Brief Overview about Type 1 Diabetes Mellitus among Children

Fahmy Attia Fahmy Attia[1], Mohamed Naguib Abo Elfettoh[1], Ashgan Abdullah Alghobashy[1], Nermin Raafat Abdel Fattah [2]

1 Department of Pediatrics, Faculty of Medicine, Zagazig University, Egypt

2 Department of Medical Biochemistry, Faculty of Medicine, Zagazig University, Egypt
Corresponding author: Fahmy Attia Fahmy Attia

E-mail: fahmyattia1981@gmail.com

Conflict of interest: None declared

Funding: No funding sources

Abstract

Type 1 diabetes mellitus (DM) is a multisystem disease with both biochemical and anatomic/structural consequences. It is a chronic disease of carbohydrate, fat, and protein metabolism caused by the lack of insulin, which results from the marked and progressive inability of the pancreas to secrete insulin because of autoimmune destruction of the beta cells. Type 1 DM can occur at any age. Although onset frequently occurs in childhood, the disease can also develop in adults. Unlike people with type 2 DM, those with type 1 DM usually are not obese and usually present initially with diabetic ketoacidosis (DKA). The distinguishing characteristic of a patient with type 1 DM is that if his or her insulin is withdrawn, ketosis and eventually ketoacidosis develop. Therefore, these patients are dependent on exogenous insulin. Treatment of type 1 DM requires lifelong insulin therapy. Epidemiological studies for childhood T1DM from Egypt are scarce. This has been attributed to many reasons including lack of diabetes registries, scattered medical facilities and suboptimal capturing of new cases. The incidence, prevalence and demographic characteristics of T1DM in children aged 0-18 years between 1994 and 2011 in an Egyptian subpopulation living in the Nile Delta region, were evaluated aiming for a better understanding of the risk factors as well as to plan future strategies to control this disease. The incidence rates in our pediatric population from the Nile Delta region were lower than those reported from neighboring countries (3.1/105/year).

Keywords: Type 1 Diabetes Mellitus, children

Tob Regul Sci. ™ 2023;9(1): 3663-3689
DOI: doi.org/10.18001/TRS.9.1.257

Introduction

Type 1 diabetes mellitus (DM) is a multisystem disease with both biochemical and anatomic/structural consequences. It is a chronic disease of carbohydrate, fat, and protein metabolism caused by the lack of insulin, which results from the marked and progressive inability of the pancreas to secrete insulin because of autoimmune destruction of the beta cells **(Atkinson et al., 2020).** Type 1 DM can occur at any age. Although onset frequently occurs in childhood, the disease can also develop in adults **(DiMeglio et al., 2018).** Unlike people with type 2 DM, those with type 1 DM usually are not obese and usually present initially with diabetic ketoacidosis (DKA). The distinguishing characteristic of a patient with type 1 DM is that if his or her insulin is withdrawn, ketosis and eventually ketoacidosis develop. Therefore, these patients are dependent on exogenous insulin. Treatment of type 1 DM requires lifelong insulin therapy (**Cashen and Petersen, 2019).**

Epidemiology

International statistics

Internationally, rates of type 1 DM are increasing. In Europe, the Middle East, and Australia, rates of type 1 DM are increasing by 2-5% per year **(Imkampe and Gulliford, 2011)**. The prevalence of type 1 DM is highest in Scandinavia (ie, approximately 20% of the total number of people with DM) and lowest in China and Japan (ie, fewer than 1% of all people with diabetes). The 10th edition of the International Diabetes Federation Diabetes Atlas, published in December 2021, reported that worldwide, 1 in 10 adults has diabetes. The data predicted that there would be a global increase in the number of adults with diabetes from 537 million in 2021 to 786 million by 2045, a 46% rise. Although increases are expected throughout the world, Africa, the Middle East, and Southeast Asia are predicted to have the greatest expansion (**Tucker, 2021b).**

United States statistics

A **2011** report from the US Centers for Disease Control and Prevention (CDC) estimated that approximately 1 million Americans have type 1 DM. The CDC estimated that each year from 2002 to 2005, type 1 DM was newly diagnosed in 15,600 young people. Among children younger than 10 years, the annual rate of new cases was 19.7 per 100,000 population; among those 10 years or older, the rate was 18.6 per 100,000 population. Type 1 DM is the most common metabolic disease of childhood. About 1 in every 400-600 children and adolescents has type 1 DM. In adults, type 1 DM constitutes approximately 5% of all diagnosed cases of diabetes. The incidence of type 1 and type 2 DM saw a significant rise among youths in the United States between 2002 and 2012. According to the report, after the figures were adjusted for age, sex, and race or ethnic group, the incidence of type 1 (in patients aged 0-19 years) and type 2 DM (in patients aged 10-19 years) during this period underwent a relative annual increase of 1.8% and 4.8%, respectively. The greatest increases occurred among minority youths **(Mayer-Davis et al., 2017).**

In Egypt

Epidemiological studies for childhood T1DM from Egypt are scarce. This has been attributed to many reasons including lack of diabetes registries, scattered medical facilities and suboptimal capturing of new cases. The incidence, prevalence and demographic characteristics of T1DM in children aged 0-18 years between 1994 and 2011 in an Egyptian subpopulation living in the Nile Delta region, were evaluated aiming for a better understanding of the risk factors as well as to plan future strategies to control this disease **(El-Ziny, 2014).** The incidence rates in our pediatric population from the Nile Delta region were lower than those reported from neighboring countries ($3.1/10^5$/year) **(Karvonen et al., 2014).**

T1DM was made in a total of 1600 patients in the 0-18 year age group at Mansoura University Children's Hospital (MUCH) over a period of 18 years starting on 1 January 1994 and ending on 31 December 2011. Annual numbers of diagnosed cases were found to increase slowly over many years, reaching highest levels in 2008, 2010 and 2011. The median age at T1DM diagnosis was recorded at 12 and 10 years in females and males, respectively. All patients originated from the Nile Delta governorates at Northern Egypt The group included 1162 patient from Dakahlia (72.6%), 175 from Damietta (10.9%), 50 from Kafr el-Sheikh (3.12%), 155 from Gharbia (9.6%) and 58 patients were from other governorates (3.78%) **(El-Ziny, 2014).**

Age-related demographics

Previously referred to as juvenile-onset diabetes, type 1 DM is typically diagnosed in childhood, adolescence, or early adulthood. Although the onset of type 1 DM often occurs early in life, 50% of patients with new-onset type 1 DM are older than 20 years of age. Type 1 DM usually starts in children aged 4 years or older, appearing fairly abruptly, with the peak incidence of onset at age 11-13 years (ie, in early adolescence and puberty). There is also a relatively high incidence in people in their late 30s and early 40s, in whom the disease tends to present less aggressively (ie, with early hyperglycemia without ketoacidosis and gradual onset of ketosis). This slower-onset adult form of type 1 DM is referred to as latent autoimmune diabetes of the adult (LADA) as proved in **2011** by U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

A study by Thomas et al, using data from the UK Biobank, determined that in 42% of type 1 DM cases reviewed, disease onset occurred in patients aged 31 to 60 years. The report also found that because type 2 DM is far more common than type 1 in individuals in the 31- to 60-year age group, with type 1 DM making up only 4% of all diabetes cases in this population, identification of type 1 DM is difficult in patients over age 30 years. The presence of type 1 DM was identified in the study using a genetic risk score that employed 29 common genetic variants **(Thomas et al., 2017).** The risk of development of antibodies (anti-islet) in relatives of patients with type 1 DM decreases with increasing age. This finding supports annual screening for antibodies in relatives younger than 10 years and 1 additional screening during adolescence **(Tucker, 2017).**

Etiology

There are two forms of type 1 diabetes:

- **Type 1a** (immune-mediated diabetes) – an autoimmune disorder in which the body's immune system destroys, or attempts to destroy, the cells in the pancreas that produce insulin. It represents about 90% of type 1 cases in Europe **(American Diabetes Association, 2021).**
- **Type 1b** (Idiopathic type 1) – refers to rare forms of the disease with no known cause. There is no evidence of autoimmunity, it represent about 10% of cases of type 1 in Europe It may be etiologically heterogeneous, including insulin secretory defects caused by extensive pancreatic islet β-cell destruction or dysfunction **(American Diabetes Association, 2021).**

Genetic factors

Although the genetic aspect of type 1 DM is complex, with multiple genes involved, there is a high sibling relative risk (**Delli and Lernmark, 2016).** Whereas dizygotic twins have a 5-6% concordance rate for type 1 DM (**DiMeglio et al., 2018)**, monozygotic twins will share the diagnosis more than 50% of the time by the age of 40 years **(Redondo et al., 2018).** For the child of a parent with type 1 DM, the risk varies according to whether the mother or the father has diabetes. Children whose mother has type 1 DM have a 2-3% risk of developing the disease, whereas those whose father has the disease have a 5-6% risk. When both parents are diabetic, the risk rises to almost 30%.

