JAMA | Review

Type 1 Diabetes
A Review

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IMPORTANCE Type 1 diabetes is defined by hyperglycemia due to autoimmune destruction of the insulin-producing beta cells in the pancreas, leading to insulin deficiency, and accounts for 5% to 10% of all cases of diabetes. Type 1 diabetes affects approximately 2 million people in the US and 8.4 million people worldwide and is associated with microvascular and macrovascular complications such as retinopathy, nephropathy, neuropathy, and cardiovascular disease.

OBSERVATIONS Ninety percent to 95% of people with type 1 diabetes have at least 1 autoantibody when they are diagnosed with diabetes. These autoantibodies include autoantibodies to insulin, glutamic acid decarboxylase 65, insulinoma-associated 2, and zinc transporter 8 autoantibodies and are absent in type 2 diabetes or monogenic diabetes (a rarer form of diabetes caused by a single genetic variant). These autoantibodies are present before clinical symptoms develop and can identify early stages of type 1 diabetes. Up to 44% of children and 23% of adults with type 1 diabetes present with diabetes-related ketoacidosis. Type 1 diabetes is most commonly diagnosed between ages 10 and 14 years, but the median age of diagnosis in the US is 24 years. People with type 1 diabetes require lifelong insulin replacement, which can be administered via subcutaneous injection or insulin pump. Insulin regimens that mimic normal physiology include long-acting basal insulin (eg, glargine or degludec) administered once to twice daily and rapid-acting bolus insulin (eg, aspart or lispro) administered prior to meals that contain carbohydrates and during periods of hyperglycemia. Randomized clinical trials have demonstrated that continuous glucose monitors with insulin pumps, which automatically adjust insulin delivery in response to glucose levels, result in less hypoglycemia and improved hemoglobin A_{1c} levels (with the greatest improvement occurring in those with higher starting levels [eg, >8.0%]).

CONCLUSIONS AND RELEVANCE Type 1 diabetes accounts for 5% to 10% of all cases of diabetes and is characterized by the presence of islet autoantibodies in 90% to 95% of patients. Lifelong use of insulin therapy is currently required for treatment of type 1 diabetes.

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Type 1 diabetes affects approximately 2 million people in the US and 8.4 million people worldwide.[1,2] Approximately 0.5 million new cases of type 1 diabetes are diagnosed per year worldwide.[1] Although type 1 diabetes can be diagnosed at any age, it is most commonly diagnosed between ages 10 and 14 years. In 2021, the median age at diagnosis was 29 years worldwide, and in 2016-2022 the median age at diagnosis was 24 years in the US.[1,3,4] Onset of type 1 diabetes is more common in fall and winter, likely because viral infections, which precipitate hyperglycemia in people who are developing type 1 diabetes, are more common in fall and winter.[5,6] While prevalence of type 1 diabetes is higher in first-degree relatives of people with type 1 diabetes (6% vs 0.4% in the general population), 85% of people diagnosed with type 1 diabetes do not have a first-degree relative with the disease.[7,8]

This review summarizes current evidence regarding diagnosis and treatment of type 1 diabetes.

Methods

We searched PubMed from January 1, 2015, to September 30, 2025, for English-language articles. We prioritized randomized clinical trials (RCTs) and meta-analyses that included only people with type 1 diabetes. References of identified articles were manually searched for additional articles. Of 1438 identified articles, 123 were included, consisting of 51 RCTs, 13 meta-analyses, 29 longitudinal cohort studies, 24 clinical practice guidelines, and 6 preclinical or translational research studies. For reference, to convert glucose values from mg/dL to mmol/L, multiply by 0.0555. To

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convert hemoglobin A_{1c} (HbA_{1c}) values to mmol/mol, use the following equation: (10.93 × HbA_{1c}[%]) − 23.50.

Pathophysiology

Type 1 diabetes consists of an acquired insulin deficiency due to autoimmune-mediated destruction of pancreatic beta cells. Insulin is a peptide hormone secreted continuously at a low level from the beta cells within the pancreatic islets. In response to eating and rising glucose levels, insulin secretion increases. Enzymatic steps in the synthesis of insulin include production of a prohormone, proinsulin, which is cleaved into mature insulin and a connecting peptide (C-peptide). Insulin and C-peptide are secreted from the beta cell in equimolar amounts, but C-peptide is the preferred diagnostic test of endogenous insulin production because it has a longer half-life (30 minutes compared with 5 minutes for insulin), is not increased or decreased by insulin antibodies, and is not a component of exogenous insulin.

The autoimmune process in type 1 diabetes involves the adaptive and innate immune responses.[9] Islet-specific autoantigens direct CD8 T cells to the pancreatic islet, where they bind to the antigen-specific class I major histocompatibility complex on the beta cell surface, causing release of perforin and granzyme B, which leads to beta cell apoptosis (**Figure 1**). People with type 1 diabetes may have defects in the beta cell, such as altered prohormone processing, that facilitate the development of autoimmunity.[10] In type 1 diabetes, the endoplasmic reticulum within the beta cell, which is responsible for insulin synthesis and protein folding, accumulates misfolded proteins, including abnormal accumulations of proinsulin,[10] which contributes to beta cell death and the release of islet autoantigens into the peripheral circulation. Islet-specific autoantibodies form in response to islet autoantigens detected in the circulation and are a marker of disease activity but are not directly pathogenic.

Type 1 diabetes can be detected prior to symptom onset by the presence of multiple islet autoantibodies, such as glutamic acid decarboxylase 65 autoantibodies, insulin autoantibodies, insulinoma-associated 2 antigen autoantibodies, or zinc transporter 8 autoantibodies, accompanied by normoglycemia with fasting glucose level less than 100 mg/dL, 2-hour glucose level less than 140 mg/dL after an oral glucose tolerance test (OGTT), and/or HbA_{1c} level less than 5.7% (termed stage 1) (Figure 1). People with stage 1 type 1 diabetes have a nearly 100% lifetime risk of developing symptomatic type 1 diabetes.[11] As the disease progresses, patients develop dysglycemia (termed stage 2), defined by 1 or more of the following: fasting glucose level of 100 to 125 mg/dL, stimulated glucose during an OGTT of 200 mg/dL or greater at 30, 60, or 90 minutes after oral glucose load or 2-hour glucose level of 140 to 199 mg/dL, HbA_{1c} level of 5.7% to 6.4%, or a 10% or greater rise in HbA_{1c} level. Subsequently, continued beta cell destruction leads to stage 3 type 1 diabetes, defined as fasting glucose level 126 mg/dL or greater, 2-hour glucose level of 200 mg/dL or greater during an OGTT, or HbA_{1c} level 6.5% or greater (**Figure 2**). Hyperglycemia and often symptoms of diabetes (described below) are seen in stage 3 type 1 diabetes. This process, from stage 1 to stage 3, typically takes many years but may progress more rapidly (months to years) in prepubertal children.[11]

Clinical Presentation

At time of diagnosis, characteristic symptoms of type 1 diabetes include polydipsia, polyuria, and weight loss. Polyuria develops when plasma glucose exceeds the kidney's ability to resorb it (>180 mg/dL), so glucose is excreted in the urine, creating an osmotic effect that draws water into the urine. The resulting fluid loss causes dehydration and polydipsia. Ketones are also osmotically active and contribute to polyuria and dehydration. Additional symptoms of type 1 diabetes may include increased hunger (polyphagia), fatigue, or blurred vision (swelling in the lens of the eye due to chronically elevated blood glucose drawing in water).

