L: [Psychopathological aspects in a group of children and adolescent with insulin-dependent diabetes mellitus]. [Article in Italian] *Minerva Pediatr* 49:71–77, 1997
157. Nakazato M, Kodama K, Miyamoto S, Sato M, Sato T: Psychiatric disorders in juvenile patients with insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract* 48:177–183, 2000
158. Kovacs M, Mukerji P, Iyengar S, Drash A: Psychiatric disorder and metabolic control among youths with IDDM. A longitudinal study. *Diabetes Care* 19:318–323, 1996
159. Goldston DB, Kovacs M, Ho VY, Parrone PL, Stiffler L: Suicidal ideation and suicide attempts among youth with insulin-dependent diabetes mellitus. *J Am Acad Child Adolesc Psychiatry* 33:240–246, 1994
160. Kovacs M, Goldston D, Obrosky DS, Bonar LK: Psychiatric disorders in youths with IDDM: rates and risk factors. *Diabetes Care* 20:36–44, 1997
161. Blanz BJ, Rensch-Riemann BS, Fritz-Sigmund DI, Schmidt MH: IDDM is a risk factor for adolescent psychiatric disorders. *Diabetes Care* 16:1579–1587, 1993
162. Leong KS, Wallymahmed M, Wilding J, MacFarlane I: Clinical presentation of thyroid dysfunction and Addison's disease in young adults with type 1 diabetes. *Postgrad Med J* 75:467–470, 1999
163. Rewers M, Liu E, Simmons J, Redondo MJ, Hoffenberg EJ: Celiac disease associated with type 1 diabetes mellitus. *Endocrinol Metab Clin North Am* 33:197–214, xi, 2004
164. McAulay V, Frier BM: Addison's disease in type 1 diabetes presenting with recurrent hypoglycaemia. *Postgrad Med J* 76:230–232, 2000
165. Phornphutkul C, Boney CM, Gruppuso PA: A novel presentation of Addison disease: hypoglycemia unawareness in an adolescent with insulin-dependent diabetes mellitus. *J Pediatr* 132:882–884, 1998
166. Nielsen LR, Pedersen-Bjergaard U, Thorsteinsson B, Johansen M, Damm P, Mathiesen ER: Hypoglycemia in pregnant women with type 1 diabetes: predictors and role of metabolic control. *Diabetes Care* 31:9–14, 2008
167. Weir MA, Gomes T, Mamdani M, Juurlink DN, Hackam DG, Mahon JL, Jain AK, Garg AX: Impaired renal function modifies the risk of severe hypoglycaemia among users of insulin but not glyburide: a population-based nested case-control study. *Nephrol Dial Transplant* 26:1888–1894, 2011
168. Yun JS, Ko SH, Ko SH, Song KH, Ahn YB, Yoon KH, Park YM, Ko SH: Presence of macroalbuminuria predicts severe hypoglycemia in patients with type 2 diabetes: a 10-year follow-up study. *Diabetes Care* 36:1283–1289, 2013
169. Nishimura R, LaPorte RE, Dorman JS, Tajima N, Becker D, Orchard TJ: Mortality trends in type 1 diabetes. The Allegheny County (Pennsylvania) Registry 1965–1999. *Diabetes Care* 24:823–827, 2001
170. DiLiberti JH, Lorenz RA: Long-term trends in childhood diabetes mortality: 1968–1998. *Diabetes Care* 24:1348–1352, 2001
171. Weston PJ, Gill GV: Is undetected autonomic dysfunction responsible for sudden death in type 1 diabetes mellitus? The 'dead in bed' syndrome revisited. *Diabet Med* 16:626–631, 1999
172. Sovik O, Thordarson H: Dead-in-bed syndrome in young diabetic patients. *Diabetes Care* 22(Suppl 2):B40–B42, 1999
173. Jones TW, Porter P, Sherwin RS, Davis EA, O'Leary P, Frazer F, Byrne G, Stick S, Tamborlane WV: Decreased epinephrine responses to hypoglycemia during sleep. *N Engl J Med* 338:1657–1662, 1998
174. Golden MP, Ingersoll GM, Brack CJ, Russell BA, Wright JC, Huberty TJ: Longitudinal relationship of asymptomatic hypoglycemia to cognitive function in IDDM. *Diabetes Care* 12:89–93, 1989
175. Rovet JF, Ehrlich RM, Hoppe M: Specific intellectual deficits in children with early onset diabetes mellitus. *Child Dev* 59:226–234, 1988
