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Type 1 Diabetes

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Continuing Education Activity

Type 1 diabetes mellitus (T1D) is an autoimmune disease that leads to the destruction of insulin-producing pancreatic beta cells. Individuals with T1D require life-long insulin replacement with multiple daily insulin injections daily, insulin pump therapy, or the use of an automated insulin delivery system. Without insulin, diabetic ketoacidosis (DKA) develops and is life-threatening. In addition to insulin therapy, glucose monitoring with (preferably) a continuous glucose monitor (CGM) and a blood glucose monitor if CGM is unavailable is recommended. Self-management education and support should include training on monitoring, insulin administration, ketone testing when indicated, nutrition including carbohydrate estimates, physical activity, ways of avoiding and treating hypoglycemia, and use of sick day rules. Psychosocial issues also need to be recognized and addressed. This activity reviews the evaluation and management of T1D. It highlights the importance of a multidisciplinary approach to enhance outcomes.

Objectives:

- Describe the pathophysiology of type 1 diabetes mellitus.
- Explain the management of type 1 diabetes mellitus.
- Review other conditions for which patients with type 1 diabetes mellitus are at increased risk of developing.
- Explain the importance of improving coordination amongst the interprofessional team to enhance care for patients affected by type 1 diabetes mellitus.

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Introduction

Type 1 diabetes mellitus (T1D) is an autoimmune disease that leads to the destruction of insulin-producing pancreatic beta cells. There is heterogeneity in the metabolic, genetic, and immunogenetic characteristics of T1D and age-related differences, requiring a personalized approach for each individual. Loss of insulin secretion can occur quickly or gradually. Residual insulin production (detectable/higher c-peptide) is more common in adult-onset compared to youth-onset T1D, whereas diabetic ketoacidosis is more common in youth with T1D.[1] Detectable c-peptide is associated with better glycemic control.[2] The presence of other autoimmune conditions, obesity, comorbidities, and the development of diabetes-related complications is also variable.[3]

Successful management of T1D requires multiple daily insulin injections (MDI), insulin pump therapy, or the use of an automated insulin delivery system, as well as glucose monitoring, preferably with a continuous glucose monitor (CGM). All people with T1D should be able to perform capillary blood glucose monitoring (BGM) if CGM is unavailable. Self-management education, training, and support, as well as addressing psychosocial issues, help to optimize outcomes. A collaborative multidisciplinary approach, utilizing medical providers, nurse and dietitian educators, pharmacists, community resources, and specialists as needed (including podiatrists, mental health professionals, social workers, ophthalmologists, cardiologists, and others), is recommended.[4]

Etiology

...re is autoimmune destruction of the beta cells in the pancreatic islets over months or years, causing an ...iciency of insulin. Although the exact etiology of T1D is still unknown, researchers believe there is a

genetic predisposition with a strong link with specific HLA (DR and DQ) alleles. This association is more pronounced in youth-onset T1D compared to adult-onset T1D.[5] Multiple other genes contribute to heritability as well.[6]

In those at risk, it is generally believed that viruses, environmental including dietary factors, and/or other stressors can trigger autoimmune beta-cell destruction. Some studies have found an increased risk of development of T1D related to infection with Coxsackie virus, enteroviruses, cytomegalovirus, rubella virus, influenza B, mumps virus, and more recently, SARS-CoV-2 (COVID-19).[7][8][9] In The Environmental Determinants of Diabetes in the Young (TEDDY) study, breastfeeding was not associated with the risk of islet autoimmunity in children genetically at increased risk. However, a systematic review and meta-analysis concluded that breastfeeding and the later introduction of gluten, fruit, and cow's milk were associated with a lower risk of developing T1D.[10] Research to better understand the etiology of T1D is ongoing.