Urinary excretion of glucose in addition to lipolysis (ie, fat breakdown) from insulin deficiency causes weight loss. Without insulin, glucose accumulates in the blood because muscle and fat (adipocytes) cannot bring glucose transporters (specifically GLUT4 [glucose transporter 4]) to the cell surface to allow glucose to enter. When glucose is unavailable to muscle and other cells in the body for energy, the liver generates ketone bodies from fatty acids released from adipocytes, producing an alternative source of energy. Ketone bodies are acidic, and accumulation in the blood can cause abdominal pain, nausea, vomiting, and Kussmaul breathing (a deep and rapid breathing pattern that occurs to exhale excess carbon dioxide and reduce blood acidity).

Diabetes-related ketoacidosis (DKA), which involves hyperglycemia, ketonemia, and acidosis, is caused by insulin deficiency and is often present at diagnosis of type 1 diabetes (stage 3). Viral illness, other infections, or acute inflammatory conditions such as myocardial infarction (MI) can rapidly increase plasma glucose levels due to increased release of hormones such as glucagon, cortisol, growth hormone, and catecholamines. These counterregulatory hormones accelerate glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis.[12] In an analysis of registries of 9269 children newly diagnosed with type 1 diabetes in 7 European countries, New Zealand, and the US, 34.2% presented with DKA.[13] In a study of 18 European diabetes centers, DKA at diagnosis occurred in 32.8% of children (aged 1-9 years [n = 279]), 43.9% of adolescents (aged 10-17 years [n = 270]), and 23.0% of adults (mean age, 28.0 [SD, 7.2] years [n = 100]).[14]

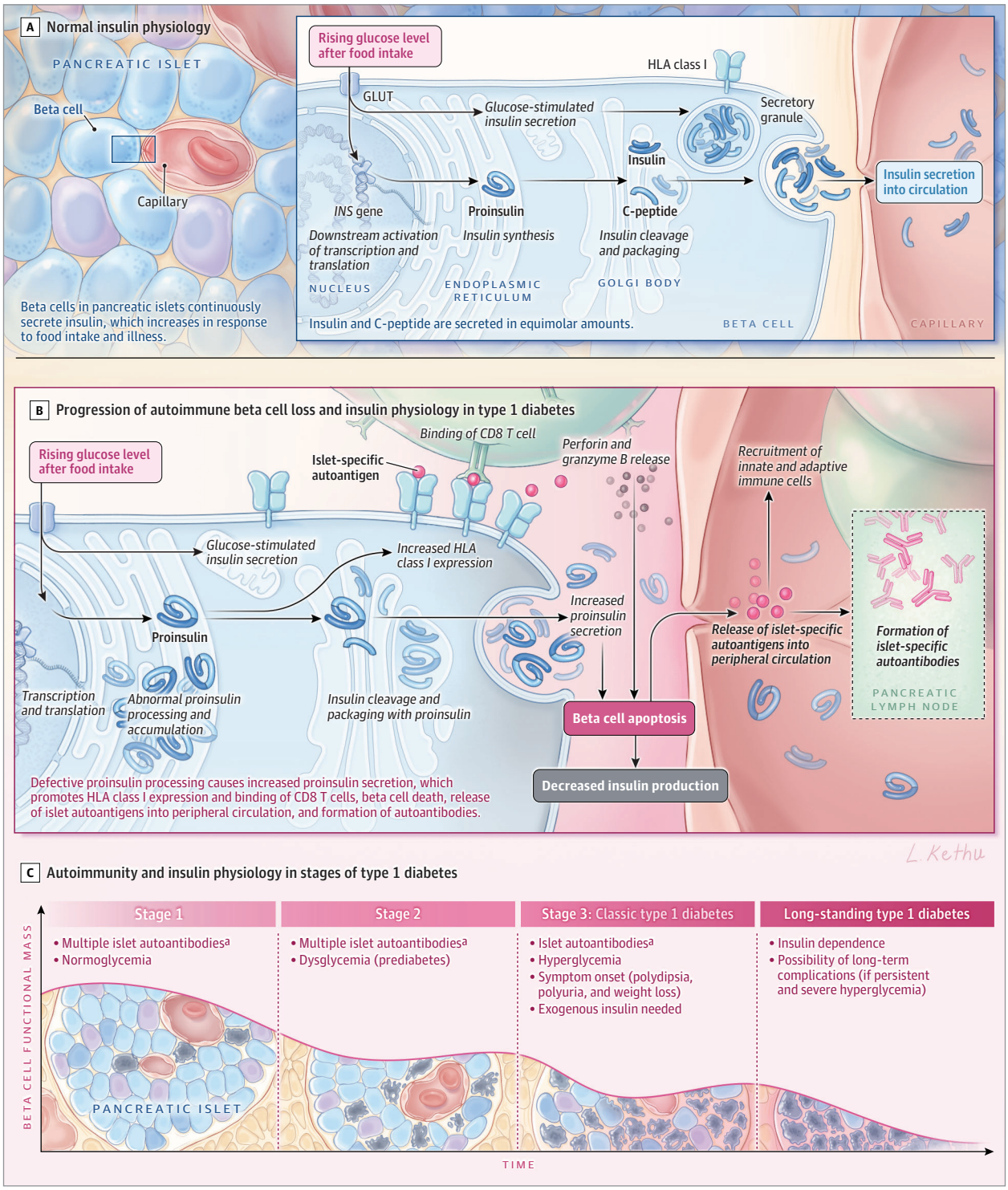
Young children (infants to approximately age 5 years) with type 1 diabetes may present with nonspecific symptoms such as irritability, lethargy, secondary nocturnal enuresis (ie, urinary incontinence at night in a child who was previously dry at night), perineal candidiasis (due to glucosuria), nausea, and vomiting.[15] These nonspecific symptoms may delay the diagnosis of type 1 diabetes by weeks and even months in young children.[15] Delay of months to years may occur for adults with type 1 diabetes, when the diagnosis is missed because patients are assumed to have type 2 diabetes. Ninety percent to 95% of adults with diabetes have type 2 diabetes.[2]

Diagnosis

The American Diabetes Association (ADA) defines type 1 diabetes as the presence of classic symptoms, such as polyuria, polydipsia, and weight loss, in combination with a single random plasma glucose level of 200 mg/dL or greater or, if classic symptoms are ab-