The genetic contribution to type 1 DM is also reflected in the significant variance in the frequency of the disease among different ethnic populations. Type 1 DM is most prevalent in European populations, with people from northern Europe more often affected than those from Mediterranean regions (**Atkinson et al., 2020). American Diabetes Association (2021)** has found that type 1 DM disease is least prevalent in East Asians. Genome-wide association studies have identified several loci that are associated with type 1 DM, but few causal relations have been established. The genomic region most strongly associated with other autoimmune diseases, the major histocompatibility complex (MHC), is the location of several susceptibility loci for type 1 DM in particular, class II HLA DR and DQ haplotypes **(Redondo et al., 2018).**

A hierarchy of DR-DQ haplotypes associated with increased risk for type 1 DM has been established. The most susceptible haplotypes are as follows **(Katsarou et al., 2017)**:

- DRB1*0301 - DQA1*0501 - DQB1*0201 (odds ratio [OR] 3.64)
- DRB1*0405 - DQA1*0301 - DQB1*0302 (OR 11.37)
- DRB1*0401 - DQA1*0301 - DQB*0302 (OR 8.39)
- DRB1*0402 - DQA1*0301 - DQB1*0302 (OR 3.63)

- DRB1*0404 - DQA1*0301 - DQB1*0302 (OR 1.59)
- DRB1*0801 - DQB1*0401 - DQB1*0402 (OR 1.25)

Other haplotypes appear to offer protection against type 1 DM. These include the following **(Redondo et al., 2018)**:

- DRB1*1501 - DQA1*0102 - DQB1*0602 (OR 0.03)
- DRB1*1401 - DQA1*0101 - DQB1*0503 (OR 0.02)
- DRB1*0701 - DQA1*0201 - DQB1*0303 (OR 0.02)

The insulin gene (INS), which encodes for the pre-proinsulin peptide, is adjacent to a variable number of tandem repeats (VNTR) polymorphism at chromosome 11p15.5 **(Atkinson et al., 2020).** Different VNTR alleles may promote either resistance or susceptibility to type 1 DM through their effect on INS transcription in the thymus; for example, protective VNTRs are associated with higher INS expression, which may promote deletion of insulin-specific T cells **(Delli and Lernmark, 2016).** Other genes that have been reported to be involved in the mechanism of type 1 DM include CTLA4 (important in T-cell activation), PTPN22 (produces LYP, a negative regulator of T-cell kinase signaling), and IL2RA (encodes for CD25 which is involved with regulating T-cell function). UBASH3A (also known as STS2), may be involved in the increased risk not only of type 1 DM but also of other autoimmune disease and Down syndrome; it is located on locus chromosome 21q22.3 **(Redondo et al., 2018).** In addition, genome-wide association studies have implicated numerous other genes, including the following SH2B3, ERBB3, CLEC16A, IL18RAP, PTPN2 and CCR5 (**Atkinson et al., 2020).**

Pathophysiology

Type 1 DM is the culmination of lymphocytic infiltration and destruction of insulin-secreting beta cells of the islets of Langerhans in the pancreas. As beta-cell mass declines, insulin secretion decreases until the available insulin no longer is adequate to maintain normal blood glucose levels. After 80-90% of the beta cells are destroyed, hyperglycemia develops and diabetes may be diagnosed **(Lamb, 2022).**

Currently, autoimmunity is considered the major factor in the pathophysiology of type 1 DM. In a genetically susceptible individual, viral infection may stimulate the production of antibodies against a viral protein that trigger an autoimmune response against antigenically similar beta cell molecules. Approximately 85% of type 1 DM patients have circulating islet cell antibodies, and the majority also have detectable anti-insulin antibodies before receiving insulin therapy. The most commonly found islet cell antibodies are those directed against glutamic acid decarboxylase (GAD), an enzyme found within pancreatic beta cells. The prevalence of type 1 DM is increased in patients with other autoimmune diseases, such as Graves disease, Hashimoto thyroiditis, and

Addison disease. A higher prevalence of islet cell antibodies (IA2) and anti-GAD antibodies has been found in patients with autoimmune thyroiditis **(Katsarou et al., 2017).**

A study by **Philippe et al (2011)** used computed tomography (CT) scans, glucagon stimulation test results, and fecal elastase-1 measurements to confirm reduced pancreatic volume in individuals with DM. This finding, which was equally present in both type 1 and type 2 DM, may also explain the associated exocrine dysfunction that occurs in DM.

Polymorphisms of the class II human leukocyte antigen (HLA) genes that encode DR and DQ are the major genetic determinants of type 1 DM. Approximately 95% of patients with type 1 DM have either HLA-DR3 or HLA-DR4. Heterozygotes for those haplotypes are at significantly greater risk for DM than homozygotes. HLA-DQs are also considered specific markers of type 1 DM susceptibility. In contrast, some haplotypes (eg, HLA-DR2) confer strong protection against type 1 DM (**Redondo et al., 2018).**

Management of type 1 diabetes

Clinical Presentation

The most common symptoms of type 1 diabetes mellitus (DM) are polyuria, polydipsia, and polyphagia, along with lassitude, nausea, and blurred vision, all of which result from the hyperglycemia itself. Polyuria is caused by osmotic diuresis secondary to hyperglycemia. Severe nocturnal enuresis secondary to polyuria can be an indication of onset of diabetes in young children. Thirst is a response to the hyperosmolar state and dehydration. Fatigue and weakness may be caused by muscle wasting from the catabolic state of insulin deficiency, hypovolemia, and hypokalemia. Muscle cramps are caused by electrolyte imbalance. Blurred vision results from the effect of the hyperosmolar state on the lens and vitreous humor. Glucose and its metabolites cause osmotic swelling of the lens, altering its normal focal length. Symptoms at the time of the first clinical presentation can usually be traced back several days to several weeks. However, beta-cell destruction may have started months, or even years, before the onset of clinical symptoms **(Khardori, 2022).**

The onset of symptomatic disease may be sudden. It is not unusual for patients with type 1 DM to present with diabetic ketoacidosis (DKA), which may occur de novo or secondary to the stress of illness or surgery. An explosive onset of symptoms in a young lean patient with ketoacidosis always has been considered diagnostic of type 1 DM. Over time, patients with new-onset type 1 DM will lose weight, despite normal or increased appetite, because of depletion of water and a catabolic state with reduced glycogen, proteins, and triglycerides. Weight loss may not occur if treatment is initiated promptly after the onset of the disease **(Lamb, 2022).**

Gastrointestinal (GI) symptoms of type 1 DM are as follows:

- Nausea, abdominal discomfort or pain, and change in bowel movements may accompany acute DKA.
- Acute fatty liver may lead to distention of the hepatic capsule, causing right upper quadrant pain.
- Persistent abdominal pain may indicate another serious abdominal cause of DKA (eg, pancreatitis).
- Chronic GI symptoms in the later stage of DM are caused by visceral autonomic neuropathy.

Neuropathy affects up to 50% of patients with type 1 DM, but symptomatic neuropathy is typically a late development, developing after many years of chronic prolonged hyperglycemia. Peripheral neuropathy presents as numbness and tingling in both hands and feet, in a glove-and-stocking pattern; it is bilateral, symmetric, and ascending **(Tucker, 2022)**.

In new cases of diabetes, physical examination findings are usually normal. Patients with DKA, however, will have Kussmaul respiration, signs of dehydration, hypotension, and, in some cases, altered mental status. In established cases, patients should be examined every 3 months for macrovascular and microvascular complications. They should undergo funduscopic examination for retinopathy and monofilament testing for peripheral neuropathy **(Lamb, 2022)**.