The presence of circulating pancreatic islet autoantibodies suggests that the individual is at risk for or has developed T1D. These antibodies include islet cell cytoplasmic antibodies (ICA), antibodies to insulin (IAA), glutamic acid decarboxylase isoform 65 (GAD65), insulinoma antigen 2/islet tyrosine phosphatase 2 (IA-2) and zinc transporter isoform 8 (ZnT8). IAAs are primarily detected in children.[11] GAD65 is the most common autoantibody detected in adults[3]. ICA is no longer routinely recommended, as it is an imprecise assay. The greater the number of detectable antibodies and the higher their titers, the greater the risk of developing T1D.

Epidemiology

T1D is one of the most frequent chronic diseases in children but can have its onset at any age. In adults, new-onset type 1 diabetes may be misdiagnosed as type 2 diabetes and is more common than youth-onset T1D.[3][[5] There has been a steady increase in the incidence and prevalence of T1D, representing approximately 5% to 10% of people with diabetes. A systematic review and meta-analysis reported that the worldwide prevalence of T1D was 9.5%, with an incidence of 15 per 100,000 people.[12] Worldwide, there is also a considerable geographic variation in incidence. The highest reported incidences are in Finland and other Northern European nations, with rates approximately 400 times greater than those seen in China and Venezuela, where there is the lowest reported incidence.

Pathophysiology

The development of T1D occurs in 3 stages. Stage 1 is asymptomatic and characterized by normal fasting glucose, normal glucose tolerance, and the presence of ≥2 pancreatic autoantibodies. Stage 2 diagnostic criteria include the presence of pancreatic autoantibodies (usually multiple) and dysglycemia: impaired fasting glucose (fasting glucose 100 to 125 mg/dL) or impaired glucose tolerance (2-hour post-75 gm glucose load glucose 140 to 199 mg/dL) or an HbA1c 5.7% to 6.4%. Individuals remain asymptomatic. In stage 3, there is diabetes, defined by hyperglycemia (random glucose ≥200 mg/dL) with clinical symptoms, fasting glucose ≥126 mg/dL, glucose ≥200 mg/dL two hours after ingesting 75 g of glucose during an oral glucose tolerance test and/or HbA1c ≥6.5%. If the individual lacks classic symptoms of hyperglycemia or hyperglycemic crisis, it is recommended that two tests be performed (simultaneously or at different times) to confirm the diagnosis. If there is an acute onset of symptoms with hyperglycemia, as more often occurs in youth-onset T1D, HbA1c may be misleading at the time of diagnosis, and glucose criteria should be used.[4]

T1D, especially in children, classically presents with hyperglycemic symptoms, which can be sudden, and include polydipsia, polyuria, polyphagia, nocturnal enuresis, blurred vision, unintentional weight loss, fatigue, and weakness. If not evaluated and treated promptly, it can become a medical emergency. In addition to hyperglycemia, electrolyte abnormalities may be present. If these individuals are not treated, DKA can develop, requiring hospitalization and treatment with intravenous fluids, insulin, potassium, and careful monitoring. Almost one-third of youth present with DKA.[13]

In adult-onset diabetes, the onset of symptoms is more variable than in youth, and DKA is less common. It can be difficult to distinguish T1D and type 2 diabetes. GAD65 should be the initial antibody tested when diagnosing T1D in adults is suspected. If negative and/or if available, IA2 and/or ZNT8 should be measured as well. C-peptide levels can be used when there is a question about which type of diabetes is present. A random C-peptide should be drawn with concurrent serum glucose. If the duration of diabetes exceeds three years, c-peptide >600 pmol/L strongly suggests type 2 diabetes. A low (<200 pmol/L) or undetectable c-peptide confirms the diagnosis of T1D.[3]