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Figure 1. The Pathophysiology, Natural History, and Stages of Type 1 Diabetes



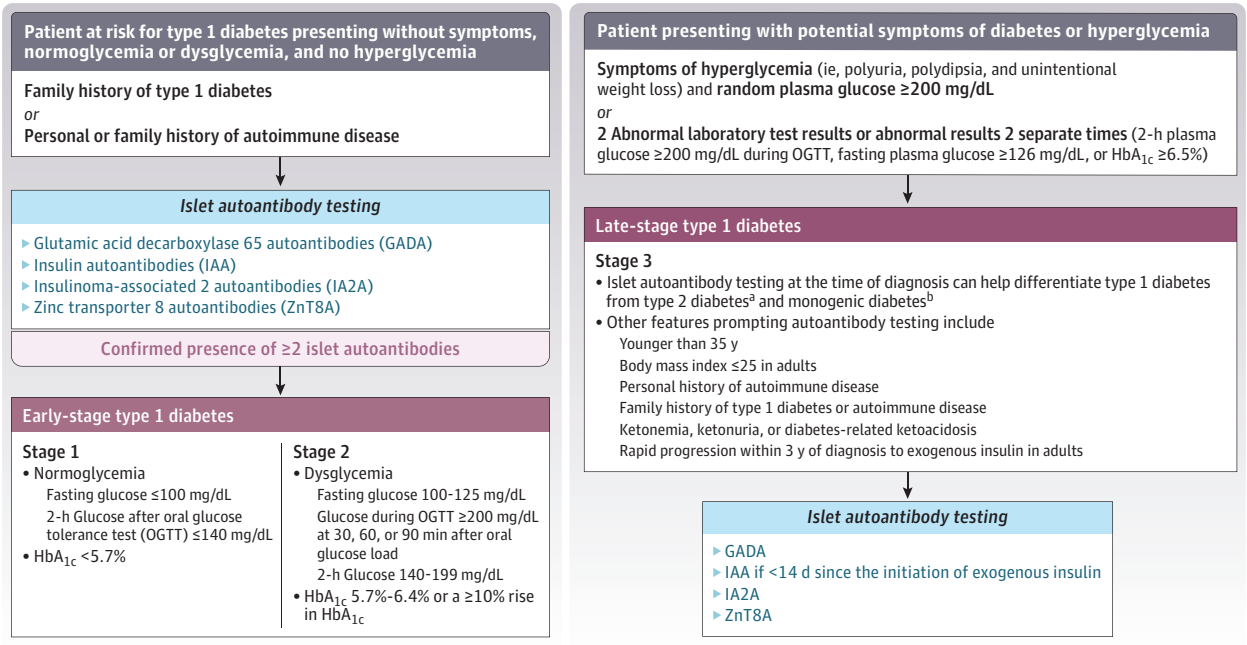
GLUT indicates glucose transporter protein; HLA, human leukocyte antigen.

[a]Possible islet autoantibodies include insulin autoantibodies and antibodies to glutamic acid decarboxylase 65, insulinoma-associated 2 antigen, and zinc transporter 8.

sent, 2 abnormal plasma glucose test results (defined as fasting glucose level ≥126 mg/dL, 2-hour glucose level ≥200 mg/dL during OGTT, or HbA_{1c} level ≥6.5%) (Figure 2).[12] Confirmation of type 1 diabetes is typically recommended by measuring islet autoantibody levels.[16,17] Islet autoantibodies include insulin autoantibodies, glutamic acid decarboxylase 65 autoantibodies, insulinoma-

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Figure 2. Flowchart for the Diagnosis of Diabetes Mellitus With Considerations for Islet Autoantibody Testing



To convert glucose values to mmol/L, multiply by 0.0555. Body mass index calculated as weight in kilograms divided by square of height in meters. This algorithm has not been validated. HbA_{1c} indicates hemoglobin A_{1c}.

[a]Type 2 diabetes may present with increased body mass index, less marked hyperglycemia, longer prodrome of milder symptoms prior to diagnosis, signs of metabolic syndrome, and/or insulin resistance.

[b]Monogenic diabetes may present with consecutive generations in the family with diabetes or syndromic features that may be seen in certain variants (eg, deafness, severe insulin resistance without obesity, partial lipodystrophy, kidney cysts).

associated 2 autoantibodies, and zinc transporter 8 autoantibodies. Ninety percent to 95% of people with type 1 diabetes have at least 1 islet autoantibody at the time of diagnosis, the most common being glutamic acid decarboxylase 65 autoantibodies. The diagnosis of type 1 diabetes in adults can be more challenging, and while testing all adults with new-onset diabetes is not practical, the presence of unintentional weight loss, body mass index less than 25 (calculated as weight in kilograms divided by square of height in meters), personal history of autoimmune disease, family history of type 1 diabetes (or other autoimmune disease), ketonemia/ketonuria or DKA, or rapid progression to the need for insulin can be used to direct islet autoantibody testing (Figure 2).

C-peptide may be helpful as part of the diagnostic process. An undetectable C-peptide level can confirm the diagnosis of type 1 diabetes, because it indicates a very low level of endogenous insulin production. However, early in type 1 diabetes the C-peptide level may be normal. Obesity and insulin resistance can increase insulin and C-peptide secretion, which may confound the diagnosis. The prevalence of obesity in adolescents and adults with type 1 diabetes is similar to the rate of obesity in the general population.[18]

Latent autoimmune diabetes in adults (LADA) is defined by the World Health Organization as a slowly evolving immune-related diabetes. LADA consists of a slow progressive loss of endogenous insulin, occurs in adults after age 35 years, and may present with features of type 1 (eg, weight loss or history of other autoimmune disease) or type 2 (eg, obesity and acanthosis nigricans [sign of insulin resistance]) diabetes. It remains unclear whether LADA represents a milder form of type 1 diabetes, type 2 diabetes, or a unique form of diabetes.[17,19] Another form of diabetes that may confound the diagnosis is monogenic diabetes, also called maturity-onset diabetes of the young. People with monogenic diabetes typically develop symptoms during adolescence and young adulthood (<25 years) that occurs in consecutive generations in the family due to its autosomal dominant inheritance, is autoantibody negative, and may include features associated with genetic variants (eg, deafness, severe insulin resistance without obesity, partial lipodystrophy, kidney cysts).

