DIABETES TYPE I:
CURRENT MODALITIES OF TREATMENT

Abstract

Type 1 diabetes mellitus is a chronic, autoimmune disease that occurs due to pancreas beta cell destruction and insulin deficiency. Symptoms of type 1 diabetes result from high levels of blood glucose which is also known as hyperglycemia. Type 1 diabetes generally begins in children and adolescents; however, can also develop later on in adults. The etiology of type 1 diabetes remains unknown; however, it is widely believed to improve because of T cell-mediated destruction of beta cells and autoantibody activity that affect the production of insulin. Environmental triggers and genetic factors will influence the type of autoantibody that influences disease progression. A cure for diabetes is currently not available, and disease management depends on lifelong insulin injections. Varied approaches to insulin administration may be introduced to type 1 diabetics, including continuous glucose monitoring and insulin pumps. Treatment options related to type 1 diabetes and several case studies are discussed.

Statement of Learning Need

In type 1 diabetes a person's body does not produce insulin and clinicians need to be educated and continuously updated on ways the body breaks down nutrients into blood sugar for energy. Conventional and new insulin therapy treatments are available to help patients live in good health.

Course Purpose

To inform health clinicians of the recognition, diagnosis and treatment of diabetes type 2.

Target Audience

Advanced Practice Registered Nurses, Registered Nurses, and other Interdisciplinary Health Team Members.

Self-Assessment of Knowledge Pre-Test:

1. **In prediabetes, a person's blood sugar level is higher than normal, which means that**

    a. The person has type 2 diabetes.
    b. Without lifestyle changes, progression to type 2 diabetes is likely.
    c. Progression to type 2 diabetes is inevitable.
    d. The person probably has type 1 diabetes.

2. **_____ is a formula for calculating the insulin-to-carbohydrate ratio.**

    a. The 1500 rule
    b. The correction factor
    c. The 500 rule
    d. Insulin sensitivity factor (ISF)

3. **In cases of type 1 diabetes, the use of rapid-acting insulin is recommended**

    a. At every meal (three times daily).
    b. Between meals.
    c. Once daily at the time of the patient's heaviest meal.
    d. Once daily in the morning.

4. **Short-acting insulins take effect in the bloodstream within _____ of administration.**

    a. 15 minutes
    b. 2 to 4 hours
    c. one to three hours
    d. 30 to 60 minutes

5. **True or False: Short-acting insulins have a peak period that is within two to four hours, and the effects can last for five to eight hours.**

    a. True
    b. False

Introduction

Diabetes is a disease that occurs when a person's blood glucose is elevated. Blood glucose is regulated by insulin, and the main source of blood glucose people receive is through daily nutrition. Insulin is produced by the pancreas, and without insulin, glucose is unable to be used by body cells for energy. An insufficient amount or non-production of insulin in the body leads to high levels of glucose in the blood that do not reach the body cells, which is diabetes. The following sections discuss the basic causes of diabetes and some of the more current treatment modalities to support healthy blood glucose levels and body metabolism, and case studies are provided uniquely to each section.

Epidemiology

Diabetes is the seventh leading cause of death in the United States. There is no cure for diabetes, but there are steps that can be taken to manage diabetes and to help in promoting health.[1] According to a report released in 2017 by the Centers for Disease Control and Prevention (CDC), there are more than 100 million U.S. adults living with diabetes or prediabetes. The report found that as of 2015, 9.4 percent of the U.S. population or 30.3 million Americans, have diabetes.[2] Another 84.1 million have prediabetes, a condition that if not treated often leads to type 2 diabetes within five years.[2] The 2017 Report included the following national statistics:[2]

- In 2015, an estimated 1.5 million people 18 years and older were diagnosed with diabetes.[2]
- There were 7.2 million people in the U.S., approximately 1 in 4 four adults who had diabetes but were unaware they were living with the disease. For those living with prediabetes, only 11.6 percent of adults were aware they had the condition.[2]
- As people aged, so did, the rates of adults diagnosed diabetes:[2]
    - In ages 18-44, 4 percent had diabetes
    - In ages 45-64 years, 17 percent had diabetes
    - In ages 65 years and older, 25 percent had diabetes.
- Higher rates of diabetes occurred in American Indians and Alaska Natives (15.1 percent), non-Hispanic blacks (12.7 percent), and Hispanics (12.1

percent); and the rates were lower in Asians (8.0 percent) and non-Hispanic whites (7.4 percent).[2]

In the U.S., the prevalence of diabetes tended to vary according to a person's level of education. Adults with less than a high school education had a 12.6 percent incidence of diabetes. In people with a high school education, 9.5 percent had diabetes, and in people with greater than high school education, 7.2 percent had diabetes.[2]

There were gender disparities as well. Men had a higher rate of prediabetes (36.6 percent) than women (29.3 percent). In all racial/ethnic groups or educational levels, there was no difference in the rates of prediabetes between men and women.[2] Southern and Appalachian regions of the U.S., were found to have the highest rates of diagnosed diabetes, which included new cases of diabetes being diagnosed.[2]

Prediabetes versus Diabetes

In prediabetes, the blood sugar level is higher than normal but not yet elevated to a level of type 2 diabetes. Without lifestyle changes, people with prediabetes are very likely to progress to type 2 diabetes. Progression from pre-diabetes to type 2 diabetes is not inevitable, and choosing healthy foods, being physically active and maintaining a healthy weight can help a person maintain normal blood glucose levels.[3]

There are physical signs that a person may be at risk of type 2 diabetes. Darkened areas will appear on the skin at certain areas of the body, such as the neck, armpits, elbows, knees and knuckles. Classic signs and symptoms that indicate a condition of diabetes rather than prediabetes is increased thirst, frequent urination, fatigue, and blurred vision. In prediabetes blood glucose is not being utilized and the blood glucose will appear elevated. Muscle and other tissue cells become deprived of needed energy.[3]

Most of the glucose in the body is derived from food in a person's diet, which is digested and then enters the bloodstream. For glucose to be transferred from the bloodstream to body cells, insulin is needed. Insulin is

produced by one of the largest body glands, the pancreas. When a person eats food, the pancreas is triggered to secrete insulin into the bloodstream, and the insulin circulates to help with the transport of glucose into the body cells, lowering the blood glucose level. The secretion of insulin from the pancreas lowers in proportion to lower levels of blood glucose. However, in a prediabetic individual, the process of insulin release is deficient and body cells become deprived of needed energy while the blood glucose becomes elevated.

Diabetes Type 2 versus Type 1

While type 1 diabetes involves an autoimmune reaction where the pancreas has poor to no insulin production, type 2 diabetes is a chronic condition that develops based on a person's glucose metabolism and is more common than type 1 diabetes. In type 2 diabetics, there is either insulin resistance or low insulin production and abnormal blood glucose levels develop. In the past, Type 2 diabetes was referred to as "adult-onset diabetes", however, the pediatric population is increasingly being diagnosed with type 2 diabetes, which is believed to correlate to a higher incidence of pediatric obesity.[4]

No cure for type 2 diabetes exists, but a person can better manage the disease by maintaining a healthy weight, proper diet and exercise. When lifestyle practices are not adequate to maintain healthy blood glucose, oral medications or insulin therapy may need to be implemented to achieve normal blood glucose levels.[4]

The symptoms of Type 2 diabetes are typically gradual, and include increased thirst, frequent urination, increased hunger, unintended weight loss, fatigue, blurred vision, recurrent infections, slow healing skin sores, darkened skin areas (armpits and neck, typically).[4] Type 2 diabetes develops when the pancreas to unable to produce enough insulin, however, the exact cause has not been determined, although genetics and environmental factors are believed to be triggering factors, such as when an individual is obese or sedentary.[4] An elevated blood glucose occurs when not the pancreas produces enough insulin or the body cells become resistant to insulin action, or both.

The following sections will focus on type 1 diabetes using a case study approach to illustrate some of the common problems that may arise during intensive insulin therapy in patients with type 1 diabetes mellitus.

Type 1 Diabetes

Type 1 diabetes has also been referred to as "insulin-dependent diabetes" or "juvenile diabetes."[5] It typically develops during childhood, adolescence or young adulthood.[5] Type 1 diabetics will have poor insulin production by the pancreas. As mentioned, poor insulin (the hormone that enables blood glucose to be used by the body cells) release leads to poor utilization of body glucose and poor levels of energy. Elevated blood glucose in type 1 is damaging to the body and causes many of the symptoms and complications of diabetes.[5]

Type 1 diabetes is caused by an autoimmune reaction that destroys pancreas beta cells that produce insulin. As the pancreas beta cells are destroyed over time the symptoms of type 1 diabetes begin to be noticed. Medical experts suggest that type 1 diabetics may notice symptoms of elevated blood glucoses within a few weeks or months, and generally by the time the diabetic person notices physical signs and symptoms of elevated blood glucose they can tend to be severe.[5] Environmental triggers is believed to include exposure to a virus, which has a role in the development of type 1 diabetes. In type 1 diabetics, their condition is not induced by lifestyle or dietary habits; it is caused by an autoimmune condition of an unknown origin, with an increased risk based on family history.[5]

Case Study: Dietary Control in Type 1 Diabetes

This case study illustrates the importance of dietary control to good diabetes management. A 57-year-old female with type 1 diabetes for 15 years reported finding it difficult to maintain strict glycemic control.[6] The patient was employed as a hospital administrator and had a very busy and active role. She attempted to stay physically fit by exercising and would adjust both her insulin dose and food intake and exercise pattern in response to her blood glucose levels; and, her usual insulin doses included:

- Before breakfast: 6 units regular insulin and 26 units NPH insulin
- Before lunch: 4 units regular insulin
- Before evening meal:4 units regular insulin
- Before bedtime: 26 units NPH insulin

The patient's blood glucose levels remained unpredictable, as shown in the table below (in mg/dL and, in parentheses, mmol/L).

Day	Before	Before	Before	Before
	Before Breakfast	Before Lunch	Before Dinner	Bedtime
1	195 (10.8)	52 (2.9)	126 (7.0)	88 (4.9)
2	61 (3.4)	46 (2.6)	210 (11.7)	197 (10.9)
3	287 (15.9)	222 (12.3)	161 (8.9)	72 (4.0)

Discussion

The patient in this case example has been continually trying to adjust insulin to regulate blood glucose levels. When a person continually adjusts insulin doses, food intake, and exercise, identifying patterns that could be corrected becomes more difficult to achieve. For this person there are some strategies that would help her alongside her medical provider to evaluate any dietary patterns that need to be adjusted. For example, she could maintain an dietary log of her meals and the amount of food intake. In the above chart of the patient's food intake the total carbohydrate intake is widely variable between meal periods and from day to day. Such a variability in a person's dietary intake would interfere with an ability to maintain strict glycemic control while on an intensive insulin regimen.[6]

The patient's dietary inconsistency will need to be corrected. Members of the diabetes health team will need to address these needs. Referring the

patient to a nutritionist for consultation will increase her learning options, such as attending a diabetes diet workshop. Often these workshops will include small groups where a meal plan and recipes can be exchanged. Meals can be laid out that include breakfasts, fast food lunches, fancy evening meals, and snacks. Patients learn to estimate the amount of grams of carbohydrate in each meal. They have a chance to see inaccuracies in the meal planning and to learn ways to improve meal preparation. The goal of such workshops and nutritionist consultations is to develop a consistent carbohydrate profile for each patient. During follow up clinic visits the patient may refer to this carbohydrate profile for review and feedback until this method of meal preparation is an ongoing lifestyle pattern.[6]

Members of the diabetes health team will need to incorporate motivational techniques to help patients adjust meal patterns that do not work. Rather than continuing to eat the same amount of carbohydrate at the same meal every day, and using a fixed dose of insulin, patients may improve their diabetes management by being educated on how to calculate a carbohydrate: insulin ratio. In the case of this female patient, she may need 1 unit of regular insulin to cover 15 g of carbohydrate. Although she typically eats 90 grams of carbohydrate for breakfast (and takes six units of regular insulin), if she were to eat 30 grams on one morning, the regular insulin dose could be reduced to 2 units. Use of an insulin algorithm may be used to adjust this basic dose based on the patient's blood glucose level.[6]

Case Study: Type I Diabetes, Uncontrolled[6]

The authors of this case study reported on a 51-year-old white male who was diagnosed with type 1 diabetes for the past 21 years. The patient believed that his diabetes was adequately controlled for the past 20 years, but that most recently he noticed more erratic blood sugar levels and his need for more insulin had increased.