Diagnosis of type 1 diabetes

In **2021**, diagnostic criteria by **American Diabetes Association** (ADA) include the following:

- A fasting plasma glucose (FPG) level ≥126 mg/dL (7.0 mmol/L), or
- A 2-hour plasma glucose level ≥200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test (OGTT), or
- A random plasma glucose ≥200 mg/dL (11.1 mmol/L), or
- Glycated Hemoglobin (Hemoglobin A1C) levels ≥48 mmol/mol (A1C ≥6.5%) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

Laboratory Studies

Plasma glucose

Patients with type 1 diabetes mellitus (DM) typically present with symptoms of uncontrolled hyperglycemia (eg, polyuria, polydipsia, polyphagia). In such cases, the diagnosis of DM can be confirmed with a random (nonfasting) plasma glucose concentration of 200 mg/dL or a fasting plasma glucose concentration of 126 mg/dL (6.99 mmol/L) or higher **(DiMeglio et al., 2018)**.

A fingerstick glucose test is appropriate in the emergency department (ED) for virtually all patients with diabetes. All fingerstick capillary glucose levels must be confirmed in serum or plasma to make the diagnosis. All other laboratory studies should be selected or omitted on the basis of the individual clinical situation. Intravenous (IV) glucose testing may be considered for possible early detection of subclinical diabetes.

Individually measured glucose levels may differ considerably from estimated glucose averages calculated from measured hemoglobin A1c (HbA1c) levels (**Smith and Harris, 2018**). Therefore, caution is urged when the decision is made to estimate rather than actually measure glucose concentration; the difference between the 2 has a potential impact on decision making.

Hemoglobin A1c

HbA1c is the stable product of nonenzymatic irreversible glycation of the beta chain of hemoglobin by plasma glucose and is formed at rates that increase with increasing plasma glucose levels. HbA1c levels provide an estimate of plasma glucose levels during the preceding 1-3 months. The reference range for nondiabetic people is 6% in most laboratories. Glycated hemoglobin levels also predict the progression of diabetic microvascular complications **(Zheng et al., 2018)**.

American Diabetes Association (ADA) guidelines recommend measuring HbA1c at least every 6 months in patients with diabetes who are meeting treatment goals and who have stable glycemic control. For patients whose therapy has changed or who are not meeting glycemic goals, the guidelines recommend HbA1c testing every 3 months **(Lamb, 2022)**.

In the past, HbA1c measurements were not considered useful for the diagnosis of DM. Drawbacks included a lack of international standardization and insensitivity for the detection of milder forms of glucose intolerance. In a 2009 report, however, an international expert committee appointed by the ADA, the European Association for the Study of Diabetes (EASD), and the International Diabetes Association recommended the HbA1c assay for diagnosing type 1 and type 2 DM. In the case of type 1 DM, however, the committee recommended using the test only when the condition is suspected but the classic symptoms of type 1 DM polyuria, polydipsia, polyphagia, a random glucose level of 200 mg/dL, and unexplained weight loss are absent.

The committee noted the improvement in standardization and cited the following advantages of HbA1c testing over glucose measurement:

- Ability to capture long-term glucose exposure
- Less biologic variability
- No requirement for fasting or timed samples
- Current use in guiding management decisions

Consequently, since 2010 the ADA has included an HbA1c level of 6.5% or higher as a criterion for diabetes diagnosis, with confirmation from repeat testing (unless clinical symptoms are present and the glucose level exceeds 200 mg/dL). HbA1c testing cannot be used in patients with abnormal red blood cell (RBC) turnover (as in hemolytic or iron-deficiency anemia). In children with rapidly evolving type 1 DM, HbA1c may not be significantly elevated despite frank diabetes **(Khardori, 2022)**.

One study found seasonal variability in HbA1c levels of school-age children with higher levels (0.44%) coinciding with colder outdoor temperatures, fewer hours of sunlight, and lower levels of solar irradiance **(Wolsdorf and Garvey, 2016)**. This effect was seen in school-aged children but not preschoolers and may hold importance for studies using HbA1c as a primary endpoint and HbA1c - based diagnosis of diabetes. HbA1c cannot be used as an indicator of glycemic control in patients with neonatal diabetes mellitus (NDM) because of the high levels of fetal hemoglobin (HbF) remaining in the blood. A study by **Suzuki et al (2011)** found that glycated albumin, which is not affected by HbF levels, more strongly correlated with 1-month average postprandial blood glucose and was therefore a better marker of diabetes in neonates. This finding is important to neonatologist and those caring for newborns **(Katsarou et al., 2017)**.

Moreover, the overall efficacy of HbA1c testing in diabetes diagnosis remains uncertain. A study presented in 2019, using data derived from 9000 adults, reported diabetes diagnosis with the HbA1c blood test to be unreliable. The investigators found evidence that in comparison with the oral glucose tolerance test, HbA1c testing would lead to a 42% overdiagnosis of glucose tolerance and a 73% under diagnosis of diabetes, in adults **(Brooks, 2019).**

Other laboratory studies

Fructosamine levels also test for glucose levels. Fructosamine is formed by a chemical reaction of glucose with plasma protein and reflects glucose control in the previous 1-3 weeks. This assay, therefore, may show a change in control before HbA1c and often is helpful when applying intensive treatment and in short-term clinical trials **(Lamb, 2022)**.

A white blood cell (WBC) count and blood and urine cultures may be performed to rule out infection. Urine ketones are not reliable for diagnosing or monitoring diabetic ketoacidosis (DKA), although they may be useful in screening to see whether a hyperglycemic individual may have some degree of ketonemia. The plasma acetone level specifically, the beta-hydroxybutyrate level is a more reliable indicator of DKA, along with measurement of plasma bicarbonate or arterial pH as clinically required **(Khardori, 2022)**.

Screening for type 1 DM in asymptomatic low-risk individuals is not recommended **(LeRoith et al., 2019)**. However, in patients at high risk (eg, those who have first-degree relatives with type 1 DM), it may be appropriate to perform annual screening for anti-islet antibodies before the age 10 years, along with 1 additional screening during adolescence **(Donaghue et al., 2018)**.

Type 1 versus type 2 diabetes

Determining whether a patient has type 1 or type 2 DM is an important diagnostic and therapeutic concern because patients with type 1 DM depend on continuous exogenous insulin for survival. A patient whose diabetes is controlled with diet or an oral antidiabetic agent clearly has type 2 DM. A lean patient who has had diabetes since childhood, who has always been dependent on insulin, or who has a history of diabetic ketoacidosis (DKA) almost certainly has type 1 DM. Distinguishing the type of diabetes can be difficult in (1) patients who are treated with insulin and who are younger but clinically appear to have type 2 DM and (2) older patients with late-onset diabetes who nonetheless take insulin and seem to share characteristics of patients with type 1 DM. (This latter group is now said to have latent autoimmune diabetes of the adult [LADA].) It should be noted that for many patients, it will not be possible to fully distinguish type 1 DM from type 2. When in doubt, treat the patient with insulin and close monitoring of glucose levels. It is not unusual for adolescents or young adults, particularly Hispanic or African-American patients, to present with DKA and subsequently be found to have type 2 DM **(Lamb, 2022)**.

Tests to differentiate Type 1 from Type 2 Diabetes

Although the oral glucose tolerance test with insulin levels is usually considered unnecessary for diagnosing type 1 DM, the dramatic increase of type 2 DM in the young suggests that assessment of insulin secretion may become more important. The 2011 American Association of Clinical Endocrinologists (AACE) guidelines note that to help distinguish between the 2 types in children, physicians should measure insulin and C-peptide levels and immune markers (eg, glutamic acid decarboxylase [GAD] autoantibodies), as well as obtain a detailed family history **(Smith and Harris, 2018)**.

C-peptide is formed during conversion of proinsulin to insulin. An insulin or C-peptide level below 5 µU/mL (0.6 ng/mL) suggests type 1 DM; a fasting C-peptide level greater than 1 ng/dL in a patient who has had diabetes for more than 1-2 years is suggestive of type 2 (ie, residual beta-cell function). An exception is the individual with type 2 DM who presents with a very high glucose level (eg, >300 mg/dL) and a temporarily low insulin or C-peptide level but who will recover insulin production once normal glucose is restored.

Islet-cell (IA2), anti-GAD65, and anti-insulin autoantibodies can be present in early type 1 but not type 2 DM. Measurements of IA2 autoantibodies within 6 months of diagnosis can help differentiate between type 1 and type 2 DM. These titers decrease after 6 months. Anti-GAD65 antibodies can be present at diagnosis of type 1 DM and are persistently positive over time.

Testing for islet autoantibodies can substitute for expensive genetic testing in those patients suspected of having maturity-onset diabetes of the young (MODY). The prevalence of these antibodies is the same in patients with MODY as in the healthy population. A positive test for

positive islet autoantibodies makes MODY highly unlikely (**American Diabetes Association, 2021**).