Screening first-degree relatives of people with type 1 diabetes for islet autoantibodies with or without genetic testing for high-risk alleles such as human leukocyte antigen (HLA) DR3 or DR4 is recommended by the ADA[16] and International Society for Pediatric and Adolescent Diabetes.[20] While no RCTs have shown that testing first-degree relatives for autoantibodies improves health outcomes, many longitudinal studies documented reductions in DKA prevalence at diagnosis among people identified by autoantibody screening.[21-28]

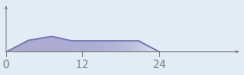
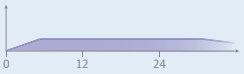
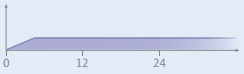
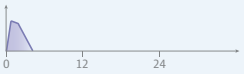
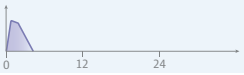
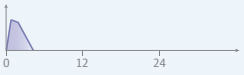
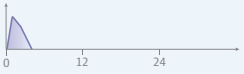
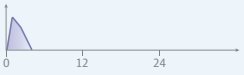
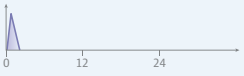
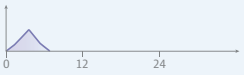
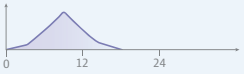
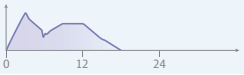
Treatment

Insulin

All people with stage 3 type 1 diabetes require treatment with insulin, which can be administered by multiple daily subcutaneous injections (via insulin pen or syringe) or by a continuous subcutaneous insulin infusion (ie, an insulin pump). No RCTs have assessed the

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Figure 3. Insulin Regimen and Dosing Descriptions

	Insulin examples[a]	Onset/duration of action	Concentration over 24 h	Frequency of administration[b]
Basal insulins (background insulin to suppress lipolysis)	**Glargine (U-100)**[c,d]	1-3 h/24 h		Fixed dose and fixed time of day once or twice daily
	Glargine (U-300)[c,d]	1-6 h/24-36 h		Fixed dose and fixed time of day once or twice daily
	Degludec	1-3 h/24-42 h		Fixed dose and fixed time of day once daily
Bolus insulins[e] (insulin given in response to hyperglycemia and carbohydrate ingestion[b])	**Aspart**	10-20 min/3-4 h		Variable or fixed dose, 10-20 min before meals Administer for hyperglycemia if needed
	Lispro	10-20 min/3-4 h		Variable or fixed dose, 10-20 min before meals Administer for hyperglycemia if needed
	Glulisine	10-20 min/3-4 h		Variable or fixed dose, 10-20 min before meals Administer for hyperglycemia if needed
	Aspart with niacinamide	5-15 min/3-4 h		Variable or fixed dose, 5-15 min before meals Administer for hyperglycemia if needed
	Lispro-aabc	5-15 min/3-4 h		Variable or fixed dose, 5-15 min before meals Administer for hyperglycemia if needed
	Regular human insulin powder	5-12 min/1.5-2 h		Variable or fixed dose, 0-12 min before meals (inhaled) Administer for hyperglycemia if needed
Older insulins (not standard of care)	**Regular human insulin**	30-60 min/6-8 h		Variable or fixed dose, 30 min before meals Administer for hyperglycemia if needed
	Neutral protamine Hagedorn (NPH)	1-3 h/12-18 h		Fixed dose, fixed time, twice daily
	Aspart 70/30 (70% aspart protamine/30% aspart)	Aspart protamine: 1-3 h/12-18 h or longer Aspart: 10-20 min/3-4 h		Fixed dose, fixed time, twice daily
	Lispro 75/25 (75% lispro protamine/25% lispro)	Lispro protamine: 1-3 h/12-18 h or longer Lispro: 10-20 min/3-4 h		Fixed dose, fixed time, twice daily
	Lispro 50/50 (50% lispro protamine/50% lispro)	Lispro protamine: 1-3 h/12-18 h or longer Lispro: 10-20 min/3-4 h		Fixed dose, fixed time, twice daily
	NPH/Regular (70% NPH/30% regular)	NPH: 1-3 h/12-18 h Regular: 30-60 min/6-8 h		Fixed dose, fixed time, twice daily

[a]All administrated subcutaneously except for regular human insulin powder, which is inhaled.

[b]Typical insulin pens come at a concentration of 100 units of insulin per mL (U-100). More concentrated formulations are available (eg, glargine U-300, lispro U-200, lispro-aabc U-200, regular human insulin U-500). Of note when using concentrated insulin pens, the insulin should not be drawn out of the pen with a syringe due to the risk for overdose.

[c]Including biosimilars.

[d]If blood glucose level is less than 100 mg/dL (5.55 mmol/L), rapid-acting insulin may be administered just prior to eating.

[e]The sensitivity factor in a 45-kg (99.2-lb) person would be 1 unit of rapid-acting insulin needed for every 40 mg/dL (2.22 mmol/L) that the glucose level is above the target (eg, 150 mg/dL [8.32 mmol/L]). The carbohydrate ratio for a 45-kg person would be 1 unit of rapid-acting insulin for every 10 g of carbohydrates.

optimal time that insulin should be initiated for individuals without symptomatic hyperglycemia.[29]

For individuals taking multiple daily injections, insulin can be administered as a daily (or twice daily) long-acting insulin (basal insulin) (such as glargine or degludec) combined with rapid-acting insulin (such as aspart, lispro, or glulisine) administered at mealtimes and as needed (bolus insulin) (**Figure 3**). Insulin administered in this basal-bolus regimen most closely mimics endogenous insulin secretion because the pancreas endogenously and continuously releases 30% to 50% of total daily insulin needs continuously through-

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Table 1. Glucose Monitoring and Insulin Delivery Technologies for Type 1 Diabetes

Type of technology and examples	Method of measurement	Duration of use	Considerations	Limitations
Continuous glucose monitors				
Dexcom G6/G7 Libre 2+/3/3+ Libre 2 (requires scanning of the device to obtain readings) Medtronic Guardian Connect	Sensor worn on the skin with thin filament inserted to measure interstitial glucose every 1-5 min	7-15 d for the sensors	Rapidly rising or falling glucose levels can be detected and treated Alarms may prevent missed hypoglycemia Data can be shared through a smartphone	CGM and glucometer may differ by up to 20% above or below Glucometer is the preferred test when there is a discrepancy Skin sensitivities to adhesives
Eversence 365[a]	Removable transmitter worn on the skin with small sensor placed under the skin of the outer upper arm to measure interstitial glucose every 5 min	1 y for the sensor	Rapidly rising or falling glucose levels can be detected and treated Alarms may alert people to an impending hypoglycemic event	Placement requires a trained professional
Insulin pens with Bluetooth to connect to mobile app				
Medtronic InPen and InPen app Novo Nordisk NovoPen Echo Lilly Diabetes Tempo Pen and TempoSmart app Abbott Unity Pen and Unity app	Insulin pens that contain Bluetooth or have a device that can be attached to an insulin pen that can record insulin doses on an accompanying app	Insulin: ≈1 mo Device: ≈1 y	App records insulin dosing App can assist with insulin dose calculations	Insulin pen must go with the patient to all locations for the app to provide benefit
Insulin pumps				
Automated insulin delivery (AID) systems Tandem T-slim X2 or Mobi[a] Insulet Omnipod 5[b] Medtronic 780G Beta Bionics iLet Sequel Med Tech twiist[a]	Insulin pumps deliver insulin every 5 min in preprogrammed rates and have algorithms to adjust insulin delivery in response to high/low glucose levels in addition to rapidly rising or falling glucose levels from the CGM	2-3 d for the part worn on the body (7 d for Medtronic extended infusion set and Tandem SteadiSet)	Tubed device: tube connecting the pump device (that contains the reservoir of insulin) to the infusion set (cannula located subcutaneously and taped in place) Tubeless device: all components are contained in a single device worn on the body	Skin sensitivity to the device adhesive is common (self-reported in up to 93% of individuals)[49]

Abbreviation: CGM, continuous glucose monitor.