The patient's psychosocial history included that he was recently remarried, and his wife was part of his family support structure and was assisting him with diabetes care. The patient's medical history noted he had chronic problems with asymptomatic hypoglycemia. During his last medical assessment approximately 3–4 weeks prior, his endocrinologist had

documented areas of hypertrophy at his insulin injection sites. His endocrinologist suggested that he rotate his injection sites from the thighs to the abdomen because of a recent emergency room (ER) encounter where he had become hypoglycemic despite consistent blood glucose monitoring and proper adherence to treatment.

The endocrinologist also referred the patient to a dietician for an urgent visit following the hypoglycemic event. During the ER encounter, he required immediate treatment to address hypoglycemia. The patient did not think he needed additional diabetes education but felt the need to lose an additional 10 lb (body mass index is 25 kg/m^2).

The patient's diabetes treatment included routine administration of 1) pravastatin (Pravachol®) 10 mg daily, 2) NPH insulin 34 units in the morning and 13 units at bedtime and 3) regular insulin at breakfast and dinner following a sliding-scale algorithm. Lispro (Humalog®) insulin was also administered as needed to correct high blood glucose.

The authors noted that before the patient's arrival at the ER, he had become more lackadaisical about monitoring his blood glucose. During the period of significant life changes, such as a new marriage, he resorted to minimal blood glucose monitoring in the morning before eating, and only occasional blood glucose testing before dinner. He also had stopped trending his blood glucose values and was not keeping a record of the daily results. Following the recent episode of severe hypoglycemia, he was encouraged to check his blood glucose more consistently, four times a day, before meals and bedtime. Laboratory testing was ordered by his endocrinologist, and the following test values were reported.

- A1C: 8.3% (normal 4.2–5.9%)
- Total cholesterol: 207 mg/dl (normal: 100–200 mg/dl)
- HDL cholesterol: 46 mg/dl (normal: 35–65 mg/dl)
- LDL cholesterol: 132 mg/dl (normal: <100 mg/dl)
- Triglycerides: 144 mg/dl (normal: <150 mg/dl)

- Creatinine: 0.9 mg/dl (normal: 0.5–1.4 mg/dl)
- Microalbumin: 4 µg (normal: 0–29 µg)

During the patient's initial appointment with the dietician for crisis management of asymptomatic hypoglycemia, the dietician examined the patient's injection sites to determine whether the patient had started rotating his injection sites as recommended by his physician. She reviewed the patient's injection technique, and his history of dietary management, the recent incidence of hypoglycemia, and the patient's hypoglycemia treatment management while at home. The main goals of his dietary education involved reducing his risks of hypoglycemia, which included food choices, the timing of insulin administration, and consistent rotation of injection sites.[6]

The dietician reinforced the physician's instruction to avoid old injection sites and added a new recommendation to lower insulin doses because of improved absorption at the new sites. The patient improved his blood glucose monitoring and was recording results in a handheld electronic device in a form that could be downloaded, e-mailed, or faxed, but he was not recording his food choices. The dietitian began carbohydrate-counting education with the patient and asked him to keep food records that would be reviewed at weekly follow-up visits.[6]

At the second visit, the patient's mid-afternoon blood glucose was <70 mg/dl. He did not respond to treatment with 15 g carbohydrate from 4 oz. of regular soda. His blood glucose continued to drop, measuring 47 mg/dl 15 minutes later. Another 8 oz. of soda was ingested, and the patient's blood glucose increased to 63 mg/dl one hour later. Another 8 oz. of soda and a sandwich was eaten before leaving the dietitian's office. The patient called the dietician in one hour later to report that his blood glucose was finally up to 96 mg/dl.[6]

The patient's health records showed a pattern of mid-afternoon hypoglycemia. He was willing to add a shot of lispro at lunch to his regimen, and the dietician recommended that he reduce the morning NPH insulin dose to prevent low blood glucose readings later in the day. The dietician also

calculated insulin and carbohydrate ratios for blood glucose correction and meal-related insulin coverage using the "1500 rule" and the "500 rule."[6]

The 1500 and 500 Rule

The 1500 rule is a commonly accepted formula for estimating the drop in a person's blood glucose per unit of fast-acting insulin. This value is referred to as an "insulin sensitivity factor" (ISF) or "correction factor."[6] The total daily dose (TDD) of all rapid- and long-acting insulin must first be determined, and then the evaluator must divide 1500 by the TDD to find the ISF (the number of mg/dl that 1 unit of rapid-acting insulin will lower the blood glucose level). Here, the patient's average TDD was 41 units, and therefore his estimated ISF was 37 mg/dl per 1 unit of insulin. The dietician rounded this value up to 40 mg/dl given the patient's history of hypoglycemia.[6]

The 500 rule is a formula for calculating the insulin-to-carbohydrate ratio. The evaluator would divide 500 by the TDD. For the patient, the insulin-to-carbohydrate ratio was calculated at 1:12 (1 unit of insulin to cover every 12 g of carbohydrate), and this was rounded up to 1:14 for safety. Later, the patient's carbohydrate ratio was adjusted down to 1:10 based on blood glucose monitoring results before and 2 hours after meals.[6]

Using this tool to determine carbohydrate ratio helps to educate the patient on moving away from a sliding scale to adjust his insulin based on how to use the insulin-to-carbohydrate ratio and to follow the new recommendations of diabetes management. The dietician consulted with the patient's endocrinologist for approval before recommending to the patient a reduction of his NPH doses to 34 units and the addition of an injection of lispro at lunchtime; this would be a dose based on the amount of carbohydrate in the meal and the patient's before-meal blood glucose level. While transitioning the patient to this new regime, he was asked to keep follow up weekly visits to be evaluated on progress and to continually review of his new diabetes control regimen.

Within three days of beginning this new regimen, the patient returned following another severe episode of hypoglycemia. By using motivational

techniques to engage the patient with the ability to obtain good accurate reporting of progress is improved. The dietician and other members of the diabetes health team want to develop a trusting rapport with the patient. By doing so, the patient will feel freer to report challenges or barriers in their diabetes treatment. The patient, in this case, began to reveal difficulties in his understanding of how hypo- and hyperglycemia felt and in his ability to accurately determine insulin adjustments that had contributed to his episodes of hypoglycemia.[6]

The diabetes health team worked with the patient to better understand his insulin dosing and blood glucose responses, and his skill level at making insulin dose adjustments. Until the patient's insight and ability to appropriately adjust insulin dosing based on his blood glucose requirements improved, he remained at risk for asymptomatic hypoglycemia. Glucagon was prescribed to treat hypoglycemic reactions, and the patient was educated by the pharmacist on its proper use. The patient's family members were also provided literature and instructions on the administration of glucagon should the patient be unable to self-administer it during a hypoglycemic event.[6]

Eventually, the patient's morning NPH dose was reduced to 22 units because of his rapid drop in blood glucose between noon and 1:00 p.m. This reduction helped to eliminate mid-afternoon low glucose levels. Additionally, the patient had started using carbohydrate counting to formulate a decision about lunchtime insulin dosing. Carbohydrate counting began to make better sense as he tested his blood glucose more frequently and had better control over the steps to self manage his blood glucose. As he had aged, the patient recognized that managing his hypoglycemia had become more difficult to do.[6]

In this case, the patient became frustrated with treatment outcomes and eventually had stopped checking his blood glucose levels because he felt powerless to improve his situation. The patient's endocrinologist had started to educate him on self-adjusting insulin doses, but the patient reported that he was always *chasing* his blood glucose, and eventually gave up. By learning the technique of carbohydrate counting, he could better know what to do to

improve his blood glucose levels and gave him hope that he was more in control of his diabetes management and treatment outcomes.

Dietary and Lifestyle Factors

Problems with the timing of the patient's long-acting insulin peak resulting in early nocturnal low blood glucose levels were discovered. Based on the clinical experience of the dietician of line demonstrating a slightly smoother peak, a change was recommended in the long-acting insulin unit-for-unit from NPH to lente. At the patient's next visit, a review was made of his insulin doses of 22 units of late in the morning and 11 units of late at night. The patient's TDD including premeal lispro now averaged 49 units. His average blood glucose levels were 130 mg/dl fasting, 100 mg/dl mid-afternoon, 127 mg/dl before dinner, and 200 mg/dl at bedtime.[6]

It was discovered that the patient routinely had late meals, ate higher fat content meals in restaurants, and that his meat food choices and the patient's inexperience at counting carbohydrates for prepared foods were the reason for higher blood glucose bedtime levels. This led to a medical recommendation of mixing regular and lispro insulin to try and get the average bedtime blood glucose level to 140 mg/dl.[6] Mixing the patient's calculated dose to be one-third regular and two-third lispro would provide coverage lasting a little longer than that of just lispro to cover higher-fat foods that took longer to digest. The dietitian encouraged the patient to also choose lower-fat foods to help reduce his LDL cholesterol and to assist with weight loss. Accurate food records were encouraged to help the patient accurately calculate insulin doses.

The dietician also reviewed with the patient his decisions for treating low blood glucose levels. Initially, the patient would eat any type of food and as much as he could eat when experiencing hypoglycemia, resulting in blood glucose levels >400 mg/dl. He was taught to appropriately use 15–30 g of quick-acting glucose (usually 4–8 oz. of orange juice). This amount was based on his blood glucose level, expecting about a 40-mg/dl rise over 30 minutes from 10 g of carbohydrate. He was taught to check his glucose level before treating the hypoglycemia when possible and always to check it again 15–30 minutes after treatment to evaluate the results. Once the patient's glucose

reached 80 mg/dl or above, to prevent a recurrence of hypoglycemia, he avoided eating until his next meal.[6]

Chronic Medical Issues and Lifestyle Changes

The patient's physician had identified a problem of erectile dysfunction and made a referral to a urologist. Eventually, the urologist diagnosed reduced blood flow and started the patient on sildenafil (Viagra®).[6]

The patient had also gained weight and was encouraged to resume exercise to help with weight loss. Because exercise improves insulin sensitivity and can acutely lower blood glucose, he was taught how to reduce his insulin doses by 25–50% for planned physical activity to further reduce the risk of hypoglycemia. He was taught to carry his blood glucose meter, to carry fluids with him, and to have carbohydrate foods ready if needed during and after exercise. His pre-exercise blood glucose goal was set at 150 mg/dl. He was taught to test his blood glucose again after exercise and to eat carbohydrate foods if it was <100 mg/dl.[6]

He was also provided instructions for unplanned exercise. He would require additional carbohydrate depending on his blood glucose level before exercise, his previous experience with similar exercise, and the timing of the exercise. Follow-ups were scheduled with the patient's physician, and dietitian was scheduled out to every month after a while, and then every three months thereafter.[6]

At an annual eye exam, the patient was informed that he had background retinopathy. He began expressing that his daily injection regimen had become too complicated. New physical limitations related to his diabetes and aging contributed to his sense of being unable to control his diabetes, and he began to search for an alternative to insulin injections. The option of continuous subcutaneous insulin infusion therapy (insulin pump therapy) was raised. The patient's diabetes treatment team discussed the benefits and risks of insulin pump therapy with the patient and its impact on his current situation. The available insulin pump systems were reviewed, and a decision was made on which ones would best meet the patient's needs.[6] The insulin

pump equipment was ordered, and a training session was scheduled with the dietitian (also a certified pump trainer).