ADA/EASD consensus statement

A consensus statement published in 2021 by the ADA and the EASD provided an algorithm meant to aid in avoiding the misdiagnosis of adult-onset type 1 DM. In the algorithm, which was devised using data from White European populations, an islet autoantibody test is first carried out; if positive, type 1 diabetes is diagnosed. A negative test in a patient younger than 35 years and with no signs of type 2 diabetes means that C-peptide testing is advised. A C-peptide level below 200 pmol/L points to a diagnosis of type 1 diabetes, while a level above 200 pmol/L indicates that genetic testing for monogenic diabetes should be carried out. If signs of type 2 diabetes exist and/or the patient is over age 35 years, the individual most likely has type 2 diabetes **(Holt et al., 2021)**.

Monogenic diabetes

Although monogenic diabetes syndromes are not very common, representing fewer than 5% of pediatric diabetes cases, it is important to avoid misdiagnosis of monogenic DM as type 1 or type 2 DM. In **2021**, The American Diabetes Association (ADA) advises considering a diagnosis of monogenic diabetes when the following criteria are present:

- Diabetes is diagnosed within 6 months of birth
- A strong family history of diabetes is present, without type 2 features (eg, obesity or higher-risk ethnicity)
- Mild fasting hyperglycemia is observed, especially in young, nonobese children
- Diabetes is present, but islet cell autoantibodies, obesity, and insulin resistance are absent

If a form of monogenic diabetes is suspected, it is increasingly feasible to obtain a true genetic diagnosis through commercially available genetic testing. For further information about the diagnosis and management of monogenic diabetes, the ADA suggests consulting the 2018 clinical practice consensus guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) at the ISPAD website **(DiMeglio et al., 2018)**.

Complications

Infection

Infections cause considerable morbidity and mortality in patients with diabetes. Infection may precipitate metabolic derangements, and conversely, the metabolic derangements of diabetes may facilitate infection. Patients with long-standing diabetes tend to have microvascular and macrovascular disease with resultant poor tissue perfusion and increased risk of infection. The ability of the skin to act as a barrier to infection may be compromised when the diminished

sensation of diabetic neuropathy results in unnoticed injury. Diabetes increases susceptibility to various types of infections. The most common sites are the skin and urinary tract. Dermatologic infections that occur with increased frequency in patients with diabetes include staphylococcal follicular skin infections, superficial fungal infections, cellulitis, erysipelas, and oral or genital candidal infections. Both lower urinary tract infections and acute pyelonephritis are seen with greater frequency. A few infections, such as malignant otitis externa, rhinocerebral mucormycosis, and emphysematous pyelonephritis, occur almost exclusively in patients with diabetes, though they are fairly rare even in this population. Infections such as staphylococcal sepsis occur more frequently and are more often fatal in patients with diabetes than in others. Infections such as pneumococcal pneumonia affect patients with diabetes and other patients with the same frequency and severity **(Brownlee et al., 2020).**

Diabetic nephropathy

About 20–30% of patients with type 1 DM develop evidence of nephropathy and all patients with diabetes should be considered to have the potential for renal impairment unless proven otherwise **(Brownlee et al., 2020)**. Chronically elevated blood pressure contributes to the decline in renal function. The use of contrast media can precipitate acute renal failure in patients with underlying diabetic nephropathy. Although most recover from contrast medium–induced renal failure within 10 days, some have irreversible renal failure.

Diabetic neuropathy

In the peripheral nerves, diabetes causes peripheral neuropathy. The 4 types of diabetic neuropathy are as follows:

- Peripheral distal symmetrical polyneuropathy, predominantly sensory.
- Autonomic neuropathy.
- Proximal painful motor neuropathy.
- Cranial mononeuropathy (ie, cranial nerve III, IV, or VI).

Of these 4 types, distal symmetric sensorimotor polyneuropathy (in a glove-and-stocking distribution) is the most common (**Atkinson et al., 2020)**. Besides causing pain in its early stages, this type of neuropathy eventually results in the loss of peripheral sensation. The combination of decreased sensation and peripheral arterial insufficiency often leads to foot ulceration and eventual amputation. Acute-onset mononeuropathies in diabetes include acute cranial mononeuropathies, mononeuropathy multiplex, focal lesions of the brachial or lumbosacral plexus, and radiculopathies. Of the cranial neuropathies, the third cranial nerve (oculomotor) is most commonly affected, followed by the sixth nerve (abducens) and the fourth nerve (trochlear). Patients can present with diplopia and eye pain. In diabetic third-nerve palsy, the pupil is usually

spared, whereas in third-nerve palsy due to intracranial aneurysm or tumor, the pupil is affected in 80-90% of cases.

It is important to consider nondiabetic causes of cranial nerve palsies, including intracranial tumors, aneurysms, and brainstem stroke **(American Diabetes Association, 2021)**. Therefore, evaluation should include nonenhanced and contrast-enhanced computed tomography (CT) or, preferably, magnetic resonance imaging (MRI). Neurologic consultation is recommended. Acute cranial-nerve mononeuropathies usually resolve in 2-9 months. Acute thrombosis or ischemia of the blood vessels supplying the structure involved is thought to cause these neuropathies.

Macrovascular complications

People with diabetes experience accelerated atherosclerosis, affecting the small arteries of the heart, brain, lower extremity, and kidney **(Lamb, 2022)**. Coronary atherosclerosis often occurs at a younger age and is more severe and extensive than in those without diabetes, increasing the risk of ischemic heart disease. Atherosclerosis of the internal carotid and vertebrobasilar arteries and their branches predisposes to cerebral ischemia. Severe atherosclerosis of the iliofemoral and smaller arteries of the lower legs predisposes to gangrene. Ischemia of a single toe or ischemic areas on the heel are characteristic of diabetic peripheral vascular disease; these result from the involvement of much smaller and more peripheral arteries. Atherosclerosis of the main renal arteries and their intrarenal branches causes chronic nephron ischemia, which is a significant component of multiple renal lesions in diabetes. However, not all people with type 1 DM are at risk for nephropathy, because there are some polymorphisms in the various factors involved in its pathogenesis, which can modulate the course of this disease from one person to the other.

Risk factors for macrovascular disease

Macrovascular disease is the leading cause of death in patients with diabetes, causing 65-75% of deaths in this group, compared with approximately 35% of deaths in people without diabetes. Diabetes by itself increases the risk of myocardial infarction (MI) 2-fold in men and 4-fold in women, and many patients have other risk factors for MI as well.

The HbA1c value per se, rather than self-reported diabetes status or other established risk factors, robustly predicts MI odds. Each 1% increment in HbA1c independently predicts 19% higher odds for MI **(de Boer et al., 2017)**. The risk of stroke in people with diabetes is double that of nondiabetic people, and the risk of peripheral vascular disease is 4 times that of people without diabetes. Patients with diabetes may have an increased incidence of silent ischemia **(Jenkins, 2017)**. Diastolic dysfunction is common in patients with diabetes and should be considered in patients who have symptoms of congestive heart failure and a normal ejection fraction.

Treatment of type 1 diabetes

Patient education

Education is a vital aspect of diabetes management. Patients with new-onset type 1 DM require extensive education if they are to manage their disease safely and effectively and to minimize long-term complications. Such education is best coordinated by the patient's long-term care providers. At every encounter, the clinician should educate the patient—and, in the case of children, the parents—about the disease process, management, goals, and long-term complications (**Tucker, 2021a)**.

ADA guidelines urge that attention be paid to older adolescent patients who may be leaving their home and their current health care providers. In **2021**, **American Diabetes Association** proved that at the transition between pediatric and adult health care, older teens can become detached from the health care system, putting their medical care and their glycemic control at risk. The guidelines identify the National Diabetes Education Program (NDEP) as a source of materials that can help smooth the transition to adult health care. Education about an appropriate treatment plan and encouragement to follow the plan are especially important in patients with diabetes. Physicians must ensure that the care for each patient with diabetes includes all necessary laboratory tests, examinations (eg, foot and neurologic examinations), and referrals to specialists (eg, an ophthalmologist or podiatrist). A dietitian should provide specific diet control education to the patient and family. A nurse should educate the patient about self–insulin injection and performing fingerstick tests for blood glucose level monitoring.