[a] Requires a smartphone to operate.

[b] Requires a smartphone to initiate CGM.

out the day (basal) to suppress glucagon release, lipolysis, and proteolysis. In addition, the pancreas releases a bolus of insulin in response to food and in response to acute rises in glucose.

At diagnosis of type 1 diabetes, total exogenous insulin requirements typically range from 0.4 to 1.0 unit/kg per day. For adolescents and adults presenting with DKA at the time of diagnosis of stage 3 type 1 diabetes, typical dosing is 1.0 unit/kg per day with 30% to 50% of the total dose given as long-acting basal insulin.[30] Hyperglycemia and hypoglycemia are reduced using newer, long-acting insulins compared with older, intermediate-acting insulins.[31-38] A meta-analysis of 27 RCTs in adults with type 1 diabetes (n = 7394) reported that, compared with older intermediate-acting insulin (such as neutral protamine Hagedorn), long-acting insulins such as glargine and detemir were associated with lower HbA_{1c} values (mean difference, −0.31% [95% CI, −0.48% to −0.14%]).[31]

Rapid-acting insulins (such as aspart, lispro, and glulisine), ultrarapid-acting insulins (such as aspart with nicotinamide and lispro-aabc), or inhaled insulin (such as regular human insulin powder) that treat acute rises in glucose levels should be administered approximately 0 to 30 minutes prior to eating (preprandial insulin) (Figure 3). Dosing is often determined through calculation of an insulin sensitivity factor (previously termed the sliding scale) and a carbohydrate ratio. The insulin sensitivity factor is defined by change in glucose in response to 1 unit of rapid-acting or ultrarapid-acting insulin and can be estimated by 1800 divided by weight in kilograms. The carbohydrate ratio is defined by the grams of carbohydrates ingested per unit of insulin and can be estimated by 450 divided by weight in kilograms. In 9 RCTs that included 608 children and 3295 adults with type 1 diabetes, compared with rapid-acting insulins, ultrarapid insulins administered via injection or insulin pump were associated with lower 1-hour postprandial glucose values but no difference in HbA_{1c} values[39-47]; for example, in adults with more than 1 year duration of type 1 diabetes (n = 472) using the same pump for at least 6 months, those who used faster aspart insulin had an estimated treatment difference in 1-hour postprandial glucose of −16.4 mg/dL (95% CI, −25.7 to −7.0; P = .001) compared with aspart insulin with noninferior change in HbA_{1c} (−0.1% for both treatment groups).[47] Among 122 adults with type 1 diabetes randomized to either inhaled insulin or ultrarapid-acting insulin, inhaled insulin was associated with lower mean postprandial peak glucose values (248 [SD, 65] mg/dL vs 268 [SD, 58] mg/dL; P = .02).[48] Inhaled insulin is inhaled into the lungs and rapidly absorbed into the bloodstream, which attains faster onset and clearance, but is contraindicated in those with underlying lung disease.

Glucose Monitoring and Insulin Delivery

Glucose readings from a glucometer (capillary blood acquired via fingerstick) are typically obtained while fasting, preprandially and prior to bedtime and have been largely replaced by continuous glucose monitoring (CGM) (**Table 1**), which is typically a device worn on the

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body for 7 to 15 days that measures glucose readings obtained from the interstitial fluid that surrounds the cells just under the skin every 1 to 5 minutes. These data inform insulin dose adjustments. Insulin pumps can deliver rapid or ultrarapid-acting insulin 6 to 9 mm into subcutaneous tissue below the skin at a basal rate and in boluses. Automated insulin delivery systems share CGM glucose data and insulin pump data via Bluetooth, which can be analyzed by computer algorithms to adjust insulin delivery based on the current and predicted glucose readings and the amount of insulin delivered.

Compared with administering insulin based on fingerstick glucose readings, CGM combined with an insulin pump reduced time spent in hypoglycemia (adjusted between-group difference, −0.7% [95% CI, −1.5% to −0.1%]; P = .002) over a 24-hour period and reduced HbA_{1c} values by −0.37 percentage points (95% CI, −0.66 to −0.08; P = .01) in adolescents and young adults[50] (eTable 1 in the Supplement).[51-58] Automated insulin delivery systems reduce hyperglycemia and hypoglycemia compared with insulin injections with or without CGM and use of a nonautomated pump with or without CGM. Specifically, the mean difference in HbA_{1c} values between automated insulin delivery and nonautomated insulin delivery system users (includes people using CGM, self-monitoring of blood glucose, insulin injections, or insulin pump) in RCTs ranged from 0.32 to 0.80 percentage points (sample size ranged from 133-302 participants).[59-63] The greatest improvement in HbA_{1c} occurred in those with higher starting HbA_{1c} levels (eg, >8.0% [n = 155]).[61] Continuous glucose monitoring time in range (70-180 mg/dL) increased by 6.7% to 21.5% and time below range (<70 mg/dL) decreased by 1.8% to 3.7%.[64-72]

Currently, the ADA recommends automated insulin delivery as first-line therapy for children and adults with type 1 diabetes.[73]

Glucose Targets

For people with type 1 diabetes, the fasting glucose goal is 80 to 130 mg/dL.[74,75] Fasting glucose values are primarily determined by the basal insulin dose. The amount of preprandial, bolus insulin administered should be based on the grams of carbohydrates that will be ingested (ie, using a carbohydrate ratio and the accurate counting of carbohydrates [Children's Diabetes Foundation]) and the preprandial glucose value (ie, using a scale based on insulin sensitivity, previously referred to as a sliding scale) (Figure 3).[30,75] Patients should be taught how to interpret food nutrition labels, calculate total grams of carbohydrates, and divide the total grams of carbohydrates by their predetermined carbohydrate ratio. The carbohydrate ratio is defined as the number of grams of carbohydrate that 1 unit of rapid-acting or ultrarapid-acting insulin will need to maintain euglycemia. Treatment should aim to attain a postprandial glucose level (within 2 hours of eating) of 180 mg/dL or less and glucose values of less than 130 to 140 mg/dL by 2 to 3 hours after eating.[74] Rapid-acting, ultrarapid-acting, or inhaled insulin administration may be required at a higher dose during intercurrent illness or a lower dose if activity or exercise is anticipated.