176. Rovet JF, Ehrlich RM, Czuchta D: Intellectual characteristics of diabetic children at diagnosis and one year later. *J Pediatr Psychol* 15:775–788, 1990
177. Ryan C, Vega A, Drash A: Cognitive deficits in adolescents who developed diabetes early in life. *Pediatrics* 75:921–927, 1985
178. Rovet JF, Ehrlich RM: The effect of hypoglycemic seizures on cognitive function in children with diabetes: a 7-year prospective study. *J Pediatr* 134:503–506, 1999
179. Kaufman FR, Epport K, Engilman R, Halvorson M: Neurocognitive functioning in children diagnosed with diabetes before age 10 years. *J Diabetes Complications* 13:31–38, 1999
180. Hagen JW, Barclay CR, Anderson BJ, Feeman DJ, Segal SS, Bacon G, Goldstein GW: Intellective functioning and strategy use in children with insulin-dependent diabetes mellitus. *Child Dev* 61:1714–1727, 1990
181. Ryan CM, Williams TM, Finegold DN, Orchard TJ: Cognitive dysfunction in adults with type 1 (insulin-dependent) diabetes mellitus of long duration: effects of recurrent hypoglycaemia and other chronic complications. *Diabetologia* 36:329–334, 1993
182. Eeg-Olofsson O, Petersen I: Childhood diabetic neuropathy; a clinical and neurophysiological study. *Acta Paediatr Scand* 55:163–176, 1966
183. Schlack H, Palm D, Jochmus I: [Influence of recurrent hypoglycemia on the EEG of the diabetic child]. [Article in German] *Monatsschr Kinderheilkd* 117:251–253, 1969
184. Gilhaus KH, Daweke H, Lulsdorf HG, Sachsse R, Sachsse B: [EEG changes in diabetic children]. [Article in German] *Dtsch Med Wochenschr* 98:1449–1454, 1973
185. Soltesz G, Acsadi G: Association between diabetes, severe hypoglycaemia, and electroencephalographic abnormalities. *Arch Dis Child* 64:992–996, 1989
186. Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. *Ann Intern Med* 124:379–388, 1996
187. Austin EJ, Deary IJ: Effects of repeated hypoglycemia on cognitive function: a psychometrically validated reanalysis of

the Diabetes Control and Complications Trial data. *Diabetes Care* 22:1273–1277, 1999
188. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group; Jacobson AM, Musen G, Ryan CM, Silvers N, Cleary P, Waberski B, Burwood A, Weinger K, Bayless M, Dahms W, Harth J: Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med* 356:1842–1852, 2007
189. Arbelaez AM, Semenkovich K, Hershey T: Glycemic extremes in youth with T1DM: the structural and functional integrity of the developing brain. *Pediatr Diabetes* 14:541–553, 2013
190. Hammer M, Lammert M, Mejias SM, Kern W, Frier BM: Costs of managing severe hypoglycaemia in three European countries. *J Med Econ* 12:281–290, 2009
191. Karter AJ, Ackerson LM, Darbinian JA, D'Agostino RB, Jr., Ferrara A, Liu J, Selby JV: Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente Diabetes registry. *Am J Med* 111:1–9, 2001
192. Kubiak T, Hermanns N, Schreckling HJ, Kulzer B, Haak T: Evaluation of a self-management-based patient education program for the treatment and prevention of hypoglycemia-related problems in type 1 diabetes. *Patient Educ Couns* 60:228–234, 2006
193. Boland EA, Grey M, Oesterle A, Fredrickson L, Tamborlane WV: Continuous subcutaneous insulin infusion. A new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care* 22:1779–1784, 1999
194. Maniatis AK, Klingensmith GJ, Slover RH, Mowry CJ, Chase HP: Continuous subcutaneous insulin infusion therapy for children and adolescents: an option for routine diabetes care. *Pediatrics* 107:351–356, 2001