Diet

Diet management includes education about how to adjust the timing, size, frequency, and composition of meals so as to avoid hypoglycemia or postprandial hyperglycemia. All patients on insulin should have a comprehensive diet plan, created with the help of a professional dietitian, that includes the following:

- A daily caloric intake prescription.
- Recommendations for amounts of dietary carbohydrate, fat, and protein.
- Instructions on how to divide calories between meals and snacks.

Caloric distribution is an important aspect of dietary planning in these patients. A recommended distribution consists of 20% of daily calories for breakfast, 35% for lunch, 30% for dinner, and 15% for a late-evening snack. The minimum protein requirement for good nutrition is 0.9 g/kg/day (usual range, 1-1.5 g/kg/day), but a reduced protein intake is indicated in cases of nephropathy. Fat intake should be limited to no more than 30% of the total calories, and a low-cholesterol diet is recommended. Patients should minimize consumption of sugars and ensure that

they have adequate fiber intake. In some cases, midmorning and midafternoon snacks are important to avoid hypoglycemia **(Wolsdorf and Garvey, 2016)**.

Activity

Exercise is an important aspect of diabetes management. Patients should be encouraged to exercise regularly. Educate the patients about the effects of exercise on the blood glucose level. If patients participate in rigorous exercise for more than 30 minutes, they may develop hypoglycemia unless they either decrease the preceding insulin injection by 10-20% or have an extra snack. Patients must also make sure to maintain their hydration status during exercise **(Lamb, 2022)**.

Tight glycemic control

The association between chronic hyperglycemia and increased risk of microvascular complications in patients with type 1 DM was demonstrated in the Diabetes Control and Complications Trial (DCCT) (**Brownlee et al., 2020**). In that trial, intensive therapy designed to maintain normal blood glucose levels greatly reduced the development and progression of retinopathy, microalbuminuria, proteinuria, and neuropathy, as assessed over 7 years. The DCCT ended in 1993. However, the Epidemiology of Diabetes Interventions and Complications Study (EDIC), an observational study that continues to follow the patients previously enrolled in the DCCT, has demonstrated continued benefit from intensive treatment **(Katsarou et al., 2017)**.

Self-Monitoring of Glucose Levels

Optimal diabetic control requires frequent self-monitoring of blood glucose levels, which allows rational adjustments in insulin doses. All patients with type 1 DM should learn how to self-monitor and record their blood glucose levels with home analyzers and adjust their insulin doses accordingly. Insulin-dependent patients ideally should test their plasma glucose daily before meals, in some cases 1-2 hours after meals, and at bedtime. In practice, however, patients often obtain 2-4 measurements each day, including fasting levels and levels checked at various other times (eg, preprandially and at bedtime). Instruct patients with type 1 DM in the method of testing for urine ketones with commercially available reagent strips **(Lamb, 2022)**.

Continuous Glucose Monitoring

Continuous glucose monitors (CGMs) contain transcutaneous or subcutaneous sensors depending on whether the devices are externally worn or fully implantable, respectively that measure interstitial glucose levels every 1-5 minutes, providing alarms when glucose levels are too high or too low or are rapidly rising or falling **(Sherwood et al., 2020)**. CGMs transmit to a receiver, which either is a pagerlike device or is integral to an insulin pump. Looking at the continuous glucose graph and responding to the alarms can help patients avoid serious hyperglycemia or hypoglycemia.

CGMs have several drawbacks. Firstly, there is a lag between glucose levels in the interstitial space and levels in capillary blood, so that the levels recorded by the CGM may differ from a fingerstick (capillary) glucose reading. For that reason, the trends (ie, whether the glucose levels are rising or falling) tend to be more helpful. Secondly, patients may over treat hyperglycemia (repeatedly giving insulin because the glucose levels do not fall rapidly enough, a phenomenon known as stacking), as well as over treat low glucose levels (because the glucose levels rise slowly with ingestion of carbohydrate) **(Lamb, 2022)**.

Flash glucose monitoring

Another technology, flash glucose monitoring, stores data in a wearable sensor that can be scanned for this information via a dedicated receiver or smartphone **(Sherwood et al., 2020)**. The FreeStyle Libre Flash Glucose Monitoring System (Abbott Diabetes Care), approved by the FDA in September 2017, allows patients to reduce the number of required finger-stick tests by measuring glucose levels using a self-applied sensor inserted into the back of the upper arm **(Nelson and Tucker, 2017)**:

Insulin Therapy

Types of insulin

Rapid-, short-, intermediate-, and long-acting insulin preparations are available. Various pork, beef, and beef-pork insulins were previously used; however, in the United States, recombinant human insulin is now used almost exclusively. Commercially prepared mixtures of insulin are also available. Rapid-acting insulins include lispro, glulisine, and aspart insulin. Lispro insulin is a form of regular insulin that is genetically engineered with the reversal of the amino acids lysine and proline at B28, 29 in the B chain. Glulisine insulin substitutes glutamic acid for lysine in position B29. Aspart insulin substitutes aspartic acid for proline in position 28 of the B chain **(Qaseem, 2011)**.

These insulins are absorbed more quickly and have a rapid onset of action (5-10 minutes), a short interval to peak action (45-75 minutes), and a short duration of action (2-4 hours). Therefore, they can be administered shortly before eating. In addition, neutral protamine Hagedorn (NPH) insulin will not inhibit the action of insulin lispro when the 2 agents are mixed together right before injection; this is not true of regular insulin **(Lamb, 2022)**.

A rapid-acting inhaled insulin powder (Afrezza) for types 1 and 2 diabetes mellitus was approved by the FDA in June **2014**. It is regular insulin but is considered rapid-acting because it peaks at 12-15 minutes and returns to baseline levels at about 160 minutes. Approval was based on a study involving over 3,000 patients over a 24-week period. In persons with type 1 diabetes, the inhaled insulin was found to be noninferior to standard injectable insulin when used in conjunction with basal insulin at reducing hemoglobin A1c. In persons with type 2 diabetes, the inhaled insulin was

compared to placebo inhalation in combination with oral diabetic agents and showed a statistically significant lower hemoglobin A1c (**Tucker, 2014b)**.

In **2012, US Food and Drug Administration** has proved that short-acting insulin includes regular insulin. Regular insulin is a preparation of zinc insulin crystals in solution. When it is administered subcutaneously, its onset of action occurs in 0.5 hours, its peak activity comes at 2.5-5 hours, and its duration of action is 4-12 hours. The standard strength of regular insulin is 100 U/mL (U-100), but 500 U/mL (U-500) insulin is increasingly used, albeit mostly in type 2 DM. Accidental prescribing of U-500 rather than U-100 is a potential safety issue. A study by **de la Pena et al (2011)** found that although the overall insulin exposure and effects of 500 U/mL insulin are similar to those of 100 U/mL insulin, peak concentration was significantly lower with U-500, and the effect after the peak was prolonged; areas under the curve were similar for the 2 strengths.

Both regular human insulin and rapid-acting insulin analogues are effective at lowering postprandial hyperglycemia in various basal bolus insulin regimens used in type 1 DM. Rapid-acting insulin analogues may be slightly better at lowering HbA1c and are preferred by most US diabetologists, but the differences are clinically insignificant **(Cashen and Petersen, 2019)**.

In September 2017, the FDA approved the rapid-acting insulin aspart Fiasp for the treatment of adults with diabetes. This human insulin analog is formulated with niacinamide, which aids in speeding the initial absorption of insulin. Dosing can occur at the beginning of a meal or within 20 minutes after the meal commences. In a study of adult patients with type 1 DM, Fiasp could be detected in the circulation about 2.5 minutes after it was administered. Maximum insulin levels occurred approximately 63 minutes after the drug's administration (**Nainggolan, 2017a)**. Semilente insulin is like regular insulin and is a rapid-acting insulin with a slightly slower onset of action. It contains zinc insulin microcrystals in an acetate buffer. It is not readily available in the United States.

Intermediate-acting insulins include NPH insulin, a crystalline suspension of human insulin with protamine and zinc. NPH provides a slower onset of action and longer duration of action than regular insulin does. The onset of action usually occurs at 1-2 hours, the peak effect is noted at 4-12 hours, and the duration of action is normally 14–24 hours.

Lente insulin is a suspension of insulin in buffered water that is modified by the addition of zinc chloride. This insulin zinc suspension is equivalent to a mixture of 30% prompt insulin zinc (Semilente) and 70% extended insulin zinc (Ultralente). It is not used in the United States.