All people with type 1 diabetes should have access to a CGM and should be treated to attain an HbA_{1c} less than 7% (or lowest HbA_{1c} safely achievable without significant hypoglycemia, which is equivalent to a CGM time in range [70-180 mg/dL]) of greater than 70% in a 24-hour period (**Box**).[74] However, HbA_{1c} thresholds higher than 7% (such as less than 8%) may be appropriate for older people and those with multiple chronic conditions. CGM variability (number of peaks and troughs on the sensor tracing) should be minimized because maintaining a coefficient of variation less than or equal to 36% may reduce the risk of severe hypoglycemia, defined as glucose values less than 54 mg/dL and/or loss of consciousness or seizure.[76,77]

For people 65 years or older with type 1 diabetes and those with debilitating medical conditions, higher glucose and HbA_{1c} values may be acceptable to protect against episodes of severe hypoglycemia.[74] In an observational study that included 1051 adults with type 1 diabetes followed up for 32 years, there were 1608 episodes of severe hypoglycemia (self-reported loss of consciousness, seizure, or coma) in 482 participants.[78] Having 1 or more episodes of severe hypoglycemia was associated with a decline in psychomotor and mental efficiency equivalent to an additional 4.6 years of age.[78] Therefore, to reduce the risk of hypoglycemia, for people 65 years or older and those with debilitating medical conditions such as individuals with end-stage chronic illnesses or moderate to severe cognitive impairment, the CGM goal for time below range (<70 mg/dL) should be limited to less than 1%, compared with less than 4% in healthy and younger people with type 1 diabetes, and CGM time in range (70-180 mg/dL) should be more than 50% of time rather than more than

Box. Questions Commonly Asked About Management of Type 1 Diabetes

What are optimal glucose targets for people with type 1 diabetes?
HbA_{1c} level less than 7% or CGM time in range (70-180 mg/dL) greater than 70% per 24-hour period reduces the risk of long-term complications such as retinopathy, nephropathy, and neuropathy. For people 65 years or older and/or with debilitating medical conditions such as end-stage chronic illnesses or moderate to severe cognitive impairment, individualized HbA_{1c} goals, such as level less than 8%, may be acceptable.

How should glucose be monitored?
Glucose levels can be monitored with a glucometer 4 to 6 times/d, measured on waking, before meals, and before bed. Compared with glucometer measures, CGM is associated with improved HbA_{1c} levels (−0.37 percentage points [95% CI, −0.66 to −0.08])[50] and lower rates of hypoglycemia (blood glucose values <70 mg/dL in a 24-hour period were reduced by up to 4.6% or over 1 h/d)[55] and is recommended for patients with type 1 diabetes.

How should an insulin regimen be selected for an individual patient?
Insulin may be administered as (1) multiple daily injections with a long-acting (basal) insulin such as glargine or degludec given once or twice daily and a rapid-acting (bolus) insulin such as aspart or lispro given 3 or more times per day in response to carbohydrate ingestion and hyperglycemia or (2) rapid-acting insulin in a continuous subcutaneous insulin infusion (ie, an insulin pump). Automated insulin delivery devices, consisting of a CGM and a paired insulin pump that communicate and adjust insulin delivery via an algorithm, are the preferred insulin delivery method for children and adults with type 1 diabetes because they are associated with improved HbA_{1c} values (−0.80 percentage points [95% CI, −1.1 to −0.4])[61] and less hypoglycemia (blood glucose values <70 mg/dL in a 24-hour period were reduced by up to 3.7% or over 53 minutes per day compared with nonautomated insulin delivery users).[71]

Abbreviations: CGM, continuous glucose monitor; HbA_{1c}, hemoglobin A_{1c}.

SI conversion factor: To convert glucose values to mmol/L, multiply by 0.0555.

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70%.[76,79,80] For pregnant people with type 1 diabetes, glucose targets should be lower to reduce the risk of macrosomia and preterm birth, preeclampsia, and congenital anomalies. Goal preconception HbA_{1c} level should be less than 6.5%, with fasting glucose level 70 to 95 mg/dL, 1-hour postprandial glucose level 110 to 140 mg/dL, and 2-hour postprandial glucose level 100 to 120 mg/dL.[81]

Adjunctive Therapies

Pramlintide, an amylin analogue, is the only noninsulin medication currently approved by the US Food and Drug Administration (FDA) for management of type 1 diabetes.[30] Pramlintide may be added if glucose targets are not attained after optimizing insulin therapy. Pramlintide slows gastric emptying and suppresses postmeal glucagon secretion, which contributes to hyperglycemia. Similar to insulin, pramlintide is a peptide hormone and must be injected subcutaneously. Few RCTs have been conducted using pramlintide, and pramlintide is infrequently used due to the need for additional mealtime injections and adverse effects such as nausea, vomiting, and decreased appetite due to delayed gastric emptying.[82] Other drug classes, not FDA approved for adjunctive treatment of type 1 diabetes (eTable 2 in the Supplement), include medications to improve insulin sensitivity (such as metformin), reduce glucagon and delay gastric emptying (such as glucagon-like peptide 1 [GLP-1] receptor agonists), and promote kidney excretion of glucose (such as sodium-glucose cotransporter 2 [SGLT2] inhibitors). Metformin increases secretion and sensitivity of cells to GLP-1, and this hormone causes delayed gastric emptying and reduced glucagon secretion but has common gastrointestinal adverse effects such as nausea, vomiting, diarrhea, or constipation.[83] Metformin is associated with weight loss of approximately 2 kg in adolescents with overweight/obesity and type 1 diabetes[84]; GLP-1 receptor agonists, such as liraglutide and exenatide, demonstrate mean weight loss of approximately −4.89 kg (95% CI, −5.33 to −4.45) and HbA_{1c} reduction of approximately −0.28 percentage points (95% CI, −0.38 to −0.19) compared with placebo.[85] SGLT2 inhibitors, such as dapagliflozin, sotagliflozin, and empagliflozin, directly lower glucose levels by preventing reabsorption of glucose and sodium in the kidney. Due to the insulin-independent lowering of glucose levels by SGLT2 inhibitors, DKA may occur if exogenous insulin doses are lowered such that a minimum amount of basal insulin is no longer present to suppress ketogenesis. Other adverse effects of SGLT2 inhibitors are related to urinary glucose losses and include urinary tract infection, genital yeast infection, and dehydration.[86-90]

Behavioral Modifications

Few RCTs lasting more than 4 weeks have tested dietary plans[91-94] or exercise[95-98] to improve glycemia in type 1 diabetes. People diagnosed with type 1 diabetes should be referred for medical nutrition therapy,[99,100] which is an individualized, diabetes-specific program provided by a registered dietitian, and ongoing medical nutrition counseling may be helpful. Exercise can improve insulin sensitivity, may lower insulin doses, and can improve overall well-being.