The patient started using an insulin pump two years after his first visit with the dietitian related ongoing issues of hypoglycemia. His insulin-to-carbohydrate ratio was adjusted for his new insulin therapy regimen, and a new ISF was calculated to help him reduce high blood glucose levels. The patient's endocrinologist set basal insulin rates at 0.3 units/hour to start at midnight and 0.5 units/hour to start at 3:00 a.m. This more natural delivery of insulin based on the patient's body rhythms and lifestyle further improved his diabetes control.[6]

One week after starting insulin pump therapy, the patient called the dietitian to report large urine ketones and a blood glucose level of 317 mg/dl. This was after the endocrinologist had changed his basal rates. An appointment was set to review this concern, and to review the patient's sites, set insertion, troubleshooting skills, and related issues. Working together with the diabetic treatment team, the patient eventually discovered that problems with his pump sites required using a bent-needle set to resolve absorption issues.[6]

The patient had developed a trusting and ongoing relationship with his endocrinologist, dietitian and other members of the diabetes treatment team. He was able to engage and to recognized when he needed more time to work through problems. The patient met with the diabetes treatment team for over three years. Eventually, he was able to recover from symptoms of hypoglycemia when his blood glucose levels had been as low as 70 mg/dl.[6] After six months of education meetings, his lab values had reached target ranges. Most recently, the patient's LDL cholesterol was <100 mg/dl, his A1c results were <7%, his hypoglycemia symptoms were maintained at a blood glucose level of 70 mg/dl, and his blood glucose had been stabilized using the square-wave and dual-wave features on his insulin pump.[6]

Discussion[6]

Carbohydrate counting involves more frequent testing of the blood glucose and, concurrently, there is better blood glucose control than by using the sliding scale method. In this case, the patient became frustrated with his former approach of blood glucose management with the use of the sliding scale. This is not an uncommon dilemma encountered by diabetic health team members faced with patient adherence to a diabetes regimen; patients tend to give up trying when glucose management is not working. The patient, in this case, was educated on the new technique of carbohydrate counting and was able to realize better success in the control of glucose regulation.

Individuals who eat their meals in a variety of settings, such as fast foods or restaurants, may find carbohydrate counting more challenging. They may need to be education on carrying different types of insulin and on the need to change types of insulin.[6] In this case, the patient was changed from regular to lispro insulin. He continued checking his blood glucose around meal times - before and after eating. His insulin-to-carbohydrate ratio of 1:10 g and his ISF of 1:40 mg/dl allowed him to stay within his goal of no more than a 30-mg/dl increase in blood glucose after his meals.[6] In this way, the patient's hypoglycemia could be better managed with less occurrence of low blood glucose levels.

The patient's new goal of diabetes therapy was to recover his hypoglycemia symptoms at a more normal level of about 70 mg/dl. He underwent frequent follow-up visits at the diabetes clinic and motivational interventions to support adherence to treatment. Most importantly, through motivational techniques employed by the diabetes treatment team, the patient learned how to achieve recommended goals to self-manage his diabetes.[6.7] With the help of the interdisciplinary diabetes care team, the endocrinologist, dietician, pharmacist and other members of the medical and nursing team involved in the patient's health needs, the patient was able to achieve a significantly improved level of type 1 diabetes control and management.[6]

Diabetes Type I Treatments

Type 1 diabetes is managed through the use of a variety of insulins. This section discusses the various types of insulins that people with Type 1 diabetes may be prescribed. Diabetic individuals must be educated to interact closely with the diabetes interdisciplinary team, which generally includes an endocrinologist or other specially trained medical professionals, dietician, pharmacist, and nursing or other diabetes health team members.[6,7] An individualized type 1 diabetes medical regime is critical to control blood glucose and to avoid a serious diabetes health complication or crisis. In a later section, case studies of type 1 diabetics will cover the importance of the interdisciplinary health team to support patient adherence to treatment and diabetes control.

The diabetes health team will need to educate type 1 diabetics on their available options of insulin administration. Insulin can be delivered via syringes or pens, pumps or new artificial pancreas systems.[6,7] The administration method will need to be individualized to meet the patient's preferences and needs, and the frequency and type of insulin dosage will vary on a case-by-case basis. It is important for the patient to become comfortable with the fact that injections may be needed multiple times per day to help regulate blood glucose levels. There are many different insulins on the market that can be used.[6,7] From rapid-acting insulin to intermediate-acting insulins and finally long-acting insulins. These different insulins are categorized by their function as either prandial or "mealtime" insulins, which include bolus, rapid, or short-acting insulins, and basal insulins, which include intermediate or long-acting insulin.

Rapid-acting Insulin

Rapid-acting insulins will take effect within 15 minutes after being administered.[8] The peak period is within 30 to 90 minutes following injection, and the effects of rapid-acting insulin will last for three to five hours. In cases of type 1 diabetes, the use of rapid-acting insulin is recommended at every meal three times daily, as compared to cases of type 2 diabetes where the rapid-acting form of insulin is usually just once daily at the time of the patient's heaviest meal.[8]

All rapid-acting insulins are clear and colorless formulations that are administered by the subcutaneous route. *Humalog*® 100 unit/mL, *Novolog*®, *Apidra*®, and *Admelog*® can be given subcutaneously via an insulin pump. *Fiasp*, *Humalog*® 100 unit/mL, *Apidra*®, *NovoLog*®, and *Admelog*® can be given by intravenous infusion.[8]

Short-acting Insulin

Short-acting insulins, which have been called "regular-acting insulin," will take effect in the bloodstream within 30 to 60 minutes after being administered. The short-acting insulins can be given via subcutaneous injection or intravenous infusion. They are a clear and colorless insulin product.[8]

The peak period is within two to four hours, and the effects can last for five to eight hours. There is a longer period to onset and longer duration than rapid-acting insulins. For type 1 diabetics, it is a non-preferred alternative to rapid-acting insulin at each meal. For type 2 diabetics, the use of short-acting insulin is typically once daily at the time of their largest meal. Also, the lag time between regular insulin administration and meals may not be necessary for all patients with type 2 diabetes.[8,9]

Intermediate Insulin

Intermediate insulin takes one to three hours to start working and will peak in eight hours.[8,9] This insulin type works for 12 to 16 hours after administration and is used to help control the blood glucose between meals. Intermediate-acting insulin is a product of human insulin complexed with a substance to delay its absorption and prolong its action. It starts working within 1-2 hours and reaches its highest level in the blood around 4-12 hours following administration.[8,9]

Long-acting Insulin

Long-acting insulin takes the longest amount of time to start working, up to 4 hours to enter the bloodstream. It is administered via subcutaneous injection and appears as a clear and colorless product.[8] For the type 1 diabetic, the long-acting form of insulin injection is preferred as the *basal (base)*

component of basal-prandial regimens. For type 2 diabetics, the long-acting form of insulin is typically considered an initial insulin option and is often used as an adjunct or add-on to oral agents. As type 2 diabetes progresses, insulin may be changed to a rapid- or short-acting form for use during mealtime at the largest meal of the day.[8]

Pre-mixed Insulin

Pre-mixed insulin is a combination of two different types of insulin: one that controls blood sugar at meals and another that controls blood sugar between meals.[8,9] Generally, the insulin mixes are not considered appropriate for type 1 diabetes due to the lack of dose flexibility. In elderly individuals diagnosed with type 2 diabetes, insulin mixes are considered due to their ease of use.[8] This insulin regime is administered by a subcutaneous injection before breakfast and supper, or before breakfast, lunch, and supper. Mixed insulin will appear cloudy.[9]

Oral Agents

Oral agents are generally used for the treatment of type 2 diabetes; however, mention should be made here of oral agents as researchers are working on an oral agent of insulin delivery. Additionally, type 2 diabetics using oral agents may need to treat episodes of higher blood glucose values during times of poor control, such as during infection or age-related disease progression, with combination oral and insulin treatment to better manage diabetes. A brief review of the oral agents will be listed next.[10]

Metformin (Glucophage®, Glumetza®, others):

Generally, metformin is the first medication prescribed for type 2 diabetes and functions by lowering glucose production in the liver and improving the body's sensitivity to insulin. Metformin helps to achieve more effective use of insulin.[10]

Sulfonylureas:

These medications help a person’s body secrete more insulin. Examples include glyburide (DiaBeta®, Glynase®), glipizide (Glucotrol®) and glimepiride (Amaryl®).[10]

Meglitinides:

These medications — such as repaglinide (Prandin®) and nateglinide (Starlix®) — work like sulfonylureas by stimulating the pancreas to secrete more insulin, but they're faster acting, and the duration of their effect in the body is shorter.[10]

Thiazolidinediones:

Like metformin, these medications — including rosiglitazone (Avandia®) and pioglitazone (Actos®) — make the body's tissues more sensitive to insulin.[10]

DPP-4 inhibitors:

These medications — sitagliptin (Januvia®), saxagliptin (Onglyza®) and linagliptin (Tradjenta®) — help reduce blood sugar levels but tend to have a very modest effect.[10]

GLP-1 Receptor Agonists:

These injectable medications slow digestion and help lower blood sugar levels. Exenatide (Byetta®, Bydureon®), liraglutide (Victoza®) and semaglutide (Ozempic®) are examples of GLP-1 receptor agonists. Recent research has shown that liraglutide and semaglutide may reduce the risk of heart attack and stroke in people at high risk of those conditions.[10]

SGLT2 Inhibitors:

These drugs prevent the kidneys from reabsorbing sugar into the blood. Instead, the sugar is excreted in the urine. Examples include canagliflozin (Invokana®), dapagliflozin (Farxiga®) and empagliflozin (Jardiance®).[10]

Fast-acting Insulin

The fast-acting insulin products include Humalog® (lispro), Novolog®, Apidra® (glulisine), and Afrezza® (inhaled insulin).[9] The fast-acting insulins are used to help imitate the meal-induced secretion of insulin. They have a quick onset of action which is approximately 15 to 20 minutes, and they have

a short duration of action approximately two to four hours. This section discusses the adult, pediatric and type 2 diabetes dosing algorithms.[9]

Humalog® (lispro)[9]

Adult Dosing:

- Dosage forms: INJ (U-100 vial): 100 units per mL; INJ (U-100 pen): 100 units per mL; INJ (U-200 pen): 200 units per mL
- Strength Clarification: 200 units/mL for SC injection use diabetes
- Individualize dose SC/IV twice daily or four times daily
- Usual total daily insulin requirement 0.5-1 units/kg/day (basal+prandial); give <15 min before or immediately after meals (SC injection) or continuous infusion (SC pump); admin. IV only in clinical setting; SC onset <0.5h, peak 0.5-1.5h, duration <6h (rapid-acting insulin analog)
- Renal Dosing [adjust dose amount]:
  - CrCl 10-50: decrease dose 25%
  - CrCl <10: decrease dose 50%; HD/PD: no supplement
- Hepatic Dosing [adjust dose amount]
- Hepatic impairment: decrease dose, amount not defined

Pediatric Dosing:

- Dosage forms include: INJ (U-100 vial): 100 units per mL; INJ (U-100 pen): 100 units per mL; INJ (U-200 pen): 200 units per mL
- Strength clarification: 200 units per mL for SC injection use only; diabetes mellitus, type 1

Dose: 3-year-old and Older:

- Individualize dose SC twice daily to four times daily
- Usual total daily insulin requirement 0.5-1 units/kg/day (basal+prandial)
- Adolescents may require higher doses. Give <15 min before or immediately; after meals (SC injection) or continuous infusion (SC pump); SC onset <0.5h, peak 0.5-1.5h, duration <6h (rapid-acting insulin analog)

Diabetes Mellitus, Type 2:

- Individualize dose SC twice daily to four times daily
- Usual total daily insulin requirement 0.5-1 units/kg/day (basal+prandial)

- Adolescents may require higher doses; give <15 min before or immediately after meals (SC injection); SC onset <0.5 hours, peak 0.5-1.5h, duration <6 hours (rapid-acting insulin analog)
- Renal Dosing [adjust dose amount]:
  - Renal impairment: decrease dose, amount not defined; HD: not defined
- Hepatic Dosing [adjust dose amount]:
  - Hepatic impairment: decrease dose, amount not defined

Manufacturer/Pricing: Eli Lilly and Co:
- 100 units/mL (1 vial, 3 mL): $113.01 solution for injection:
- 100 units/mL (1 vial, 10 mL): $338.15 solution for injection:
- 100 units/mL (5 cartridge, 3 mL): $703.99 solution for injection:
- 100 units/mL (1 kwikpen, 3 mL): $137.30 (usually pharmacies will not break a box of 5 kwikpens)

Novolog® (aspart)[9]

Adult Dosing:

The dosage forms include INJ (U-100 pen): 100 units per mL; INJ (U-100 vial): 100 units per mL

Diabetes Mellitus:
- Individualize dose SC/IV twice daily to four times daily
- Usual total daily insulin requirement 0.5-1 units/kg/day (basal + prandial); give 5-10 min before meals (SC injection) or continuous infusion (SC pump); admin. IV only in clinical setting; SC onset <0.25h, peak 1-3h, duration 3-5h (rapid-acting insulin analog)
- Renal Dosing [adjust dose amount]:
  - Renal impairment: decrease dose, amount not defined; HD/PD: not defined
- Hepatic dosing [adjust dose amount]:
  - Hepatic impairment: decrease dose, amount not defined

Pediatric Dosing:

The dosage forms include: INJ (U-100 pen): 100 units per mL; INJ (U-100 vial): 100 units per mL

Diabetes Mellitus, Type 1: dose for a 2-year-old and older includes

- Individualize dose SC twice daily to four times daily
- The usual total daily insulin requirement is 0.5-1 units/kg/day (basal+prandial); adolescents may require higher doses; give 5-10 min before meals (SC injection) or continuous infusion (SC pump); SC onset <0.25h, peak 1-3h, duration 3-5h (rapid-acting insulin analog)

Diabetes Mellitus, Type 2:

- Individualize dose SC twice daily to four times daily
- Usual total daily insulin requirement 0.5-1 units/kg/day (basal+prandial).
- Adolescents may require higher doses. Give 5-10 min before meals (SC injection); SC onset <0.25h, peak 1-3h, duration 3-5h (rapid-acting insulin analog)

- Renal Dosing [adjust dose amount]:
  - Renal impairment: decrease dose, amount not defined; HD/PD: not defined
- Hepatic Dosing [adjust dose amount]:
  - Hepatic impairment: decrease dose, amount not defined

Manufacturer/Pricing - Novo Nordisk A/S markets Novolog® insulin as:

- 100 units/mL (5 pre-filled syringes, 3 mL): $589.99 solution for injection
- 100 units/mL (5 cartridges, 3 mL): $674.99 solution for injection
- 100 units/mL (1 vial, 10 mL): $359.99

Case Study: Bedtime Hyperglycemia[6]

The following case study is of a 27-year-old woman with type 1 diabetes who was treated with the following insulin regimen.