History and Physical

At the initial outpatient visit, obtaining a complete medical, surgical, psychosocial, and family history, including pregnancy and contraception history, is essential. History of prior diabetes education, monitoring of BG and ketones, use of CGM, administration of insulin, recognition/treatment of hypoglycemia, use of glucagon, diet, physical activity, smoking and alcohol use, understanding of sick-day rules, ability to problem solve and immunization history, should also be obtained. Particular attention should be paid to the date of diagnosis, prior treatment, current medications, presence of hypoglycemia unawareness, and history of acute complications (hypoglycemia including severe episodes and episodes of DKA) and chronic complications (skin disorders, dental problems, retinopathy, macular edema, neuropathy, kidney disease, cardiovascular disease, peripheral arterial disease, stroke, foot ulcers, amputations, hearing loss, sleep disorders). Since people with type 1 diabetes are at increased risk of other autoimmune disorders, including autoimmune thyroid disease and celiac disease, the history should also focus on these conditions.[3]

Clinicians should measure height, weight, and blood pressure. The skin should be examined, especially at insulin injection or infusion sites. If lipodystrophy is evident, they should be educated on the importance of varying insulin injection/infusion sites. The thyroid, heart, chest, and abdomen should also be examined. A foot exam is performed to examine pedal pulses and detect foot deformities, pre-ulcerative lesions, ulcerations, calluses, and onychomycosis. It is also important to test vibratory and protective sensations; abnormal testing with a 10-g monofilament exam suggests an increased risk of ulceration.

When screening for psychosocial issues, a number of measures are available such as the Patient Health Questionnaire (PHQ-2/PHQ-9) for Depression and Generalized Anxiety Disorder (GAD-7). Diabetes distress and social determinants of health should be assessed. Since eating disorders are more common in type 1 diabetes, particularly in young women, evaluation should be considered clinically indicated. Early cognitive decline is also common, so cognitive testing should be considered when impairment is suspected.[3]

Data from CGMs, blood glucose meters, insulin pumps, and automated insulin delivery systems should be downloaded, examined, and discussed at each visit and between visits when needed to adjust treatment regimens to achieve glycemic goals.

CGMs are devices that measure glucose in interstitial fluid and are extremely useful tools for people with T1D. Sensors are inserted into the subcutaneous tissue and transmit glucose readings every 5 minutes to a receiver where they can be displayed in real-time. One can examine trends and use low and high glucose alarms to prevent serious hypoglycemia and hyperglycemia episodes. Alarms can also alert to a rapid change in glucose value. Readings from certain CGM sensors can be transmitted to smartphones and can be shared with relatives, friends, or caregivers. A less expensive CGM option uses a “reader” (a device the user scans over the site of sensor placement) or a smartphone to visualize recent glucose readings and trends. All these devices make it easier to monitor glucose values throughout the day and night. Users examine trends and are provided with important information to guide insulin therapy and food intake to help avoid wide glycemic excursions and hypoglycemia.

Data from CGMs can be uploaded and stored in cloud-based systems. These data include percent: *Time in range* TIR, usually 70 to 180 mg/dL; TIR targets are lower during pregnancy and higher in those who are frail and/or with complex comorbidities or limited life expectancy), *time below range* (TBR; <70 mg/dL; level 1 hypoglycemia is 54-69 mg/dL and level 2 hypoglycemia is <54 mg/dL); *time above range* (TAR; usually >180 mg/dL; level 1 hyperglycemia is 181 to 250 mg/dL and level 2 hyperglycemia is >250 mg/dL); and *glycemic variability* (% CV; coefficient of variation). These data should be reviewed with the goal of understanding factors contributing to hypoglycemia and hyperglycemia and to help guide insulin dosing, diet, and physical activity to achieve goals. A primary goal should be minimizing hypoglycemia. A higher percent TIR is associated with decreased diabetes-related complications.[14][15] HbA1c, TIR, and TBR improve when MDI or pump therapy is augmented with CGM use. The glucose management indicator (GMI) is calculated using average sensor readings over a 14-day period and correlates with the estimated HbA1c.[16]

When CGM data are unavailable, examination of BG data fasting, pre-meal, 1 to 3 hours postprandial (when adjusting prandial dosing), bedtime, when hypoglycemia is suspected, and occasionally in the middle of the night, should be used to direct insulin dosing. Insulin dosing data from connected insulin pens and pumps should also be discussed.