Long-acting insulins used in the United States include insulin glargine (Lantus, Toujeo) and insulin detemir (Levemir). Insulin glargine has no peak and produces a relatively stable level lasting more than 24 hours. In some cases, it can produce a stable basal serum insulin concentration with a single daily injection, though patients requiring lower doses typically are given twice-daily

injections. Insulin detemir has a duration of action that may be substantially shorter than that of insulin glargine but longer than those of intermediate-acting insulins **(Lamb, 2022)**.

Toujeo 300 U/mL is a newer dosage strength and form of insulin glargine than Lantus 100 U/mL, having been approved by the FDA in February 2016. Compared with those of Lantus 100 U/mL, the pharmacokinetic and pharmacodynamic profiles of Toujeo are more stable and prolonged; the duration of action exceeds 24 hours. Clinical trials showed comparable glycemic control between Lantus and Toujeo, although the trials noted the need for higher daily basal insulin doses (ie, 12-17.5%) with Toujeo. The risk for nocturnal hypoglycemia was lower with Toujeo in insulin-experienced patients with type 2 diabetes, but this was not the case for insulin-naive patients with type 1 DM or for patients with type 2 DM **(Blair and Keating, 2016)**. With its March 2018 approval by the FDA, Toujeo Max SoloStar became the highest capacity long-acting insulin pen on the market. Toujeo Max necessitates fewer refills and, for some diabetes patients, fewer injections to deliver the required Toujeo dosage.

A new ultralong-acting basal insulin, insulin degludec (Tresiba), which has a duration of action beyond 42 hours, has also been approved by the FDA. It is indicated for diabetes mellitus types 1 and 2. A combination product of insulin degludec and the rapid-acting insulin aspart was also approved (Ryzodeg 70/30). Approval was based on results from theBEGIN trial **(Davies et al., 2014)** that showed noninferiority to comparator productions. The cardiovascular outcomes trial (DEVOTE) comparing cardiovascular safety of insulin degludec tothat of insulin glargine in patients with type 2 DM is ongoing.

Mixtures of insulin preparations with different onsets and durations of action frequently are administered in a single injection by drawing measured doses of 2 preparations into the same syringe immediately before use. The exceptions are insulin glargine and insulin detemir, which should not be mixed with any other form of insulin. Preparations that contain amixture of 70% NPH and 30% regular human insulin (eg, Novolin 70/30, Humulin 70/30, Ryzodeg 70/30) are available, but the fixed ratios of intermediate-acting or long-acting torapid-acting insulin may restrict their use **(Khardori, 2022)**.

An ultrafast-acting insulin aspart formulation for mealtimes (Fiasp), for adult patients with type 1 or 2 DM, was approved in January 2017 for use in Canada and the Europe Union. The drug contains conventional mealtime insulin aspart in combination with two ingredients, vitamin B3 and the amino acid L-arginine that are meant to allow faster insulin absorption so the medication can better mimic natural physiologic insulin. Unlike in the European Union, however, the new formulation is not approved for insulin pumps in Canada. The product has not yet been approved for use in the United States **(Nainggolan, 2017b)**.

Insulin glargine and cancer

Controversy has arisen over a disputed link between insulin glargine and cancer. On July 1, 2009, the FDA issued an early communication regarding a possible increased risk of cancer in patients using insulin glargine (Lantus) **(Heise and Pieber, 2007)**. In a study by **Suissa et al (2011)**, insulin glargine use was not associated with an increased risk of breast cancer during the first 5 years of use. The risk tended to increase after 5 years, however, and significantly so for the women who had taken other forms of insulin before starting insulin glargine.

A study by **Johnson et al (2011)** found the same incidences for all cancers in patients receiving insulin glargine as in those not receiving insulin glargine. Overall, no increase in breast cancer rates was associated with insulin glargine use, although patients who used only insulin glargine had a higher rate of cancer than those who used another type of insulin (**Nainggolan, 2017a)**.

Common insulin regimens

The goal of treatment in type 1 DM is to provide insulin in as physiologic a manner as possible. Insulin replacement is accomplished by giving a basal insulin and a preprandial (premeal) insulin. The basal insulin is either long-acting (glargine or detemir) or intermediate-acting (NPH). The preprandial insulin is either rapid-acting (lispro, aspart, or glulisine) or short-acting (regular). Currently, NPH insulin is being used less frequently, whereas insulin glargine and insulin detemir are being used more frequently **(Lamb, 2022)**.

For patients on intensive insulin regimens (multiple daily injections or insulin pumps), the preprandial dose is based on the carbohydrate content of the meal (the carbohydrate ratio) plus a correction dose if their blood glucose level is elevated (eg, an additional 2 U of rapid-acting insulin to correct the blood glucose from a level of 200 mg/dL to a target of 100 mg/dL). This method allows patients more flexibility in caloric intake and activity, but it requires more blood glucose monitoring and closer attention to the control of their diabetes. Common insulin regimens include the following:

- Split or mixed – NPH with rapid-acting (eg, lispro, aspart, or glulisine) or regular insulin before breakfast and supper
- Split or mixed variant – NPH with rapid-acting or regular insulin before breakfast, rapid-acting or regular insulin before supper, and NPH before bedtime (the idea is to reduce fasting hypoglycemia by giving the NPH later in the evening)
- Multiple daily injections (MDI) – A long-acting insulin (eg, glargine or detemir) once a day in the morning or evening (or twice a day in about 20% of patients) and a rapid-acting insulin before meals or snacks (with the dose adjusted according to the carbohydrate intake and the blood glucose level)

- Continuous subcutaneous insulin infusion (CSII) – Rapid-acting insulin infused continuously 24 hours a day through an insulin pump at 1 or more basal rates, with additional boluses given before each meal and correction doses administered if blood glucose levels exceed target levels

Insulin is sensitive to heat and exposure to oxygen. Once a bottle of insulin is open, it should be used for no more than 28 days and then discarded; even if there is still some insulin in the bottle, it may have lost its clinical effectiveness. Insulin kept in a pump reservoir for longer than 3 days may lose its clinical effectiveness (though insulin aspart has now been approved for use for as long as 6 days in a pump) **(Lamb, 2022)**.

Sometimes, insulin distributed from the pharmacy has been exposed to heat or other environmental factors and therefore may be less active. If a patient is experiencing unexplained high blood sugar levels, new insulin vials should be opened and used **(Khardori, 2022)**.

Initiation of insulin therapy

The initial daily insulin dose is calculated on the basis of the patient's weight. This dose is usually divided so that one half is administered before breakfast, one fourth before dinner, and one fourth at bedtime. After selecting the initial dose, adjust the amounts, types, and timing according to the plasma glucose levels. Adjust the dose to maintain preprandial plasma glucose at 80-150 mg/dL (ie, 4.44-8.33 mmol/L) **(Khardori, 2022)**.

The insulin dose is often adjusted in increments of 10% at a time, and the effects are assessed over about 3 days before any further changes are made. More frequent adjustments of regular insulin can be made if a risk of hypoglycemia is present.

Carbohydrate counting may be used to determine the meal-time insulin dose. Because patients may experience hyperglycemic episodes despite strict adherence to carbohydrate counting, particularly after meals that are high in protein or fat, Australian researchers developed an algorithm for estimating the mealtime insulin dose on the basis of measurementsof physiologic insulin demand evoked by foods in healthy adults. The researchers showed that use of this algorithm improved glycemic control **(DiMeglio et al., 2018)**.

Initiation of insulin therapy in children

Children with moderate hyperglycemia but without ketonuria or acidosis may be started with a single daily subcutaneous injection of 0.3-0.5 U/kg of intermediate-acting insulin alone. Children with hyperglycemia and ketonuria but without acidosis or dehydration may be started on 0.5-0.7 U/kg of intermediate-acting insulin and subcutaneous injections of 0.1 U/kg of regular insulin at 4- to 6-hour intervals **(Khardori, 2022)**.

Multiple daily subcutaneous insulin injections are administered to control hyperglycemia after meals and to maintain normal plasma glucose levels throughout the day. This may increase the

risks of hypoglycemia. Therefore, patients should be well educated about their disease and about self-monitoring of plasma glucose levels. About 25% of the total daily dose is administered as intermediate-acting insulin at bedtime, with additional doses of rapid-acting insulin before each meal (4-dose regimen). Where available, a basal insulin such as glargine or detemir is preferred to NPH. These patients may need additional intermediate- or long-acting insulin in the morning for all-day coverage. Patients should adjust their daily dosage(s) on the basis of their self-monitoring of glucose levels before each meal and at bedtime. Patients should also assess their plasma glucose levels at 2:00-4:00 AM at least once per week during the first few weeks of treatment and thereafter as indicated **(Lamb, 2022)**.