195. Chase HP, Lockspeiser T, Peery B, Shepherd M, Mackenzie T, Anderson J, Garg SK: The impact of the Diabetes Control and Complications Trial and Humalog insulin on glycohemoglobin levels and severe hypoglycemia in type 1 diabetes. *Diabetes Care* 24:430–434, 2001
196. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA: Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. *Diabetes Care* 23:639–643, 2000
197. Raskin P, Klaff L, Bergenstal R, Halle JP, Donley D, Mecca T: A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. *Diabetes Care* 23:1666–1671, 2000
198. Mohn A, Strang S, Wernicke-Panten K, Lang AM, Edge JA, Dunger DB: Nocturnal glucose control and free insulin levels in children with type 1 diabetes by use of the long-acting insulin HOE 901 as part of a three-injection regimen. *Diabetes Care* 23:557–559, 2000
199. Boland E, Monsod T, Delucia M, Brandt CA, Fernando S, Tamborlane WV: Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. *Diabetes Care* 24:1858–1862, 2001
200. Chase HP, Kim LM, Owen SL, MacKenzie TA, Klingensmith GJ, Murtfeldt R, Garg SK: Continuous subcutaneous glucose monitoring in children with type 1 diabetes. *Pediatrics* 107:222–226, 2001
201. UK Hypoglycaemia Study Group: Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 50:1140–1147, 2007
202. Clarke WL, Anderson S, Farhy L, Breton M, Gonder-Frederick L, Cox D, Kovatchev B: Evaluating the clinical accuracy of two continuous glucose sensors using continuous glucose-error grid analysis. *Diabetes Care* 28:2412–2417, 2005
203. Fayolle C, Brun JF, Bringer J, Mercier J, Renard E: Accuracy of continuous subcutaneous glucose monitoring with the GlucoDay in type 1 diabetic patients treated by subcutaneous insulin infusion during exercise of low versus high intensity. *Diabetes Metab* 32:313–320, 2006
204. Maia FF, Araujo LR: Efficacy of continuous glucose monitoring system to detect unrecognized hypoglycemia in children and adolescents with type 1 diabetes. *Arq Bras Endocrinol Metabol* 49:569–574, 2005
205. Streja D: Can continuous glucose monitoring provide objective documentation of hypoglycemia unawareness? *Endocr Pract* 11:83–90, 2005
206. Renard E, Costalat G, Chevassus H, Bringer J: Artificial beta-cell: clinical experience toward an implantable closed-loop insulin delivery system. *Diabetes Metab* 32:497–502, 2006
207. Sherr JL, Cengiz E, Palerm CC, Clark B, Kurtz N, Roy A, Carria L, Cantwell M, Tamborlane WV, Weinzimer SA: Reduced hypoglycemia and increased time in target using closed-loop insulin delivery during nights with or without antecedent afternoon exercise in type 1 diabetes. *Diabetes Care* 36:2909–2914, 2013
208. Hovorka R, Elleri D, Thabit H, Allen JM, Leelarathna L, El-Khairi R, Kumareswaran K, Caldwell K, Calhoun P, Kollman C, Murphy HR, Acerini CL, Wilinska ME, Nodale M, Dunger DB: Overnight closed-loop insulin delivery in young people with type 1 diabetes: a free-living, randomized clinical trial. *Diabetes Care* 37:1204–1211, 2014
209. Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, Ahmann AJ, Welsh JB, Lee SW, Kaufman FR; ASPIRE In-Home Study Group: Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med* 369:224–232, 2013
210. Halvorson M, Carpenter S, Kaiserman K, Kaufman FR: A pilot trial in pediatrics with the sensor-augmented pump: combining real-time continuous glucose monitoring with the insulin pump. *J Pediatr* 150:103–105.e1, 2007
211. Svoren BM, Volkening LK, Butler DA, Moreland EC, Anderson BJ, Laffel LM: Temporal trends in the treatment of pediatric type 1 diabetes and impact on acute outcomes. *J Pediatr* 150:279–285, 2007