Evaluation

HbA1c is recommended every 3 to 6 months. The HbA1c reflects glycemic control over the previous 2 to 3 months. A typical goal HbA1c is <7.0%, with higher goals in people with frailty, cardiovascular disease/multiple comorbidities, history of severe hypoglycemia, and/or hypoglycemia unawareness. Lower goals are used when they can be achieved safely (without an increase in hypoglycemia).

Other laboratory tests include a yearly lipid profile, serum creatinine, eGFR, and urine albumin to creatinine ratio. Serum potassium should be monitored if taking an ACE-I, ARB, or diuretic, and AST, ALT, TSH, celiac screen, vitamin B12, and vitamin D at least once and as indicated clinically. These tests could be repeated more frequently if the previous results were abnormal. Since people with T1D are at an increased risk of developing other autoimmune diseases, such as autoimmune thyroid disease, celiac disease, primary adrenal insufficiency, and rheumatoid arthritis, screening for autoimmune disorders should be considered when clinically appropriate.[17][4]

Treatment / Management

People with T1D require insulin therapy, glucose monitoring (preferably CGM), and diabetes self-management education and support. Multiple daily insulin injections (MDI) using basal (preferably a long-acting insulin) and bolus (preferably rapid-acting insulin for meals and correction)insulins, continuous subcutaneous insulin infusion (rapid-acting insulin) through an insulin pump, or use of automated insulin delivery (hybrid closed loop) systems with rapid-acting insulin, are available. Automated insulin delivery is associated with greater time in the target range and less hypoglycemia. When initiating a treatment plan, use shared decision-making, considering individualized realistic and attainable goals, risk of hypoglycemia, lifestyle, and the availability and affordability of different regimens.[4]

Hypoglycemia is the most frequent adverse effect of insulin therapy. It is important to educate people with diabetes and their partners about the signs and symptoms of hypoglycemia, which include diaphoresis, tachycardia, lightheadedness, confusion, hunger, visual changes, and tremors. With a long duration of T1D, hypoglycemia unawareness becomes more common. Generally, 15 to 20 g of glucose should be given orally for blood glucose below 70 mg/dL.[17] Glucose readings should be rechecked 15 minutes later, with additional carbohydrates given if needed.d Once the glucose reading has normalized, if glucose readings again begin to fall, a snack should be given to prevent a recurrence. Glucagon should be prescribed for emergency use for severe hypoglycemia (when there is an inability to consume carbohydrates by mouth). People with T1D should also receive sick day instructions, including how to manage hyperglycemia and ketone testing. When initiating insulin therapy in an adult, the person's weight in kilograms is multiplied by 0.2 to 0.6 units to calculate the initial total daily insulin dose (TDD). Generally, basal requirements are 40% to 50% of the TDD, and the rest approximates the daily rapid-acting insulin that must be given before or with meals. Dosing is modified based on many factors, including diet, physical activity, and CGM and/or BGM results.

When possible, people with T1D should meet with a dietitian, be taught carbohydrate counting, and be instructed to use an insulin-to-carbohydrate ratio (grams of carbohydrate covered by one unit of insulin) for mealtime dosing. If carbohydrate counting is not possible, a carbohydrate-consistent diet is helpful. Estimating the fall in glucose resulting from 1 unit of rapid-acting insulin, called a correction or insulin sensitivity factor, is also recommended when treating hyperglycemia. The correction factor can be initially estimated using the formula 1800 divided by the TDD. This number will need to be adjusted per subsequent glucose monitoring results. When using correction doses, the individual needs to be careful not to take injections too close together ("stacking") to avoid overdosing (insulin administered when there is still active insulin from previous doses causing overlapping insulin doses) and hypoglycemia.