Continuous subcutaneous insulin infusion

A small battery-operated infusion pump that administers a continuous subcutaneous infusion of rapid-acting insulin can provide selected, programmed basal rate(s) of insulin and a manually administered bolus dose before each meal. The patient self-monitors preprandial glucose levels to adjust the bolus dose(s). The CSII method provides better control than the MDI method does. Initially, hypoglycemia is common with pump therapy, but once metabolic control is achieved, the risk is the same as with MDI. **Bergenstal et al (2010)** determined that sensor-augmented pump therapy led to better glycemic control and that more patients reached targets with this technology than with injection therapy. An Australian observational case-control study involving 690 children with type 1 diabetes found that CSII, in comparison with insulin injection therapy, yielded a long-term improvement in glycemic control, as well as a reduction in complications such as severe hypoglycemia and hospitalization for diabetic ketoacidosis (DKA) **(Johnson et al., 2013)**. HbA1c improvement remained significant in the pump therapy cohort throughout 7 years of follow-up.

The rate of severe hypoglycemic events per 100 patient-years dropped from 14.7 to 7.2 with pump therapy but jumped from 6.8 to 10.2 events per 100 patient-years with injection therapy **(Busko, 2013b)**.

Increased bedtime doses of hypoglycemic agents with nighttime peaks in action may correct early morning hyperglycemia but may be associated with undesirable nocturnal hypoglycemia. Targeted CSII programming can facilitate the prevention of early-morning hyperglycemia in selected patients.

Changes in altitude may affect delivery from insulin pumps. During the flight of a commercial airliner (200 mmHg pressure decrease), excess insulin delivery of 0.623% of cartridge volume was demonstrated as a result of bubble formation and expansion of preexisting bubbles **(Smith and Harris, 2018)**.

The American Association of Clinical Endocrinologists and American College of Endocrinology released a consensus statement on insulin pump management **(Grunberger et al., 2021)**:

- Based on currently available data, continuous subcutaneous insulin infusion (CSII) is justified for basal-bolus insulin therapy in patients with type 1 diabetes mellitus.
- Only providers whose practice can assume full responsibility for a comprehensive pump management program should offer this technology.
- The ideal CSII candidate is a patient with type 1 diabetes mellitus or intensively management insulin-dependent type 2 diabetes mellitus who is currently performing 4 or more insulin injections and 4 or more self-monitored blood glucose measurements daily; is motivated to achieve optima blood glucose control; is willing and able to carry out the tasks that are required to use this complex and time-consuming therapy safely and effectively; and is willing to maintain frequent contact with their health care team.
- Adult patients

1. At CSII initiation, the patient should have daily contact with the pump trainer. a return visit with the endocrinologist/diabetologist/advanced practice nurse is advised within 3-7 days after CSII initiation.
2. Educational consults should be scheduled weekly or biweekly at first, then periodically as needed.
3. Specialist follow-up visits should be scheduled at least monthly until the pump regimen is stabilized, then at least once every 3 mo.

- Pediatric patients

1. CSII is indicated for pediatric patients with elevated hemoglobin A1C (HbA1C) levels on injection therapy; frequent, severe hypoglycemia; widely fluctuating glucose levels; a treatment regimen that compromises lifestyle; and microvascular complications and/or risk factors for macrovascular complications.
2. Ideal pediatric candidates are those with motivated families who are committed to monitoring blood glucose 4 or more times per day and have a working understanding of basic diabetes management.
3. Patient age and duration of diabetes should not be factors in determining the transition from injections to CSII.

Local allergic reactions

Generalized insulin allergy is rare. Symptoms occur immediately after the injection and include urticaria, angioedema, pruritus, bronchospasm, and, rarely, circulatory shock. As a rule, allergy may be treated with antihistamines. Some cases may require epinephrine and intravenous (IV) steroids. Local allergic reactions can occur at the site of insulin injections and can cause pain,

burning, local erythema, pruritus, and induration. These complications are less common with the human insulins now in use than with the animal insulins once widely employed. Such reactions usually resolve spontaneously without any intervention. Local fat atrophy or hypertrophy at injection sites was common with animal insulins but is rare with human insulin and insulin analogues. Patients do not require any specific treatment of local fat hypertrophy, but injection sites should be rotated. Changing to a different insulin preparation may be necessary **(Repaske, 2016)**.

New lines of treatment of type 1 diabetes

1. Pancreatic transplantation:

This procedure has been performed in over 15,000 patients worldwide with a success rate (insulin independence) of 85% at 1 year. Successful pancreas transplantation has been demonstrated to be efficacious in significantly improving the quality of life of people with diabetes, primarily by eliminating the need for exogenous insulin, frequent daily blood glucose measurements, and many of the dietary restrictions imposed by the disorder **(American Diabetes Association, 2021)**.

Transplantation can also eliminate the acute complications commonly experienced by patients with type 1 diabetes (e.g., hypoglycemia and hyperglycemia). Pancreas transplantation is only partially successful in reversing the long-term renal and neural complications of diabetes. Pancreas-only transplants require lifelong immune suppression to prevent rejection of the graft and potential recurrence of the autoimmune process that might again destroy pancreatic islet cells **(Norris et al., 2020)**.

2. Islet cells transplantation:

Islet cell transplantation, in which islets cells isolated from pancreas of cadavers are perfused percutanoeusly into the portal vein, has the advantage of being a minimally invasive procedure compared to pancreas transplantation. An islet transplantation strategy (Edmonton protocol) infuses isolated pancreatic islets into the portal vein of a group of adults with T1DM. This therapeutic strategy also involves the use of a new generation of immunosuppressive medications that apparently have lower side effect profiles than do other drugs **(Rickels and Robertson, 2019).**

3. Stem cell therapy:

Stem cells have the potential to provide an unlimited source of cells for research, replace missing or damaged insulin-producing cells, replace other cells damaged by diabetes, or reboot the faulty immune system responsible for causing Type 1 diabetes **(Smith and Harris, 2018)**.

4. Artificial pancreas:

The goal of the artificial pancreas is threefold:

- To improve insulin replacement therapy until glycemic control is practically normal.
- To ease the burden of therapy for the insulin-dependent.
- To mimic normal stimulation of the liver by the pancreas.
- Different approaches under consideration include:

➢ **The medical equipment approach:** Using an insulin pump under closed loop control using real-time data from a continuous blood glucose sensor. **In 2020**, the FDA approved Medtronic's MiniMed 770G, a Bluetooth-enabled, hybrid closed-loop device, for use in children aged 2-6 years. Another hybrid closed-loop system, Control-IQ, from Tandem Diabetes Care, was approved in 2019, and, according to the FDA, "is the first such controller that can be used with other diabetes devices that are also designed to be integrated into a customizable diabetes management system for automated insulin delivery."

➢ **The bioengineering approach:** The development of a bioartificial pancreas consisting of a biocompatible sheet of encapsulated beta cells. When surgically implanted, the islet sheet will behave as the endocrine pancreas and will be viable for years.

➢ **The gene therapy approach:** The therapeutic infection of a diabetic person by a genetically engineered virus which causes a DNA change of intestinal cells to become insulin-producing cells **(Busko, 2018)**.

5. Islet neogenesis:

Islet neogenesis associated protein (INGAP) stimulates experimental pancreatic islet growth, as evidenced by elevated markers of beta cell mass, in rodents, dogs and primates. Previous analyses of mice that have a transgenic expression of INGAP targeted to the exocrine pancreas have indicated additional biological activity attributed to INGAP. INGAP conferred beta cell protection and enhanced islet function.

Analysis of oxidative stress genes in INGAP mice revealed a decrease in islet expression of the NADPH oxidase in both basal state and in response to pro-inflammatory cytokine stimulation. These data are consistent with a pleiotropic role for INGAP and reveal new pathways to target in the discovery of improved diabetic therapies **(Shapiro et al., 2017)**.

No Conflict of interest.