- Before breakfast – 8 units insulin aspart and 20 units insulin detemir
- Before evening meal – 4 units aspart
- Before bedtime – 12 units detemir

The patient's blood glucose values (in mg/dL and, in parentheses, mmol/L) were as followed:

Day	Before	Before	Before	Before
	Before Breakfast	Before Lunch	Before Dinner	Bedtime
1	86 (4.8)	104 (5.8)	96 (5.3)	320 (17.8)
2	146 (8.1)	123 (6.8)	105 (5.8)	296 (16.4)
3	111 (6.2)	97 (5.4)	92 (5.1)	341 (18.9)

Discussion[6]

The patient's current level of glycemic control is hyperglycemia before bedtime. Increasing the dose of insulin aspart before the evening meal could probably correct the problem. Other lifestyle issues should be considered. For example, if the patient has a late evening meal she will not have time between the meal and her bedtime test. The evening meal may also be her biggest meal of the day. Reviewing the patient's diary of meals with her could assist her to recognize her distribution of food and the type of food she is eating throughout the course of the day.

The diabetes health team has a pivotal role in supporting diabetic patients to develop consistent meal preparation and planning, and to record their meals for ongoing review with the treatment team. Often reflecting back over a food diary will expose deficiencies and inform of those aspects of diet management that are also working well and that promote good blood glucose management.

Apidra® (glulisine)[11]

Adult Dosing: The dosage forms include INJ (U-100 pen): 100 units per mL; INJ (U-100 vial): 100 units per mL

Diabetes Mellitus:

- Individualize dose SC/IV twice daily to four times daily

- Usual total daily insulin requirement 0.5-1 units/kg/day (basal+prandial)
- Give <15 min before or <20 min after meals (SC injection) or continuous infusion (SC pump); admin. IV only in clinical setting; SC onset <0.5h, peak; 0.5-1.5h, duration <6h (rapid-acting insulin analog)
- Renal Dosing [adjust dose amount]
  - Renal impairment: decrease dose, not defined; HD/PD: not defined
- Hepatic Dosing [adjust dose amount]
  - Hepatic impairment: decrease dose, amount not defined

Pediatric Dosing:

The dosage forms include INJ (U-100 pen): 100 units per mL; and INJ (U-100 vial): 100 units per mL

Diabetes Mellitus, Type 1:

For a child 4-year-old and older:

- Individualize dose SC twice daily to four times daily;
- Usual total daily insulin requirement 0.5-1 units/kg/day (basal + prandial); adolescents may require higher doses; give <15 min before or <20 min after meals (SC injection); SC onset <0.5h, peak 0.5-1.5h, duration <6h (rapid-acting insulin analog)

Diabetes Mellitus, Type 2:

- Individualize dose SC twice daily to four times daily
- Usual total daily insulin requirement 0.5-1 units/kg/day (basal + prandial); adolescents may require higher doses; give <15 min before or <20 min after meals (SC injection); SC onset <0.5h, peak 0.5-1.5h, duration <6h (rapid-acting insulin analog)
- Renal Dosing [adjust dose amount]:
  - Renal impairment: decrease dose, amount not defined;
- Hepatic Dosing [adjust dose amount]:
  - Hepatic impairment: decrease dose, amount not defined
- Manufacturer/Pricing:Sanofi-Aventis U.S. LLC:
  - 100 units/mL (5 Solostar pen, 3 mL): $542.83
  - Injection sol:100 units/mL (1 vial, 10 mL): $418.87

Inhaled Insulins

An inhaled insulin, Exubera® was ultimately unsuccessful, however, innovation with regard to inhaled insulin continued and Afrezza® was launched in 2014. The AFFINITY-1 study concluded that, in patients with type 1 diabetes receiving basal insulin, A1C reduction with Afrezza® was noninferior to insulin aspart and significantly fewer patients experienced hypoglycemia. The AFFINITY-2 study confirmed that, in patients with type 2 diabetes uncontrolled on oral agents, the addition of prandial Afrezza® was effective, significantly lowering A1C ($P < 0.0001$).[6]

Afrezza® appears to have key advantages over Exubera®. Its delivery system is small, sleek, and dosed in units and provides a simple dosing conversion chart, whereas Exubera's delivery system was large, awkward, and dosed in milligrams. The modifications implemented with Afrezza allows for a more discreet administration process and a dosing regimen that is easier for both prescribers and patients to comprehend.[6] However, Afrezza's safety profile resembles that of Exubera, with a decline in pulmonary function and a slight increased incidence of lung cancer. New concerns were brought forward after Afrezza's approval, prompting the FDA to require a risk evaluation and mitigation strategy and a "black-box" warning informing patients of an increased risk of acute bronchospasm in those with chronic lung disease.

Diabetic ketoacidosis (DKA) was also found to be more common in patients in the Afrezza cohort.[6] With subcutaneous insulin administration, lipohypertrophy is one complication that can affect patients. The cause is likely multifactorial and could involve poor injection site rotation or poor injection technique, but also the growth factor properties of insulin. During clinical trials of Afrezza®, there were two cases of lung cancer during 2,750 patient-years of exposure. Both cases occurred in smokers exposed to Afrezza®; no subjects in the placebo cohorts were diagnosed with lung cancer. After clinical trial completion, the investigators reported that two nonsmokers also were diagnosed with the same type of cancer (squamous cell lung carcinoma).[6]

Cough is another side effect associated with inhaled insulin. In a 24-month trial conducted by Raskin, et al., 27.8% (257/923) of patients in the

Technosphere insulin (TI; the insulin used in Afrezza®) cohort experienced cough compared to 4.4% (42/949) in the usual care cohort. The AFFINITY-1 study documented that 27.1% of subjects in the TI cohorts (94/347) reported cough, leading to a 4.3% (15/347) discontinuation rate. Although cough may not directly cause any clinical concerns, it is likely considered an annoyance to most and may impede patients' quality of life.[6] All cohorts in the Raskin trial experienced a decline in FEV1 (a measure of lung function). The mean change in FEV1 between treatment groups at 24 months met the non-inferiority criterion. The initial decline at 3 months was greater in the TI group than in the usual care group and persisted for the duration of therapy (2 years). Visually, the reduction in FEV1 appeared to be ~100 mL for TI, ~50 mL for usual care, and ~50 mL for non-diabetes. Finally, 5.75% of patients receiving TI and 3.28% of those receiving usual care had a ≥15% decrease in FEV1 from baseline at 24 months. However, the investigators determined that only three of the subjects who had a decline in FEV1 of ≥15% had a clinically significant reduction. Again, there are not yet enough data to evaluate the long-term significance of this decline in pulmonary function.[6]

Afrezza® Inhaled Insulin[11]

Adult Dosing:
The dosage forms include 4-unit convenience pack; 8-unit convenience pack; 12-unit convenience pack; 4-unit and 8-unit convenience pack; 4-unit and 8-unit and 12-unit convenience pack

- Pack contains 4-unit (blue) DPI cartridge x 90
  [8-unit convenience pack components]
- Pack contains 8-unit (green) DPI cartridge x 90
  [12-unit convenience pack components]
- Pack contains 12-unit (yellow) DPI cartridge x 90
  [4-unit and 8-unit convenience pack components]
- Pack contains 4-unit (blue) DPI cartridge x 90 and 8-unit (green) DPI cartridge x 90
  [4-unit and 8-unit and 12-unit convenience pack components]
- Pack contains 4-unit (blue) DPI cartridge x 60 and 8-unit (green) DPI cartridge x 60 and 12-unit (yellow) DPI cartridge x 60

Diabetes Mellitus

The dose for insulin-naive patients includes:

- Individualize dose inhaled immediately before each meal
- Start: 4 units inhaled immediately before each meal; usual total daily insulin requirement 0.5-1 units/kg/day (basal+prandial)
- Consider to discontinue treatment if FEV1 decrease >20% from baseline; onset 0.2h, peak 0.6-0.9h, duration 1.5-4.5h (rapid-acting insulin)

The dose for insulin-experienced patients includes:

- Individualize dose inhaled immediately before each meal
- Start: individualize dose based on current prandial SC insulin intake (see package insert for conversion)
- Usual total daily insulin requirement 0.5-1 units/kg/day (basal+prandial)
- Consider to discontinue treatment if FEV1 decrease >20% from baseline; onset 0.2h, peak 0.6-0.9h, duration 1.5-4.5h (rapid-acting insulin)
- Renal Dosing [adjust dose amount]:
  - Renal impairment: decrease dose, amount not defined; HD/PD: not defined
- Hepatic Dosing [adjust dose amount]:
  - Hepatic impairment: decrease dose, amount not defined

Pediatric Dosing:

Pediatric dosing is currently unavailable or not applicable. The adverse reactions, contraindications and medication adjustments for pregnancy and lactation for fast-acting insulin are outlined in the following three tables.

ADVERSE REACTIONS FOR FAST-ACTING INSULIN[11]

Humalog®	NOVOLOG®	APIDRA®	AFREZZA®
Serious Reactions hypoglycemia hypokalemia hypersensitivity reaction anaphylaxis Common Reactions hypoglycemia, injection site reaction and lipodystrophy, myalgia, nasopharyngitis, pruritus, rash, URI, weight gain, headache, edema, peripheral, hypersensitivity reaction, influenza	Serious Reactions hypoglycemia hypokalemia hypersensitivity reaction anaphylaxis Common Reactions hypoglycemia injection site reaction and lipodystrophy, myalgia, pruritus, rash, URI, weight gain, headache edema, peripheral hypersensitivity, reaction, influenza	Serious Reactions hypoglycemia seizures, hypoglycemic (peds pts), hypokalemia hypersensitivity reaction, anaphylaxis Common Reactions hypoglycemia, injection site reaction and lipodystrophy, myalgia, pruritus, rash, URI, weight gain, headache, edema, peripheral hypersensitivity reaction, influenza	Serious Reactions bronchospasm, acute lung CA, pulmonary reaction decrease, hypoglycemia, seizures, diabetic ketoacidosis, hypokalemia, hypersensitivity reaction, anaphylaxis Common Reactions hypoglycemia cough, throat irritation, headache diarrhea, fatigue, nausea

CONTRAINDICATIONS FOR FAST-ACTING INSULIN[11]