It is important to note that insulin requirements vary across the lifespan and under specific circumstances. For example, larger insulin doses are typically required during puberty, pregnancy, when steroids are given, and with the development of obesity. Individuals need less insulin when they are engaged in aerobic exercise and during the "honeymoon period." The honeymoon period occurs soon after diagnosis when there can be a temporary recovery beta-cell function.

Multiple types of insulin can be used for insulin injection therapy.[18] Rapid-acting insulin (lispro, aspart, glulisine) will generally have onset in 12 to 30 minutes, peak in 1 to 3 hours, and have a duration of action of 3-6 hours. Ultra-

rapid-acting lispro or aspart have a slightly quicker onset of action and somewhat shorter duration of action. . Short-acting insulin (regular insulin) has an onset in 30 minutes to 1 hour and peak in 2 to 4 hours with a duration of 5 to 8 hours.

For basal insulin injection therapy, long-acting insulin is preferred, often given once a day (U-100 and U-300 glargine, degludec) or 1 to 2 times daily (detemir and U-100 glargine). Glargine does not have a pronounced peak and lasts approximately 20 to 24 hours. U-300 glargine lasts more than 24 hours, and degludec has a longer duration of action, up to 42 hours. Intermediate insulin (NPH, NPL) is the least expensive basal insulin, but it is associated with more hypoglycemia. It has onset in 1 to 2 hours, peak action at 2 to 8 hours, duration of 12 to 24 hours, and is usually given before breakfast and bedtime. When MDI is used, the individual will ideally use rapid-acting insulin with each meal for hyperglycemia correction and a daily long-acting basal insulin.

Insulin pumps deliver insulin every 5 minutes to provide basal needs and deliver boluses of insulin to control mealtime excursions and correct hyperglycemia. Only rapid-acting insulin is used in insulin pumps/automated insulin delivery systems. Some pumps use external tubing to infuse insulin from the pump to the infusion site in the subcutaneous tissue, while another pump uses a “pod” that contains insulin, which is directly applied to the skin and is controlled via a wireless connection to a controller or smartphone. Insulin pumps are programmed with adjustable basal rates, insulin-to-carbohydrate ratios, correction factors, and target glucose ranges.

Some insulin pumps communicate with CGMs and have threshold/predictive low-glucose suspend features. With these devices, insulin delivery is suspended when hypoglycemia occurs or is predicted to occur. In the newer hybrid closed-loop automated insulin delivery systems, the CGM sends glucose data to an insulin pump with a control algorithm. Basal insulin delivery is automated based on the CGM readings received every 5 minutes and the target glucose. Advanced systems deliver automated correction boluses as well. Mealtime bolus insulin is still required to be delivered under the direction of the user.

Several clinical trials are currently underway, testing “closed-loop” fully automated insulin delivery systems, as well as a closed-loop system that delivers insulin and glucagon. The hope is that these closed-loop automated insulin systems will lead to better glucose management, with minimal risk of hypoglycemia and reduced burden for people with T1D.

Physical activity is recommended for people with T1D. Exercise increases insulin sensitivity, improves cardiovascular health, improves lipid profiles, decreases microvascular complications, reduces the risk of osteoporosis, and decreases mortality. Glycemic control can be more difficult during times of activity related to the intensity and duration of the activity, amount of circulating insulin, glucose level before exercise, and dietary intake. Individuals should be taught the effect of different types of activity (aerobic vs. anaerobic) on glucose levels, how to balance carbohydrate intake and insulin doses when active, and how to avoid hypoglycemia and wide glycemic excursions with exercise.

In addition to insulin therapy, diet, and physical activity, individuals with T1D should generally have an annual eye exam by an eye care specialist and an annual foot exam. Those with foot deformities, neuropathy, a history of foot ulcers, or peripheral arterial disease should have their feet examined at each visit, be educated in proper foot care/footwear, and, if available, see a podiatrist and be evaluated for orthotics if indicated. Other specialists, such as nephrologists, ophthalmologists, and cardiologists, as well as referrals to community resources, social workers, and mental health professionals, may be needed. The use of statins and other anti-hyperlipidemic therapy, smoking cessation, and anti-hypertension therapy to reduce cardiovascular risk and risk of nephropathy and retinopathy are important and discussed later in this article. Pancreatic and islet cell transplantation are two treatment options that can restore normoglycemia.