References:

1. Atkinson, M. A., Eisenbarth, G. S. & Michels, A. W. (2014): Type 1 diabetes. Lancet 383, 69–82.

2. Atkinson, M.A., Mcgill, D.E., Dassau, E., Laffel, L. (2020): "Type 1 diabetes mellitus". Williams Textbook of Endocrinology. Elsevier. pp. 1403–1437.
3. Davis, SN., et al. (2010): Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. New England Journal of Medicine, 363(4):311-20.
4. Bingley, P. J. et al. (1997): Prediction of IDDM in the general population: strategies based on combinations of autoantibody markers. Diabetes 46, 1701–1710.
5. Busko, M. (2018): FDA Approves Artificial Pancreas for Children with Type 1 Diabetes. Medscape Medical News.
6. Butler, A.E., Misselbrook, D. (2020): "Distinguishing between type 1 and type 2 diabetes". BMJ. 370: m2998.
7. Chiang, JL., Maahs, DM., Garvey, KC., et al. (2018): Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association. Diabetes Care, 41(9):2026-44.
8. Davies, MJ., Gross, JL., Ono, Y., Sasaki, T., Bantwal, G., Gall, MA., et al. (2014): Efficacy and safety of insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart in type 1 diabetes: a 26-week randomized, open-label, treat-to-target non-inferiority trial. Diabetes, Obesity and Metabolism, 16 (10):922-30.
9. Dayan, C.M., Korah, M., Tatovic, D., Bundy, B.N., Herold, K.C. (2019): "Changing the landscape for type 1 diabetes: the first step to prevention". Lancet. 394 (10205): 1286–1296.
10. Delli, A.J., Lernmark, A. (2016): "Type 1 (insulin-dependent) diabetes mellitus: etiology, pathogenesis, prediction, and prevention". In Jameson JL (ed.). Endocrinology: Adult and Pediatric (7 ed.). Saunders. pp. 672–690
11. Diabetes Prevention Trial--Type 1 Diabetes Study Group. (2002): Effects of insulin in relatives of patients with type 1 diabetes mellitus. New England Journal of Medicine, 346(22):1685-91.
12. Ebekozien, OA., Noor, N., Gallagher, MP., Alonso, GT. (2020): Type 1 Diabetes and COVID-19: Preliminary Findings From a Multicenter Surveillance Study in the U.S. Diabetes Care, 43(8): e83–e85.
13. Eesmaa, A. et al. (2021): The cytoprotective protein MANF promotes neuronal survival independently from its role as a GRP78 cofactor. Journal of Biological Chemistry, 296, 100295.
14. Eizirik, D. L., Colli, M. L. & Ortis, F. (2009): The role of inflammation in insulitis and beta-cell loss in type 1 diabetes. Nature Reviews Endocrinology. 5, 219–226.
15. El-Ziny, M. A. E. M., Salem, N. A. B., El-Hawary, A. K., Chalaby, N. M., & Elsharkawy, A. A. E. (2014): Epidemiology of childhood type 1 diabetes mellitus in Nile Delta, northern Egypt-a retrospective study. Journal of clinical research in pediatric endocrinology, 6(1), 9.
16. Ferrannini, E. et al. (2010): Progression to diabetes in relatives of type 1 diabetic patients: mechanisms and mode of onset. Diabetes 59, 679–685.

17. Galli, E. et al. (2016): Increased circulating concentrations of mesencephalic astrocyte-derived neurotrophic factor in children with type 1 diabetes. Scientific Reports, 6: 29058.
18. Galli, E. et al. (2019): Mesencephalic astrocyte-derived neurotrophic factor is upregulated with therapeutic fasting in humans and diet fat withdrawal in obese mice. Scientific Reports, 9: 14318.
19. Galli, E., Härkönen, T., Sainio, M.T., Ustav, M., Toots, U., Urtti, A., Yliperttula, M., Lindahl, M., Knip, M., Saarma, M., Lindholm, P. (2016): Increased circulating concentrations of mesencephalic astrocyte-derived neurotrophic factor in children with type 1 diabetes. Scientific Reports, 6: 29058.
20. Garg, SK., Voelmle, MK., Beatson, CR., et al. (2011): Use of Continuous Glucose Monitoring in Subjects With Type 1 Diabetes on Multiple Daily Injections Versus Continuous Subcutaneous Insulin Infusion Therapy: A prospective 6-month study. Diabetes Care, 34(3):574-9.
21. Glembotski, CC. (2011): Functions for the cardiomyokine, MANF, in cardioprotection, hypertrophy and heart failure. Journal of Molecular and Cellular Cardiology, 51: 512–517.
22. Holt, RIG., DeVries, JH., Hess-Fischl, A., et al. (2021): The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia, 64(12):2609-2652.
23. Hoseki, J. et al. (2010): Solution structure and dynamics of mouse ARMET. FEBS Letters, 584: 1536–1542.
24. Hotamisligil, G.S. (2017): Inflammation, metaflammation and immunometabolic disorders. Nature, 542: 177–185.
25. Imkampe, AK., Gulliford, MC. (2011): Trends in Type 1 diabetes incidence in the UK in 0- to 14-year-olds and in 15- to 34-year-olds, 1991-2008. Diabetic Medicine, 28(7):811-4.
26. Jacobson, AM., Ryan, CM., Cleary, PA., Waberski, BH., Weinger, K., Musen, G., et al. (2011): Biomedical risk factors for decreased cognitive functioning in type 1 diabetes: an 18 year follow-up of the Diabetes Control and Complications Trial (DCCT) cohort. Diabetologia, 54(2):245-55.
27. Johnson, SR., Cooper, MN., Jones, TW., Davis, EA. (2013): Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case-control study. Diabetologia, 56(11):2392-400.
28. Katsarou, A., Gudbjörnsdottir, S., Rawshani, A., Dabelea, D., Bonifacio, E., Anderson, B.J., et al. (2017): "Type 1 diabetes mellitus". Nature Reviews. Disease Primers. 3: 17016.
29. Khardori R. (2022): Type 1 Diabetes Mellitus. emedicine.medscape.com.
30. Klinke, D.J. (2008): Extent of beta cell destruction is important but insufficient to predict the onset of type 1 diabetes mellitus. PLoS One 3, e1374.
31. Knip, M. et al. (2010): Prediction of type 1 diabetes in the general population. Diabetes Care 33, 1206–1212.
32. Lamb W H. (2022): Pediatric Type 1 Diabetes Mellitus. Emedicine. medscape.com

33. Lee, A.H. et al. (2003): XBP-1 regulates a subset of endoplasmic reticulum resident chaperone genes in the unfolded protein response. Molecular and Cellular Biology, 23: 7448–7459.
34. Lee, SH., Kim, JH., Kang, MJ., et al. (2011): Implications of nocturnal hypertension in children and adolescents with type 1 diabetes. Diabetes Care, 34(10):2180-5.
35. Leiter, LA., Lundman, P., da Silva, PM., et al. (2011): Persistent lipid abnormalities in statin-treated patients with diabetes mellitus in Europe and Canada: results of the Dyslipidaemia International Study. Diabetic Medicine, 28(11):1343-1351.
36. Mayer-Davis, EJ., Lawrence, JM., Dabelea, D., et al. (2017): Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002-2012. New England Journal of Medicine, 376 (15):1419-29.
37. Norris, J.M., Johnson, R.K., Stene, L.C. (2020): "Type 1 diabetes-early life origins and changing epidemiology". The Lancet. Diabetes & Endocrinology. 8 (3): 226–238.
38. Orban, T., Bundy, B., Becker, DJ., et al. (2011): Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet, 378(9789):412-9.
39. Redondo, M.J., Steck, A.K., Pugliese, A. (2018): "Genetics of type 1 diabetes". Pediatric Diabetes. 19 (3): 346–353.
40. Sherwood, JS., Russell, SJ., Putman, MS. (2020): New and Emerging Technologies in Type 1 Diabetes. Endocrinology and Metabolism Clinics of North America, 49 (4):667-78.
41. Smith, A., Harris, C. (2018): "Type 1 diabetes: Management strategies". American Family Physician. 98 (3): 154–156. PMID 30215903. Retrieved 12 January 2022. 3(2):217-28.
42. Thomas, NJ., Jones, SE., Weedon, MN., Shields, BM., Oram, RA., Hattersley, AT. (2017): Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. Lancet Diabetes Endocrinol, 6(2):122-129.
43. Tucker, ME. (2017): Needle in a Haystack: Type 1 Diabetes Arises Equally in Adulthood. Medscape Medical News.
44. Tucker, ME. (2018a): FDA Approves New 'Smart' Continuous Glucose Monitor for Diabetes. Medscape Medical News
45. Tucker, ME. (2021a): Type 1 Diabetes Raises COVID-19 Risk in Kids if A1c Is High. Medscape Medical News