HUMALOG®	NOVOLOG®	APIDRA®	AFREZZA®
Hypersensitivity to drug, class, and components. INJ: 200 units/mL IV, abd 200 units/mL continuous SC infusion pump; hypoglycemia. Caution: in patients 65 years old and older without concurrent basal or long-acting insulin, if infection, illness, or stress, caution if hypokalemia, caution if renal impairment, if hepatic impairment	Hypersensitivity to drug, class, and components; caution in patients 65 years and older without concurrent basal or long-acting insulin; hypoglycemia Caution: if infection, illness, or stress, if hypokalemia, if renal impairment, if hepatic impairment	Hypersensitivity to drug, class, and component: Hypersensitivity. to metacresol IM administration Hypoglycemia Caution: if infection, illness, or stress, in patients 65 years old and older without concurrent basal or long-acting insulin, if hypokalemia, if renal impairment, if hepatic impairment	Hypersensitivity to drug, class, and components: Hypoglyce mia pulmonary disease, chronic, asthma COPD Caution: if lung CA or history of CA, if lung CA risk, in smokers, if smoking hx w/in 6mo, if infection, illness, or stress, if diabetic ketoacidosis risk, if hypokalemia, if renal impairment, if hepatic impairment

PREGNANCY/LACTATION FOR FAST ACTING INSULIN[11]

HUMALOG®	NOVOLOG®	APIDRA®	AFREZZA®
Pregnancy: drug of choice for patients with gestational diabetes; no known risk of fetal harm based on human data Lactation: Caution advised while breastfeeding; no human data available, though no known risk of infant harm based on drug properties and limited human data with other insulins; possible risk of delayed milk production based on conflicting human data with other insulins	Pregnancy: drug of choice for patients with gestational diabetes; no known risk of fetal harm based on human data Lactation: May use while breastfeeding; no known risk of infant harm based on limited human data and drug properties; possible risk of delayed milk production based on conflicting human data	Pregnancy: drug of choice for patients with gestational diabetes; no human data available, though risk of fetal harm low based on animal data at 2x recommended human dose Lactation: Caution advised while breastfeeding; no human data available, though no known risk of infant harm based on drug properties and limited human data with other insulins; possible risk of delayed milk production based on conflicting human data with other insulins	Pregnancy: consider alternative; no human data available, and possible risk of teratogenicity from drug vehicle based on animal data at 14-21x systemic exposure Lactation:Caution advised while breastfeeding; no human data available, though no known risk of infant harm based on drug properties and limited human data with other insulins; possible risk of delayed milk production based on conflicting human data with other insulins

Short Acting Insulin

This section reviews the short-acting form of insulin that is administered for individuals with diabetes type 1.

Regular R or Novolin R[11]

Adult Dosing:

- Dosage forms: INJ (U-100 vial): 100 units per mL; diabetes mellitus
  - Individualize dose SC twice daily to four times daily
  - Usual total daily insulin requirement: 0.5-1 units/kg/day (basal+prandial); give 30 min before meals or sliding scale; onset 0.5-1 h, peak, and 2-4 h duration 6-12 h (short-acting insulin)
- Diabetic Ketoacidosis (DKA): [0.1 units/kg IV x1, then 0.1 units/kg/h IV]; Alt: 0.14 units/kg/h IV; if blood glucose decreases by <10% in 1st hour, give 0.14 units/kg IV x1, then resume usual dose; when blood glucose 200 mg/dL, decrease dose to 0.02-0.05 units/kg/h IV; maintain blood glucose at 150-200 mg/dL until DKA resolves.
- Hyperkalemia: 10 units IV x1; give with D50W
- Renal Dosing [adjust dose amount]
  - CrCl 10-50: decrease dose 25%; CrCl <10: decrease dose 50%; HD/PD: no supplement
- Hepatic Dosing [adjust dose amount]
  - Hepatic impairment: decrease dose, amount not defined

Pediatric Dosing:

The dosage forms include: INJ (U-100 vial): 100 units per mL

- Diabetes Mellitus, Type 1:

For a 2-year-old and older:

- Individualize dose SC twice daily to four times daily
- Usual total daily insulin requirement 0.5-1 units/kg/day (basal + prandial)

- Adolescents may require higher doses; give 30 min before meals or per sliding scale; onset 0.5-1h, peak 2-4h, duration 6-12h (short-acting insulin)

- Diabetic Ketoacidosis [0.1 units/kg/h IV]:
  - Start: 1-2h after initial fluid treatment; Info: give w/ IV potassium; for patients with marked insulin sensitivity, may decrease dose to <0.05 units/kg/h IV
  - Add dextrose 5% when blood glucose 250-300 mg/dL or if blood glucose decrease at rate >90 mg/dL/h
  - Maintain blood glucose at 200-250 mg/dL until DKA resolves; start insulin SC injection 1h before discontinuing insulin IV
- Hyperkalemia:
  - <1 month: Dose: 0.1-0.2 units/kg/h IV; Give w/dextrose; refer to institution protocol
  - 1 month and older: Dose: 0.05-0.1 units/kg/h IV; Info: give w/ dextrose; refer to institution protocol
- Renal Dosing [adjust dose amount]:
  - CrCl 10-50: decrease dose 25%
  - CrCl <10: decrease dose 50-75%; HD/PD: no supplement
- Hepatic Dosing [adjust dose amount]:
  - Hepatic Impairment: decrease dose, amount not defined

Manufacturer/Pricing: Novo Nordisk A/S

- 100 units/mL (1 vial, 10 mL): $168.54

Contraindications	Adverse Drug Reaction	Pregnancy/Lactation
Hypersensitivity: to drug/class/component Continuous SC infusion pump Hypoglycemia: caution in pts 65 yo and older w/o concurrent basal or long-acting insulin Caution if infection, illness, or stress; if hypokalemia; if renal impairment; if hepatic impairment	Serious Reactions: hypoglycemia, hypokalemia hypersensitivity reaction anaphylaxis Common Reactions: hypoglycemia, injection site reaction, injection site lipodystrophy, myalgia pruritus, rash, upper respiratory infection, weight gain, headache, edema, peripheral hypersensitivity reaction, influenza	Clinical Summary: Drug of choice for pts w/ gestational diabetes; no known risk of fetal harm based on human data Lactation: may use for breastfeeding; no known risk of infant harm based on limited human data and drug properties; possible risk of delayed milk production based on conflicting human data

Long-Acting Insulin

Insulin glargine (Lantus®, Basaglar®, Toujeo®)[11]

Lantus® Adult Dosing	**Basaglar®** Adult Dosing	**Toujeo®** Adult Dosing
Dosage forms: INJ (U-100 pen): 100 units per mL; INJ (U-100 vial): 100 units per mL Diabetes mellitus, type 1 [individualize dose SC daily] Start: ~ 33% of total daily insulin requirement; Usual total daily insulin requirement 0.5-1 units/kg/ day (basal+prandial); onset 1h, no true peak, duration 24h (long-acting basal insulin analog)	Dosage forms: INJ (U-100 pen): 100 units per mL Diabetes mellitus, type 1 [individualize dose SC daily] Start: ~ 33% of total daily insulin requirement; Usual total daily insulin requirement 0.5-1 units/kg/ day (basal+prandial) onset 1h, no true peak, duration 24h (long-acting basal insulin analog) Diabetes Mellitus, type 2 [individualize dose SC daily] Start: 0.2 units/kg SC daily, up to 10 units/day; onset 1h, no	Dosage forms: INJ (U-300 pen): 300 units per mL; clarify strength Delivery: 1-unit increments Diabetes mellitus, type 1 [individualize dose SC daily]; Start: ~ 33-50% of total daily insulin requirement; Usual total daily insulin requirement 0.5-1 units/kg/ day (basal+prandial); onset 6h, no true peak, duration 24-36h (long-acting basal insulin analog) Diabetes Mellitus, type 2 [individualize dose SC daily]

Diabetes Mellitus, type 2 [individualize dose SC daily] Start: 0.2 units/kg SC daily up to 10 units/day; onset 1h, no true peak, duration 24h (long-acting basal insulin analog) Renal dosing [adjust dose amount] renal impairment: decrease dose, amount not defined; HD/PD: not defined. Hepatic dosing [adjust dose amount] hepatic impairment: decrease dose, amount not defined Peds Dosing: Dosage forms: INJ (U-100 pen): 100 units per mL; INJ (U-100 vial): 100 units per mL; diabetes mellitus, type 1	true peak, duration 24h (long-acting basal insulin analog) Renal dosing [adjust dose amount] renal impairment: decrease dose, amount not defined; HD/PD: not defined. Hepatic dosing [adjust dose amount] hepatic impairment: decrease dose, amount not defined Peds Dosing: Dosage forms: INJ (U-100 pen): 100 units per mL diabetes mellitus, type 1 [6 yo and older] Dose: individualize dose SC daily;	Start: 0.2 units/kg SC daily; onset 6h, no true peak, duration 24-36h (long-acting basal insulin analog) Renal dosing [adjust dose amount] renal impairment: decrease dose, amount not defined; HD/PD: not defined. Hepatic dosing [adjust dose amount]; hepatic impairment: decrease dose, amount not defined Peds Dosing: Pediatric dosing is currently unavailable or not applicable for this drug.

[6 yo and older] Dose: individualize dose SC daily; Start: ~ 33% of total daily insulin requirement; Info: usual total daily insulin requirement 0.5-1 units/kg/ day (basal + prandial); onset 1h, no true peak, duration 24h (long-acting basal insulin analog) Diabetes mellitus, type 2 [individualize dose SC daily] Start: 0.2 units/kg SC daily up to 10 units/day; Info: onset 1h, no true peak, duration 24h (long-acting	Start: ~ 33% of total daily insulin requirement; Info: usual total daily insulin requirement 0.5-1 units/kg/ day (basal + prandial); onset 1h, no true peak, duration 24h (long-acting basal insulin analog Diabetes mellitus, type 2 [individualize dose SC daily] Start: 0.2 units/kg SC daily up to 10 units/day; Info: onset 1h, no true peak, duration 24h (long-acting basal insulin analog) Renal dosing [adjust dose amount] renal impairment:	

basal insulin analog) Renal dosing [adjust dose amount] renal impairment: decreased dose, amount not defined; HD: not defined; Hepatic dosing [adjust dose amount] hepatic impairment: decreased dose, amount not defined	decrease dose, amount not defined; HD/PD: not defined; Hepatic dosing [adjust dose amount] hepatic impairment: decrease dose, amount not defined	

The following case studies will help to illustrate several potential scenarios relative to insulin therapy in the setting of type 1 diabetes. For each case, a discussion is provided to help elucidate treatment options and nuances of diabetes care that may help to improve health outcomes.

Case Study: Type 1 Diabetes with Elevated A1c[12]

The following case study is of a 24-year-old insurance salesman with type 1 diabetes for two years who had been feeling stressed and tired at work and had early morning headaches. His glycated hemoglobin (A1c) value is 9.6 percent. Until fairly recently, he thought that his diabetes was well controlled. His current regimen included:

- Before breakfast – 6 units regular insulin and 28 units NPH insulin
- Before evening meal – 4 units regular insulin and 16 units NPH insulin

The patient's blood glucose values (in mg/dL, and in parentheses mmol/L) are shown in the following table.

Day	Before Breakfast	Before Lunch	Before Snack	Before Dinner	Before Bedtime
1	282 (15.7)	140 (7.8)	261 (14.5)	82 (4.6)	130 (7.3)
2	321 (17.8)	163 (9.1)	294 (16.3)	96 (5.3)	123 (6.8)
3	280 (15.6)	153 (8.5)	310 (17.2)	107 (5.9)	144 (8.0)

Discussion[12]

The difficulty of this patient to maintain glycemic control with recent-onset diabetes is likely due in part to a progressive decline in endogenous insulin secretion. In addition, the patient's insulin regimen is not ideal. Not enough regular insulin is being used, and he is taking NPH insulin too early in the evening. His high blood glucose values at 1:30 PM, for example, suggest that the patient needs to take regular insulin before lunch.

Blood glucose values of a reasonable level before bedtime, very high fasting values before breakfast and a history of tiredness and early morning headache is suggestive of a problem with the NPH insulin dose that he is taking before the evening meal. The action of the NPH insulin may be maximal in the late evening and middle of the night (causing both normoglycemia at bedtime and nocturnal hypoglycemia) and then dissipating in the early morning (causing hyperglycemia before breakfast).

The hypothesis that nocturnal hypoglycemia leads to fatigue and decreased well-being was tested in a study of 10 patients with type 1 diabetes who were evaluated on the morning after experimentally-induced nocturnal hypoglycemia (for one hour at 41 mg/dL [2.3 mM]) and on a control night when hypoglycemia was avoided. Symptoms of wellbeing and fatigue were significantly worse after the night of hypoglycemia, although higher cerebral function was unchanged.