Pancreas or Islet Cell Transplant

A whole pancreas or isolated islet cells from the pancreas of a deceased donor may be implanted into a person with type 1 diabetes to restore endogenous insulin production. The Collaborative Islet Transplant Registry (CITR) includes data collected between 1999 and 2023 that described outcomes from 1477 allogeneic islet transplants (1134 with islet transplant alone and the remaining with kidney transplant) around the world.[101] While transplant may eliminate the need for exogenous insulin, it increases the risk of severe or life-threatening adverse effects including death (10-year mortality of approximately 8%-32% in longitudinal studies) related to immunosuppression.[102,103] Pancreas or islet cell transplant could be considered in people with type 1 diabetes and end-stage kidney disease (ie, simultaneous pancreas-kidney transplant or past kidney transplant) or in patients with severe, refractory hypoglycemia and hypoglycemia unawareness.

Complications and Comorbidities of Type 1 Diabetes

Diabetes-related complications such as retinopathy, nephropathy, neuropathy, and cardiovascular disease occur in more than 95% of people with type 1 diabetes (**Table 2**).[108-112] Other comorbidities associated with type 1 diabetes include hyperlipidemia and hypertension. The Diabetes Control and Complications Trial (DCCT) was an RCT conducted from 1983-1993 of 1441 people with type 1 diabetes aged 13 years to 39 years who were randomized to intensive insulin therapy (≥3 daily insulin injections or an insulin pump with immediate dose adjustments based on glucose readings) or conventional treatment (1-2 daily insulin injections) to determine if intensive insulin therapy led to a lower incidence of clinically relevant retinopathy, defined as a change of at least 3 steps (of a total of 25 defined steps) on the Early Treatment Diabetic Retinopathy Study interim scale via fundus photography, that was sustained for at least 6 months.[113] Secondary outcomes were nephropathy (urinary albumin excretion ≥40 mg/24 h), neuropathy (diagnosed by peripheral sensorimotor testing in addition to abnormal nerve conduction testing), and development of hypercholesterolemia (elevated low-density lipoprotein cholesterol level). Over a mean 6.5-year follow-up, mean HbA_{1c} level was 7.2% in the intensive treatment group, compared with 9.1% in the conventional treatment group ($P < .001$).[113] Intensive therapy significantly reduced the primary outcome of retinopathy progression (1.2 events/100 patient-years in the intensive treatment group vs 4.7/100 patient-years in the conventional treatment group [risk reduction, 76% {95% CI, 62% to 85%}; $P \leq .002$]). Intensive insulin therapy significantly reduced the incidence of nephropathy (2.2 events/100 patient-years vs 3.4/100 patient-years; risk reduction, 34% [95% CI, 2%-56%]; $P < .04$) and neuropathy (3.1 events/100 patient-years vs 9.8/100 patient-years; risk reduction, 69% [95% CI, 24%-87%]; $P < .04$).[113] Ninety-three percent of participants were subsequently followed up in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, an observational cohort study of DCCT participants with up to 30 years of follow-up.[114] At a mean of 17 years of follow-up, the rate of the first of any type of cardiovascular event, including nonfatal MI, stroke, death judged to be due to cardiovascular disease, subclinical MI detected on electrocardiogram, or ischemic changes with exercise tolerance, was 0.38 vs 0.80/100 patient-years ($P = .007$) for the intensive and conventional treatment groups, respectively.[115] At a mean follow-up of 26 years, the cardiovascular disease event rate was not significantly different (11.5% and 14%, respectively).[98]

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Table 2. Prevalence, Screening Time Frame, and Treatment Options of Type 1 Diabetes–Related Comorbidities

Prevalence in people with type 1 diabetes	Screening	Treatment goal	Treatment(s)[a]	Evidence[b]
Hyperlipidemia				
66%-68% (Diabetes duration, 27-42 y)[102]	Lipid profile at diagnosis and every 3 y, more frequent monitoring if cardiovascular risk factors or lipid abnormalities present[68,97]	LDL-C <100 mg/dL for primary prevention of hyperlipidemia and CVD[68,97] LDL-C <70 mg/dL for treatment of hyperlipidemia and secondary prevention of CVD[97]	Children[68]—primary prevention of hyperlipidemia (LDL-C >130 mg/dL): Optimize glycemia and medical nutrition therapy After 6 mo if LDL-C >160 mg/dL or >130 mg/dL with cardiovascular risk factor such as low HDL-C, high triglycerides, hypertension, age- and sex-specific waist circumference >90th percentile, statin therapy[c] Adults[97,104]—primary prevention of hyperlipidemia (LDL-C >100 mg/dL) and CVD: Low-carbohydrate or Mediterranean eating pattern, and/or increased physical activity Statin Treatment of hyperlipidemia and secondary prevention of CVD (LDL-C >70 mg/dL): Statin such as rosuvastatin, simvastatin, or atorvastatin Cholesterol absorption inhibitor such as ezetimibe PCSK9 inhibitor such as evolocumab or alirocumab	Low-dose statin therapy lowered LDL-C 30%-49%, whereas high-intensity therapy lowered LDL-C ≥50% and should be used in the setting of CVD (level A)[97] Add ezetimibe or PCSK9 inhibitor to statin therapy if LDL-C does not meet goals of LDL-C <70 mg/dL and also reduced by 50% for the secondary prevention of CVD (level B)[97]
Hypertension				
68%-70% (Diabetes duration 27-42 y)[102]	Blood pressure every visit (minimum every 6 mo)[68,97]	Blood pressure <130/80 mm Hg for adults[97] Blood pressure <90th percentile for age, sex, and height for children younger than 13 y[68]	Blood pressure >120/80 mm Hg or 90th to <95th percentile for age, sex, and height if younger than 13 y[68,97]: DASH-style eating pattern (reducing sodium to <2300 mg/d; increasing potassium; limiting alcohol intake), exercise, weight management, smoking cessation Blood pressure >130/80 mm Hg or ≥95th percentile for age, sex, and height if younger than 13 y[68,97]: ACE inhibitor or ARB[c] CCB or diuretic Blood pressure >150/90 mm Hg[97]: ACE inhibitor or ARB and CCB or diuretic	Lifestyle changes such as DASH-style eating pattern can lower blood pressure modestly (approximately 3 mm Hg systolic) (level A)[97] ACE inhibitor or ARB first line for hypertension with diabetes and coronary artery disease, as well as with diabetes and albuminuria (level A)[97]
Albuminuria/chronic kidney disease				
Urine albumin excretion rate ≥30 mg/24 h 18.5%-24.9% (diabetes duration 24-39 y)[105]	UACR annually starting 5 y after diagnosis or puberty (whichever is earlier) and eGFR in adults[68,98]	<30 mg/g UACR	Low sodium (ie, <2300 mg/d) and/or low protein (ie, 0.6-0.8 g/kg/d) eating pattern Smoking cessation ACE inhibitor or ARB SGLT2 (or SGLT1/2) inhibitor or GLP-1 receptor agonist Nonsteroidal mineralocorticoid receptor antagonist	In coexisting hypertension, ACE inhibitor or ARB is recommended for UACR 30-299 mg/g creatinine (level B); and UACR ≥300 mg/g (level A)[98]
Retinopathy				
Lifetime prevalence of any retinopathy including microaneurysm, 95%-97%; including vision-threatening retinopathy, 3%-8%[106]	Eye examination (dilated eye examination in adults) 3-5 y after diagnosis or at time of puberty (whichever is earlier) and every 1-2 y[99]		Panretinal laser photocoagulation therapy Intravitreal anti-VEGF Macular focal/grid photocoagulation and intravitreal corticosteroid	Panretinal laser photocoagulation recommended for individuals with risk of vision loss from proliferative diabetes-related retinopathy (level A)[99] Intravitreal anti-VEGF injections are first-line treatment for most diabetes-related macular edema (level A)[99] Macular focal/grid photocoagulation and intravitreal corticosteroid recommended for persistent macular edema (level A)[99]