A pancreatic transplant is usually performed simultaneously with a kidney transplant (SPK transplant). These transplants are considered when end-stage renal disease is present, in relatively younger individuals (<50 years old without coronary artery disease), and when usual treatment options have been unsuccessful in preventing large variability and severe hypoglycemia. Individuals who receive a pancreatic transplant or an islet-cell transplantation require immunosuppressive therapy. Encapsulated islets could obviate the need for immunosuppressive therapy and are a promising future therapy. These and other research initiatives give hope to the increasing number of people with T1D that a cure is in their future.[4]

Differential Diagnosis

- Diabetes mellitus type 2
- Pancreatic diabetes
- Steroid-induced diabetes
- Diabetes insipidus
- Factitious illness
- MODY
- Psychogenic polydipsia
- Renal glycosuria

Prognosis

With better glucose, blood pressure, lipid control, and better foot care, there has been a reduction in the morbidity and mortality associated with T1D. Rates of serious diabetes-related complications are lower; if present, their onset has been delayed for many. Although people with T1D have 2 to 5-fold higher mortality than those without diabetes, mortality rates have declined. This is discussed further in other sections.[19]

Complications

The major acute complications of diabetes are hypoglycemia and serious hyperglycemia, including diabetic ketoacidosis. The major chronic complications are listed below:

- Nephropathy
- Neuropathy: peripheral and autonomic
- Retinopathy/macular edema
- Heart disease, including coronary artery disease, heart failure, cardiomyopathy
- Peripheral arterial disease
- Cerebrovascular disease, including stroke and TIA
- Hearing loss
- Diabetic foot diseases, including foot ulcers and amputations

Deterrence and Patient Education

Patient medication compliance and follow-up with specialists and educators are critical factors in preventing complications. At every patient encounter, the pharmacist, nurse, and clinicians should emphasize the importance of blood glucose control, long-term complications, and management goals. The patient should be encouraged to modify their lifestyle to reduce the risk of complications. In addition, all patients with diabetes should be made aware of the signs and symptoms of hypoglycemia and ways of managing it. Patients should be educated about available resources and the benefits of joining support groups. A dietitian should educate the patient about foods that can be consumed, and the nurse should educate the patient on blood glucose monitoring at home.

Enhancing Healthcare Team Outcomes

Self-management of T1D includes administering insulin multiple times daily with glucose monitoring and attentio to food intake and physical activity every day, which is a considerable burden. Whereas newer technologies have helped people improve their glycemic control, they are costly, complex, and require education and training. Many people with diabetes fear hypoglycemia, hyperglycemia, and the development of complications, and depression,

anxiety, and eating disorders can develop. The medical, education, training, psychological, and social challenges faced by people with T1D daily are best addressed by an interprofessional team that includes clinicians (MDs, DOs, NPs, and PAs), nurses (including diabetes nurse educators), pharmacists, dieticians, mental health professionals, social workers, podiatrists, and the use of community resources. Individualized treatment approaches, which can reduce the burden and further improve outcomes, are needed, and the interprofessional care model will yield the best possible patient outcomes.[3]

It is imperative for all interprofessional team members to coordinate their activities and interventions with the rest of the team and utilize open communication channels to ensure everyone involved in patient care, as well as the patient themselves, has access to the same accurate, updated patient information. Nurses are often crucial in coordinating activities between various professionals on the case and play a role in patient evaluation, education, and monitoring. Pharmacists should work directly with diabetes educators to ensure proper insulin dosing and participate in patient medication education and reconciliation. These examples of interprofessional care will help drive improved patient outcomes. [Level 5]

Review Questions

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