The presence of nocturnal hypoglycemia followed by early morning hyperglycemia can be confirmed by measuring blood glucose at 3 AM. One solution is to move the patient's evening dose of NPH insulin from before the evening meal to before bedtime. Another approach might be to switch from NPH insulin to insulin with a longer, flatter profile (such as insulin glargine or detemir). The patient's lifestyle should also be evaluated; he may not be eating enough carbohydrate at the evening meal or late-night snack. Alternatively, the type of food the patient is eating may be inadequate to maintain blood glucose concentration through the night. A bedtime snack that is low in protein, fat, and fiber may be entirely digested and absorbed within two or three hours.

A review of the patient's exercise patterns in the evening may also be informative. Vigorous exercise at that time makes it more likely that his blood glucose concentration will fall to low values during the night. The following changes in the patient's insulin regimen lead to marked improvement in his glycemic control:

- Eight units insulin glulisine and 30 units insulin glargine before breakfast
- Six units glulisine before lunch
- Eight units glulisine before the evening meal

Three months later the patient's blood glucose values (in mg/dL and, in parentheses, mmol/L) are shown in the following table.

Day	Before Breakfast	Before Lunch	Before Snack	Before Dinner	Before Bedtime	3 AM
1	141 (7.7)	110 (6.2)	161 (8.9)	82 (4.6)	140 (7.8)	92 (5.1)
2	121 (6.7)	163 (9.1)	134 (7.4)	96 (5.3)	93 (5.2)	
3	150 (8.3)	153 (8.5)	110 (6.2)	107 (5.9)	144 (8.0)	104 (5.9)

The patient's A1c value was now 7.8 percent. He had more energy, the headaches resolved, and the patient was eating and exercising consistently, and had just been promoted because of improved productivity. To reduce his A1c value to below 7.0 percent, the patient will probably require a pre-meal insulin algorithm.

Contraindications for long-acting insulin (Basaglar®, Lantus®, and Toujeo®) include:[11]

- hypersensitivity to drug, class, or components that make up the medication
- IM or IV administration
- continuous SC infusion pump
- hypoglycemia
- caution if infection, illness, or stress
- caution if hypokalemia
- caution if renal impairment

- caution if hepatic impairment
- caution if visual impairment

Adverse Drug Reactions:[11]

- Serious Reactions: hypoglycemia, hypokalemia, hypersensitivity reaction, anaphylaxis
- Common Reactions: hypoglycemia, nasopharyngitis, URI, injection site reaction, injection site lipodystrophy, pruritus, rash, weight gain, edema, peripheral, hypersensitivity reaction
- Pregnancy/Lactation:
  - Drug of choice for patients with gestational diabetes
  - No known risk of fetal harm based on human data

- Lactation:
  - Caution advised while breastfeeding (no human data available, though no known risk of infant harm based on drug properties and limited human data with other insulins)
  - Possible risk of delayed milk production based on conflicting human data with other insulins

Levemir® (insulin detemir)

Adult Dosing:

The dosing forms include: INJ (U-100 pen): 100 units per mL; INJ (U-100 vial): 100 units per mL

- Diabetes Mellitus, type 1:
  [individualize dose SC daily to twice daily]
  Start: approx. 33% of total daily insulin requirement; Info: usual total daily insulin requirement 0.5-1 units/kg/day (basal + prandial); for the once-daily regimen, give w/ evening meal or at bedtime; onset 1h, no true peak, duration 8-24h (long-acting basal insulin analog)
- Diabetes Mellitus, type 2:
  [individualize dose SC daily to twice daily]
  Start: 10 units/day SC divided daily to twice daily; Alt: start 0.1-0.2 units/kg/day SC divided daily to twice daily; Info: if on GLP-1 receptor

agonist treatment, start 10 units SC daily; for once-daily regimen, give with evening meal or at bedtime; onset 1h, no true peak, duration 8-24h (long-acting basal insulin analog)

- Renal Dosing [adjust dose amount]
  - Renal impairment: decrease dose, amount not defined; HD/PD: not defined
- Hepatic Dosing: [adjust dose amount]
  - Hepatic impairment: decrease dose, amount not defined

Peds Dosing: The dosing forms include: INJ (U-100 pen): 100 units per mL; INJ (U-100 vial): 100 units per mL

- Diabetes Mellitus, type 1
  For 2 yo and older dose: individualize dose SC daily to twice daily; Start: approx. 33% of total daily insulin requirement; Info: usual total daily insulin requirement 0.5-1 units/kg/day (basal + prandial); for once-daily regimen, give w/ evening meal or at bedtime; onset 1h, no true peak, duration 8-24h (long-acting basal insulin analog)
- Diabetes Mellitus, type 2
  [individualize dose SC daily to twice daily]
  Start: 10 units/day SC divided daily to twice daily; Alt: start 0.1-0.2 units/kg/day SC divided daily to twice daily; Info: if on GLP-1 receptor agonist treatment, start 10 units SC daily; for once-daily regimen, give with evening meal or at bedtime; onset 1h, no true peak, duration 8-24h (long-acting basal insulin analog)
- Renal Dosing [adjust dose amount]
  - Renal impairment: decrease dose, amount not defined; HD: not defined
- Hepatic Dosing [adjust dose amount]
  - Hepatic impairment: decrease dose, amount not defined
- *Manufacturing/Pricing:* Sanofi-Aventis U.S. LLC
  Lantus: solution for injection:
  - 100 units/mL (5 Solostar pen, 3 mL): $487.99
  - 100 units/mL (1 vial, 10 mL): $283.99

Method of Monitoring the Blood Glucose

A common method of glucose testing for improved blood glucose regulation is through the self-monitoring of blood glucose (SMBG) approach. Self-monitoring of blood glucose is an integral part of consistent, well controlled insulin therapy in type 1 diabetics because it is at the direct point of care and assists in prompt, needed insulin dosing. Self-monitoring of blood glucose requires intermittent capillary blood sampling and the use of a glucose meter. Ideally, testing at home should be done at least four times daily, before meals and at bedtime.[11]

Additional testing, two to three hours after meals and occasionally at 3 AM, as well as before and after exercise, before driving, and when hypoglycemia is suspected, may be indicated.[13]

Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) is useful for adults with type 1 diabetes who are having frequent or severe hypoglycemia and who have developed hypoglycemia unawareness. Several generations of devices to sample glucose continuously from the interstitial fluid are available, with ongoing development in progress.[13]

Most real-time CGM devices measure and transmit glucose values every five minutes to a receiver and can alert (alarm) for hypoglycemia and hyperglycemia. There are CGM systems that transmit glucose data to mobile phones and allow users to "share" their data with family members, friends, and caregivers; others require the use of device-specific receivers. The immediate feedback of glucose results allows timely intervention for high, low, or trending glucose levels to aid management and avert serious hypoglycemic events. Because of reliability issues and the need for calibration for some of the devices, CGM does not eliminate the need for at least occasional fingerstick (SMBG).[13]

Case Study: Insulin Algorithm[12]

The following study involved a 43-year-old female factory worker who used insulin three injections per day in an attempt to reach glycemic control. The patient’s blood glucose concentrations are somewhat variable due to

alterations in her food intake and exercise program. The patient had expressed an interest to use an insulin algorithm. Her current regimen had consisted of:

- Before breakfast – 8 units regular insulin and 15 units NPH insulin
- Before dinner – 7 units regular insulin
- Before bedtime – 8 units NPH insulin

The patient's blood glucose values (in mg/dL, and in parentheses mmol/L) are shown in the following table.

Day	Before	Before	Before	Before
	Breakfast	**Lunch**	**Dinner**	**Bedtime**
1	159 (8.8)	134 (7.4)	186 (10.3)	84 (4.7)
2	117 (6.5)	164 (9.1)	210 (11.7)	97 (5.4)
3	102 (5.7)	122 (6.8)	261 (14.5)	79 (4.4)

Discussion[12]

The patient's blood glucose concentrations varied before breakfast, lunch, and the evening meal. An adjustment of her doses of regular insulin would be reasonable according to an insulin algorithm that is designed specifically for the patient. Patients will vary in how much the insulin doses need to be changed and what blood glucose values are referred to for guiding the changes. Some patients will need much smaller adjustments.

Extra insulin should not be taken by the patient before bedtime and an adjust of her doses of NPH insulin should not be done. If this algorithm were applied to the patient's current insulin regimen, then the alterations in her dose of regular insulin on Day 1 according to the blood glucose concentration would be as follows.[12]

Day 1:

- Before breakfast – 159 mg/dL (8.8 mmol/L); add 1 unit regular insulin to total dose of 9 units
- Before lunch – 134 mg/dL (7.4 mmol/L); no insulin dose
- Before dinner – 186 mg/dL (10.3 mmol/L); add 2 units regular insulin to total dose of 9 units
- Before bedtime – 84 mg/dL (4.7 mmol/L); no change

Similar adjustments would be made on subsequent days until glycemic control is reached. The patient could also consider using a carbohydrate: insulin ratio to allow her to take less food and less insulin at certain meals.

Case Study: Chaotic Glucose Pattern[12]

In this case a 19-year-old college male freshman diagnosed with type 1 diabetes since age nine has an A1c 7.5 percent in his senior year of high school, but the most recent A1c was 9.4 percent. He takes a full college course load, is getting decent grades, and is involved in lots of intramural sports, drama, and campus politics. The patient is taking 32 units of insulin glargine in the morning plus 4 to 8 units of lispro insulin before meals. The patient is frustrated that his blood glucose records (in mg/dL, or in parentheses in mmol/L) do not make any sense, as shown in the following table.

Before Breakfast	After Breakfast	Before Lunch	After Lunch	Before Evenin	After Evening	Before Bedtime

				g		
165 (9.2)	78 (4.3)			317(17.6)	273 (15.2)	192(10.7)
2 hours of basketball						
2 AM candy bar, no breakfast						
392 (21.8)		68 (3.8)	274 (15.2)	274(15.2)		199
skipped breakfast. felt low after class; turkey sand and chips						
101 (5.6)		306 (17.0)	207 (11.5)	101 (5.6)		172 (9.6)

The patient reported that he stayed up late studying for midterms. He ate a fast food hamburger for breakfast.

Discussion[12]

Despite testing his blood glucose at least five times daily, there is no discernable pattern. In this situation, it is essential to take a more detailed

history of exactly what his day-to-day life is like and exactly how and where he is giving his insulin injections. Some days he is up at 7 AM, and on other days he does not get up until 1 PM. The timing of his "morning" dose of insulin glargine, therefore, varies by six hours from day to day. He has been rotating his glargine and lispro shots from his arm, leg, buttock, or abdomen just like he was told to do when he was first diagnosed at age nine. One day he went for a three-hour bike ride just after giving his morning glargine insulin in his thigh. He was severely hypoglycemic two hours into the ride. He sometimes forgets to check his blood glucose or take his lispro before he eats so then takes a dose of lispro immediately after the meal based on how much carbohydrate he thinks he just ate. He then checks his blood glucose one to two hours later and gives himself a "correction dose" of lispro at that time if his blood glucose is too high.

Chaotic blood glucose patterns usually indicate a chaotic lifestyle. The clinician can attempt to help the patient reduce sources of variability. The clinician should observe whether there a consistent time of day to administer glargine insulin in the afternoon or evening so that it is given at more or less the same time every day. The clinician should ask the patient not to exercise a leg or arm within two hours of giving an insulin injection into that limb. Glargine insulin should be given in the buttock or thigh and lispro into the abdomen. The clinician should develop strategies to remind the patient to check blood glucose levels before meals and to take the dose of lispro insulin based on the blood glucose and the estimated amount of carbohydrate he is about to eat.

Some patients such as in this case do better when using a continuous glucose monitor to show them in close to real time what their blood glucose levels are doing. The patient might also do better using an insulin pump, but neither of these technologies will magically make things better for him unless he can address some of the causes of extreme day-to-day variability in his lifestyle.

Case Study: Consistency in Glucose Pattern[12]

A 32-year-old executive has a busy office job that is unpredictable in terms of physical activity, time of meals, or the length of the workday. Her current insulin regimen is noted below:

- Before breakfast – 4 units regular insulin and 10 units NPH insulin
- Before evening meal – 8 units regular insulin and 14 units NPH insulin
- Blood glucose records (in mg/dL or, in parentheses, in mmol/L) for one week are as follows.