(continued)

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Table 2. Prevalence, Screening Time Frame, and Treatment Options of Type 1 Diabetes–Related Comorbidities (continued)

Prevalence in people with type 1 diabetes	Screening	Treatment goal	Treatment(s)[a]	Evidence[b]
Peripheral neuropathy				
Confirmed clinically (defined by symptoms, sensory signs, or reflex changes consistent with distal polyneuropathy and confirmed with nerve conduction abnormalities) 25%-35% (diabetes duration 21-35 y)[107]	Foot examination—pinprick and temperature sensation, lower-extremity reflexes, vibration perception, and 10-g monofilament test annually starting 5 y after diagnosis or puberty (whichever is earlier)[68,99]		Symptomatic treatment of neuropathic pain with gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, or sodium channel blockers	Gabapentinoid such as gabapentin and pregabalin, serotonin-norepinephrine reuptake inhibitor such as duloxetine and venlafaxine, tricyclic antidepressant such as amitriptyline and nortriptyline, sodium channel blockers such as carbamazepine, oxcarbazepine, lamotrigine, valproic acid, and lacosamide are initial therapy for neuropathic pain in diabetes (level A)[99]

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; SGLT, sodium-glucose cotransporter; UACR, urinary albumin-to-creatinine ratio; VEGF, vascular endothelial growth factor.

SI conversion factor: To convert glucose values to mmol/L, multiply by 0.0555.

[a] All treatments include the assumption that glycemic management is optimized. Before starting any medications, the adverse effects, including potential for teratogenicity or medication interactions, need to be evaluated. Other comorbidities not discussed here include, eg, hypoglycemia unawareness, urologic conditions, and dental caries.

[b] Based on the American Diabetes Association guidelines. GRADE (Grading of Recommendations, Assessment, Development and Evaluation) level of evidence reported from the American Diabetes Association guidelines. Level A: adequately powered, well-conducted, generalizable randomized controlled trials. Level B: well-conducted cohort or case-control studies. Level C: poorly controlled or uncontrolled studies. Level E: expert consensus.

[c] Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and medication should be avoided in individuals of childbearing age who are not using reliable contraception.

In the first 1.3 years of follow-up, the intensively treated group had greater weight gain (1.10 [SD, 0.049] kg/m^2 per year) compared with the conventional group (0.35 [SD, 0.049] kg/m^2 per year) and a separate control group without diabetes (0.35 [SD, 0.025] kg/m^2 per year).[116]

Prognosis

Life expectancy of people with type 1 diabetes is approximately 8 to 10 years shorter than among individuals without type 1 diabetes in the general population, and cardiovascular disease is the leading cause of death.[117-120] Intensive insulin therapy with attainment of glycemic targets is associated with significant decreases in microvascular and macrovascular complications.[113,115]

Practical Considerations

When patients with type 1 diabetes are hospitalized, they should continue their home insulin medications and doses unless they are being treated in an intensive care unit, where continuous insulin infusion may be used. Adjustments to inpatient insulin dosing are based on glucose levels measured 4 or more times per day or hourly for patients treated with a continuous insulin infusion. If patients are required to have nothing by mouth, glucose levels should be monitored closely due to the risk of hypoglycemia, but basal insulin should be continued, because discontinuing basal insulin will precipitate DKA. Computer order entry sets for glucose monitoring and insulin dosing are recommended, and glycemic goals are higher in critically ill patients (140-180 mg/dL) compared with those not in the intensive care unit (100-180 mg/dL).[104] Hypoglycemia (glucose level <70 mg/dL) should be avoided.

Type 1 diabetes is associated with an increased prevalence of other autoimmune diseases. Approximately 9.8% of people with type 1 diabetes have autoimmune thyroid disease and 5% have celiac disease. People with type 1 diabetes also have a higher prevalence of pernicious anemia, vitiligo, adrenal insufficiency, autoimmune hepatitis, and premature ovarian insufficiency.[75,105,106] Screening for autoimmune thyroid disease with thyroid stimulating hormone levels is recommended every 1 to 2 years and screening for celiac disease with antibodies against tissue transglutaminase is recommended at diagnosis and at 2- and 5-years' disease duration. However, no clinical trials have documented that screening for autoimmune diseases in patients with type 1 diabetes improves outcomes.

Polycystic ovarian syndrome affects approximately 24% of people with type 1 diabetes due to hyperinsulinemia from exogenous insulin therapy, which stimulates ovarian androgen production and can impair fertility.[107,121] Fertility goals and menstrual health should be assessed at each visit for women of childbearing age.

Future Directions

Ongoing clinical trials are assessing disease-modifying therapies, such as immunotherapies to mitigate the autoimmune-related destruction of pancreatic beta cells for people with type 1 diabetes. Teplizumab, an anti-CD3 monoclonal antibody, is an FDA-approved (2022) immune therapy indicated for individuals with stage 2 type 1 diabetes to delay the progression to clinical disease (stage 3 type 1 diabetes).[122,123] Seventy-six individuals aged 8 to 45 years were randomized 2:1 drug to placebo. The primary end point (time from stage 2 to stage 3 type 1 dia-

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betes) in the teplizumab group was 48.4 months compared with 24.4 months in the placebo group (hazard ratio, 0.41 [95% CI, 0.22-0.78]; $P = .006$). In addition, studies of beta cell replacement therapies, which take either donor or manufactured islets and implant them in people with long-standing type 1 diabetes, are also a rapidly growing area of research, especially focused on ways to hide the new islets from the immune system, negating the need for lifelong immunosuppression.

Limitations

This review has several limitations. First, only English-language publications were included. Second, the quality of the literature was not formally assessed. Third, some relevant articles may have been missed.

Conclusions

Type 1 diabetes accounts for 5% to 10% of all diabetes diagnoses and is characterized by the presence of islet autoantibodies in 90% to 95% of people. Insulin therapy is first-line treatment, and lifelong use is required with use of automated insulin delivery systems as the standard of care.

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