DAY	BEFORE BREAKFAST	BEFORE LUNCH	BEFORE EVENING MEAL	BEFORE BED	3AM
1	156 (8.7)	111 (6.2)	97 (5.4)	63 (3.5)	
2	147 (8.2)	98 (5.4)	59 (3.3)	301 (16.7)	
3	182 (10.1)	124 (7.9)	86 (4.8)	87 (4.7)	91 (5.1)
4	191 (10.6)	115 (6.4)	46 (2.6)	62 (3.4)	
5	165 (9.3)	108 (6.0)	101 (5.6)	235 (13.1)	
6	246 (13.7)	89 (4.9)	92 (5.1)	57 (3.3)	78 (4.3)
7	178 (9.9)	97 (5.4)	67 (3.7)	164 (9.1)	
8	181 (10.1)	106 (5.9)	78 (4.3)	138 (7.7)	

The patient played racquetball for one hour at 8 PM on day 4 and had a late-night pizza at 11 PM on day 5.

Discussion[12]

Evaluation of the patient's records can be best approached by considering each time period separately. Her average blood glucose value before breakfast is too high at 181 mg/dL (10.1 mmol/L). The individual

values are also fairly consistent (from 147 to 191 mg/dL [8.2 to 10.6 mmol/L]) apart from one high value (246 mg/dL [13.7 mmol/L]) on day 5, which can probably be explained by her late-night pizza the preceding day.

This patient should benefit from increasing her NPH insulin dose before the evening meal since this is the insulin that is working during the night. However, her two 3 am values are in the ideal range. There is, therefore, a risk that increasing her evening NPH insulin dose will induce nocturnal hypoglycemia. This risk can be minimized by increasing her evening NPH insulin in small increments and continuing to measure blood glucose both at 3 AM and before breakfast. Another approach is to have her take her evening dose of NPH insulin at bedtime, instead of before the evening meal. She could also be switched to insulin detemir or insulin glargine.

Before lunch, her blood glucose values are consistent and average 106 mg/dL (5.9 mmol/L). This is very good control, suggesting that her morning dose of regular insulin and her breakfast and mid-morning snacks are appropriate and consistent from day to day and that her exercise and work schedule for the morning are relatively constant. However, she may be in danger of hypoglycemia before lunch once her before breakfast glucose values are lowered as recommended above. It might, therefore, be wise to slightly decrease her morning regular insulin dose as the evening NPH insulin dose is increased. Her before evening meal blood glucose values are too low, with an average value of 78 mg/dL (4.3 mmol/L) and two hypoglycemic episodes during the week. These findings suggest that she may be taking too much NPH insulin before breakfast since this is the insulin that is acting during the afternoon. Another possible explanation might be that her lunch is too early or too light, or that she doesn't eat an adequate mid-afternoon snack. There is inadequate information to identify the primary problem.

Before bedtime her blood glucose values average 138 mg/dL (7.7 mmol/L). While this average is close to ideal, the individual values vary widely from 57 to 301 mg/dL (3.2 to 16.7 mmol/L). This suggests that some variable aspect of her lifestyle is creating fluctuations in bedtime glucose values. Possible problems include variation in the time or content of her evening meal

or in evening exercise. As an example, the blood glucose value of 301 mg/dL (16.7 mmol/L) before bedtime on day two may have resulted from dietary overcompensation for her hypoglycemic episode before the evening meal. This patient's record keeping is better than most, however, is not sufficient to permit assessment of her problems before the evening meal and before bedtime. It would be helpful to know the exact times when her blood glucose was measured and exactly when she eats and the content of each meal.

Case Study: Switching from NPH to Detemir Insulin[12]

A 33-year-old man with type 1 diabetes is treated with 28 units NPH insulin before breakfast, and 12 units NPH insulin before bedtime. He also administers insulin apart by sliding scale before each meal. Despite being extremely consistent from day-to-day in his activity level and the timing and carbohydrate content of his meals, he is having unpredictable swings in blood glucose concentrations with occasional episodes of hypoglycemia in the late morning or early afternoon.

Blood glucose values (in mg/dL and, in parentheses, mmol/L):

DAY	BEFORE BREAKFAST (8 AM)	BEFORE LUNCH (12 PM)	BEFORE EVENING MEAL (5 PM)	BEFORE BED (11 PM)
1	132 (7.3)	54 (3.0) *	206 (11.4)	118 (6.6)
2	119 (6.6)	136 (7.6)	140 (7.8)	151 (8.4)
3	141 (7.8)	108 (6.0)	125 (6.9)	107 (5.9)
4	108 (6.0)	48 (2.7)*	196 (10.9)	140 (7.8)

***Represent episodes of symptomatic hypoglycemia.**

In order to change from NPH to insulin detemir his total daily dose of NPH is calculated (28 + 12 = 40), decreased by 10 percent (4 units), and is given as a single injection of 36 units of detemir insulin at bedtime. One week later his blood glucose values (in mg/dL and, in parentheses, mmol/L) are shown in the table below.

DAY	BEFORE BREAKFAST (8 AM)	BEFORE LUNCH (12 PM)	BEFORE EVENING MEAL (5 PM)	BEFORE BED (11 PM)
1	98 (5.4)	124 (6.9)*	168 (9.3)	213 (11.8)
2	103 (5.7)	131 (7.3)	171 (9.5)	232 (12.9)
3	217 (12.1)*	127 (7.0)	192 (10.7)	251 (13.9)
4	92 (5.1)	119 (6.6)*	185 (10.3)	211 (11.7)

The patient was awakened with hypoglycemia at 4 AM and took 60 grams of carbohydrate to treat this.

Discussion[12]

The patient's blood glucose values before breakfast on days 1, 2 and 4 are slightly low. That, along with one episode of hypoglycemia at 4 AM, suggests that 36 units of insulin detemir may be too much for him. The blood glucose values before lunch are ideal, but they are too high before dinner and even higher before bedtime. This suggests that insulin detemir is not lasting 24 hours, but that its action wanes after 18 to 20 hours. After switching to 20 units insulin detemir twice daily (at about 8 AM and 8 PM) his blood glucose values became stable throughout the day.

While many patients do well with a single dose of insulin detemir at bedtime, this case illustrates two practical points. Although its peak action is less than that of NPH insulin, it can have a slight peak in some patients which

may result in hypoglycemia during the night. Also, although it lasts for 24 hours in some patients, some patients require two daily injections.

Case Study: Later Afternoon Hypoglycemia[12]

A 42-year-old garage mechanic is treated with the following insulin regimen.

- Before breakfast – 8 units insulin lispro and 16 units insulin glargine
- Before lunch – 4 units lispro
- Before evening meal – 10 units lispro and 22 units Glargine

The patient uses an algorithm to adjust pre-meal doses of lispro insulin. Blood glucose values (in mg/dL or, in parentheses, mmol/L) for one week are shown below. The doses of lispro (LP) and glargine (G) insulin are also noted. The asterisks on days 2 and 4 reflect hypoglycemic episodes.

DAY	BEFORE BREAKFAST	BEFORE LUNCH	BEFORE EVENING MEAL	BEFORE BEDTIME	3 AM
1	100 (5.6) 8LP; 16G	205 (11.4) 8LP	116 (6.4) 10LP; 22G	115 (6.4)	
2	118 (6.6) 8LP; 16G	172 (9.6) 7LP	47 (2.6) 8LP; 22G	124 (6.9)	92 (5.1)
3	77 (4.3) 6LP; 16G	145 (81) 4LP	85 (4.7) 10LP; 22G	108 (6.0)	
4	113 (6.3) 8LP; 16G	136 (7.6) 5LP	54 (3.0) 8LP; 22G	111 (6.2)	
5	132 (7.3) 9LP; 16G	97 (5.4) 4LP	103 (5.7) 10LP; 22G	97 (5.4)	87 (4.8)
6	98 (5.4) 8LP; 16G	122 (6.8) 5LP	82 (4.6) 10LP; 22G	102 (5.7)	
7	158 (8.8)	109 (6.1)	93 (5.2)	89 (4.9)	

	8LP; 16G	4LP	10LP; 22G		
8	114 (6.3)	141 (7.8)	83 (4.6)	107 (5.9)	

Discussion[12]

This patient's record is quite complete, but there is no information about the quantity of food eaten and periods of exercise. He is consistent about the timing of blood glucose testing and meals and has adjusted his insulin doses correctly using the algorithm. He made only one "mistake." His blood glucose was measured between 7:05 and 7:15 AM every day except for day seven when he slept late, and the test was done at 9:55 AM. According to the algorithm, the dose of lispro insulin should have increased by 2 to 10 units for a blood glucose value of 158 mg/dL (8.8 mmol/L). Several other patterns can be detected. He needed to take extra insulin before lunch on four of the seven days. This suggests that his pre-breakfast dose of lispro insulin may be too low or that his mid-morning snack is too large or taken too close to lunch. His average blood glucose value is too low (83 mg/dL [4.6 mmol/L]) before the evening meal, with hypoglycemia occurring on days two and four. Possible explanations include a morning dose of insulin glargine or lunchtime dose of lispro insulin that is too high, or an inadequate mid-afternoon snack. His blood glucose values before bedtime and at 3 AM are normal.

Case study: Late Morning Hyperglycemia[14]

A 21-year-old woman is 62 inches (157 cm) tall and weighs 104 lb. (47 kg). She runs 40 miles per week. Treatment consisted of a continuous subcutaneous insulin infusion (CSII) with this following insulin regimen.

- Basal infusion rate – 0.4 units/hour
- Pre-breakfast bolus dose – 3 units
- Pre-lunchtime bolus dose – 2 units
- Pre-evening meal bolus dose – 4 units

The patient adjusts the pre-meal bolus doses according to the following algorithm. A three-day record of her glycemic control, with the doses of regular insulin shown under the blood glucose values (in mg/dL, and in parentheses mmol/L), and the time of the pre-meal measurements is roughly constant from day to day.

DAY	BEFORE BREAKFAST	BEFORE LUNCH	BEFORE EVENING MEAL	BEFORE BEDTIME	3 AM
1	105 (5.8) 3 UNITS	195 (10.8) 3.5 UNITS	146 (8.1) 5 UNITS	125 (6.9)	
2	112 (6.2) 3 UNITS	122 (6.8) 2.5 UNITS	147 (8.2) 5 UNITS	94 (5.2)	89 (4.9)
3	77 (4.3) 2 UNITS	186 (10.3) 3.5 UNITS	165 (9.2) 5.5 UNITS	108 (6.0)	

Discussion[14]

This patient's records are complete about time, blood glucose values, and insulin doses. She is consistent in terms of blood glucose testing and timing of meals, but we do not have information about the size and number of meals or the schedule of exercise. This consistency is reflected in the relatively constant blood glucose levels at each time of day. She is appropriately increasing her before-lunch and before-evening meal bolus insulin doses, since her blood glucose values are elevated only at those times. The fact that she has to add insulin every day before lunch suggests that some adjustment may be needed in her overall regimen during the morning.

The patient may need a larger pre-breakfast dose of insulin, a smaller breakfast or mid-morning snack, or an increase in her basal rate of insulin infusion. She could also consider using a carbohydrate: insulin ratio to allow her to take less food and less insulin at certain meals. It would also help if she switched from using regular insulin to insulin aspart in her pump.

Case Study: Evening Hyperglycemia[12]

A 34-year-old teacher is striving for excellent glycemic control. He eats a healthy diet, counts carbohydrates, exercises at a consistent time each day, and has been taking the following regimen:

- Before breakfast (6 AM) – 4 units insulin aspart and 14 units NPH
- Before lunch – 4 units insulin aspart
- Before evening meal (6 PM) – 6 units insulin aspart and 14 units NPH insulin

Doses of insulin aspart are also adjusted using an insulin algorithm. Because of nocturnal hypoglycemia and unexplained variation in blood glucose concentrations before the evening meal, NPH insulin was stopped and replaced with a single dose of 28 units insulin glargine taken at 10 PM. Doses of insulin aspart remained the same. Typical blood glucose concentrations (in mg/dL and, in parentheses, mmol/L) a few weeks later are shown in the table below.

DAY	BEFORE BREAKFAST (6 AM)	BEFORE LUNCH (11 AM)	BEFORE EVENING MEAL (6 PM)	BEFORE BED (10 PM)
1	107 (5.9)	123 (6.8)	163 (9.1)	296 (16.4)
2	130 (7.3)	111 (6.2)	146 (8.1)	210 (11.7)
3	140 (7.8)	144 (8.0)	178 (9.9)	261 (14.5)

Discussion[12]

Blood glucose values are ideal before breakfast and lunch but are somewhat high before the evening meal and are much too high before bedtime. Since he has not changed his eating habits or doses of insulin aspart, it is likely that the effect of the insulin glargine is waning after 20 hours. He

could try increasing the dose of insulin glargine or splitting it into two equal doses taken about 12 hours apart. Alternatively, he could increase the dose of insulin aspart before the evening meal.

Summary

Type 1 diabetes treatment regimens are complex and are primarily dependent on self-care. All patients with type 1 diabetes require intensive initial assessments as well as ongoing self-management, education, and support to manage their diabetes safely and improve clinical outcomes and quality of life. It is important to understand the effects of diet, physical activity, and stress on blood glucose, prevention of hypoglycemia, and approaches for the prevention and management of complications. Diabetes therapy will have the greatest chance for success if the patient is motivated, has a good understanding of the regimen, and is supported by family, friends, and a diabetic healthcare team with enough enthusiasm and expertise to guide therapy, educate the patient, and to monitor progress continuously.

Self-Assessment of Knowledge Post-Test:

Please take time to help NurseCe4Less.com course planners evaluate the nursing knowledge needs to be met by completing the self-assessment of Knowledge Questions after reading the article and providing feedback in the online course evaluation. Completing the study questions is optional and is NOT a course requirement.

1. **In prediabetes, a person's blood sugar level is higher than normal, which means that**

    a. The person has type 2 diabetes.
    b. Without lifestyle changes, progression to type 2 diabetes is likely.
    c. Progression to type 2 diabetes is inevitable.
    d. The person probably has type 1 diabetes.

2. **_____ is a formula for calculating the insulin-to-carbohydrate ratio.**

    a. The 1500 rule
    b. The correction factor
    c. The 500 rule
    d. Insulin sensitivity factor (ISF)

3. **In cases of type 1 diabetes, the use of rapid-acting insulin is recommended**

    a. At every meal (three times daily).
    b. Between meals.
    c. Once daily at the time of the patient's heaviest meal.
    d. Once daily in the morning.

4. **Short-acting insulins take effect in the bloodstream within _____ of administration.**

    a. 15 minutes
    b. 2 to 4 hours
    c. one to three hours
    d. 30 to 60 minutes

5. True or False: Short-acting insulins have a peak period that is within two to four hours, and the effects can last for five to eight hours.

a. True
b. False

6. _____ works for 12 to 16 hours after administration and is used to help control the blood glucose between meals.

a. Long-acting
b. Intermediate insulin
c. Rapid-acting insulin
d. Short-acting insulin

7. For the type 1 diabetic, the _____ form of insulin injection is preferred as the basal (base) component of basal-prandial regimens.

a. intermediate
b. long-acting
c. rapid-acting
d. regular-acting

8. Pre-mixed insulin is considered appropriate for

a. Patients with type 1 diabetes.
b. Patients who have insulin-dependent diabetes.
c. Patients who cannot tolerate long-acting insulins.
d. Elderly patients diagnosed with type 2 diabetes.

9. Which of the following forms of insulin has a cloudy appearance?

a. Mixed insulin
b. Short-acting insulin
c. Long-acting insulin
d. Rapid-acting insulin

10. True or False: Pre-mixed insulin is a combination of two different types of insulin: one that controls blood sugar at meals and another substance to speed up absorption.

a. True
b. False

11. Metformin is a medication that functions by lowering glucose production in the _____ and improving the body's sensitivity to insulin.

a. pancreas
b. spleen
c. liver
d. kidneys

12. _____ are medications that help a person's body secrete more insulin.

a. Sulfonylureas
b. Thiazolidinediones
c. GLP-1 receptor agonists
d. SGLT2 inhibitors

13. _____ are medications that prevent the kidneys from reabsorbing sugar into the blood.

a. DPP-4 inhibitors
b. Sulfonylureas
c. GLP-1 receptor agonists
d. SGLT2 inhibitors

14. _____ requires intermittent capillary blood sampling and the use of a glucose meter.

a. Continuous glucose monitoring (CGM)
b. Glucose tolerance test (GTT)
c. Self-monitoring of blood glucose (SMBG)
d. Carbohydrate counting

15. There are real-time CGM devices that can measure and transmit glucose values to a patient or family members

a. Through mobile phone devices.
b. Regarding the patient's hypoglycemia.
c. Regarding the patient's hyperglycemia.
d. All of the above

CORRECT ANSWERS:

1. In prediabetes, a person's blood sugar level is higher than normal, which means that

b. without lifestyle changes, progression to type 2 diabetes is likely.

"*In prediabetes, the blood sugar level is higher than normal but not yet elevated to a level of type 2 diabetes. Without lifestyle changes, people with prediabetes are very likely to progress to type 2 diabetes. Progression from pre-diabetes to type 2 diabetes is not inevitable, and choosing healthy foods, being physically active and maintaining a healthy weight can help a person maintain normal blood glucose levels.*"

2. _____ is a formula for calculating the insulin-to-carbohydrate ratio.

c. The 500 rule

"*The 1500 rule is a commonly accepted formula for estimating the drop in a person's blood glucose per unit of fast-acting insulin. This value is referred to as an "insulin sensitivity factor" (ISF) or "correction factor." … The 500 rule is a formula for calculating the insulin-to-carbohydrate ratio.*"

3. In cases of type 1 diabetes, the use of rapid-acting insulin is recommended

a. at every meal (three times daily).

"*In cases of type 1 diabetes the use of rapid-acting insulin is recommended at every meal three times daily, as compared to cases of type 2 diabetes where the rapid-acting form of insulin is usually just once daily at the time of the patient's heaviest meal.*"

4. Short-acting insulins take effect in the bloodstream within _____ of administration.

d. 30 to 60 minutes

"*Short-acting insulins, which have been called "regular-acting insulin," will take effect in the bloodstream within 30 to 60 minutes after being administered.*"

5. True or False: Short-acting insulins have a peak period that is within two to four hours, and the effects can last for five to eight hours.

a. True

"*Short-acting insulins, which have been called "regular-acting insulin," will take effect in the bloodstream within 30 to 60 minutes after being administered…. The peak period is within two to four hours, and the effects can last for five to eight hours.*"

6. _____ works for 12 to 16 hours after administration and is used to help control the blood glucose between meals.

b. Intermediate insulin

"*Intermediate insulin takes one to three hours to start working, and will peak in eight hours. This insulin type works for 12 to 16 hours after administration and is used to help control the blood glucose between meals.*"

7. For the type 1 diabetic, the _____ form of insulin injection is preferred as the basal (base) component of basal-prandial regimens.

b. long-acting

"*For the type 1 diabetic, the long-acting form of insulin injection is preferred as the basal (base) component of basal-prandial regimens.*"

8. Pre-mixed insulin is considered appropriate for

d. elderly patients diagnosed with type 2 diabetes.

"*Pre-mixed insulin is a combination of two different types of insulin: one that controls blood sugar at meals and another that controls blood sugar between meals. Generally, the insulin mixes are not considered appropriate for type 1 diabetes due to the lack of dose flexibility. In the elderly individuals diagnosed with type 2 diabetes, the insulin mixes are considered due to their ease of use.*"

9. Which of the following forms of insulin has a cloudy appearance?

a. Mixed insulin

"*All rapid-acting insulins are clear and colorless formulations…. Short-acting insulins ... are a clear and colorless insulin product…. Long-acting insulin … appears as a clear and colorless product…. Mixed insulin will appear cloudy.*"

10. True or False: Pre-mixed insulin is a combination of two different types of insulin: one that controls blood sugar at meals and another substance to speed up absorption.

b. False

"*Pre-mixed insulin is a combination of two different types of insulin: one that controls blood sugar at meals and another that controls blood sugar between meals.*"

11. Metformin is a medication that functions by lowering glucose production in the _____ and improving the body's sensitivity to insulin.

c. liver

"*Generally, metformin is the first medication prescribed for type 2 diabetes and functions by lowering glucose production in the liver and improving the body's sensitivity to insulin.*"

12. _____ are medications that help a person's body secrete more insulin.

a. Sulfonylureas

"*Sulfonylureas: These medications help your body secrete more insulin.*"

13. _____ are medications that prevent the kidneys from reabsorbing sugar into the blood.

d. SGLT2 inhibitors

"*SGLT2 inhibitors: These drugs prevent the kidneys from reabsorbing sugar into the blood. Instead, the sugar is excreted in the urine. Examples include canagliflozin (Invokana®), dapagliflozin (Farxiga®) and empagliflozin (Jardiance®).*"

14. _____ requires intermittent capillary blood sampling and the use of a glucose meter.

c. Self-monitoring of blood glucose (SMBG)

"*Self-monitoring of blood glucose requires intermittent capillary blood sampling and the use of a glucose meter.*"

15. There are real-time CGM devices that can measure and transmit glucose values to a patient or family members

a. through mobile phone devices.
b. regarding the patient's hypoglycemia.
c. regarding the patient's hyperglycemia.
d. All of the above *[correct answer]*

"*Most real-time CGM devices measure and transmit glucose values every five minutes to a receiver and can alert (alarm) for hypoglycemia and hyperglycemia. There are CGM systems that transmit glucose data to mobile phones and allow users to "share" their data with family members, friends, and caregivers; others require the use of device-specific receivers.*"

Reference Section

1. National Institute of Diabetes and Digestive and Kidney Diseases (2016). US Department of Health and Humans Services. *NIDDK*. Retrieved from https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes
2. Centers for Disease Control and Prevention (2017). Media Relations. New CDC report: More than 100 Million Americans have Diabetes or Prediabetes. *CDC*. Retrieved from https://www.cdc.gov/media/releases/2017/p0718-diabetes-report.htl
3. Mayo Clinic (2019). Prediabetes Symptoms and Diagnosis. Retrieved from https://www.mayoclinic.org/diseases-conditions/prediabetes/symptoms-causes/syc-20355278
4. Mayo Clinic (2019). Type II Diabetes. Symptoms and Causes. Retrieved from https://www.mayoclinic.org/diseases-conditions/type-2-diabetes/symptoms-causes/syc-20351193
5. Centers for Disease Control and Prevention (2018). Type 1 Diabetes. CDC. Atlanta, GA. Retrieved from https://www.cdc.gov/diabetes/basics/type1.html
6. Shide-Slavin, C. (2003). Case Study: A Patient with Type 1 Diabetes Who Transitions to Insulin Pump Therapy by Working with an Advanced Practice Dietitian. Diabetes Spectrum. Retrieved from http://spectrum.diabetesjournals.org/content/16/1/37
7. Walsh J, Roberts R, and Bailey T. Guidelines for Insulin Dosing in Continuous Subcutaneous Insulin Infusion Using New Formulas from a Retrospective Study of Individuals with Optimal Glucose Levels. US National Library of Medicine. September 2010. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2956816/
8. Pharmacist Letter (2017). Treatment for Type 2 Diabetes. Pharmacist Letter. Retrieved from https://pharmacist.therapeuticresearch.com/Content/Segments/PRL/2015/Jun/Drugs-for-Type-2-Diabetes-8509
9. Wats, S. (2016). Long Acting Insulin-How it works. Healthline. Retrieved from https://www.healthline.com/health/diabetes/long-acting-insulin
10. Mayo Clinic (2019). Type 2 Diabetes Treatment. Retrieved from http://www.mayoclinic.org/disease-condition/type-2-diabetes/diagnosisandtreatment
11. Epocrates (2019). Athena Health Service. Retrieved from www.epocrates.com
12. Shide-Slavin, C. (2003). Case Study: A Patient with Type 1 Diabetes Who Transitions to Insulin Pump Therapy by Working with an Advanced Practice Dietitian. Diabetes Spectrum. Retrieved from http://spectrum.diabetesjournals.org/content/16/1/37

13. Medline Plus (2017). Insulin Injection. US National Library of Medicine. Retrieved from https://medlineplus.gov/druginfo/meds/a682611.html
14. Pharmacist Letter. Diabetes Outcomes. Therapeutic Research Center. Found online at: www.pharmacistletter.com