Case Study: Diabetes Type 1
Case Study # 1

Background Information: Type I Diabetes or Insulin-Dependent Diabetes Mellitus (IDDM). Results from a deficiency of insulin usually due to the person’s immune system (autoimmune disorder) destroying the pancreatic cells (beta cells) that produce insulin. The diagnosis of Type 1 diabetes involves testing the urine and blood. The urine will be tested for the presence of glucose and ketone bodies. Blood will be tested for glucose levels, hemoglobin A1c (HbA1c) and C-Peptide. See class notes for more information on the tests. The following information will provide the basis for the C-Peptide Test: Insulin is synthesized in the beta cells of the pancreas. Insulin is initially synthesized in the form of proinsulin which consists of three chains of peptides, A, B, and C. Further modification by the Golgi apparatus cleaves portions of the molecule to form insulin, composed of the A and B chain connected by disulfied linkages, and the C chain peptide, called connecting peptide (C-peptide). The secretory vesicle then releases insulin and C-Peptide into the blood. The C-peptide test measures the level of this peptide in the blood. It is generally found in amounts equal to insulin because insulin and C-peptide are linked when first made by the pancreas. Insulin helps the body use and control the amount of sugar (glucose) in the blood. Insulin allows glucose to enter body cells where it is used for energy. The level of C-peptide in the blood can show how much insulin is being made by the pancreas. C-peptide does not affect the blood sugar level in the body. A C-peptide test can be done when diabetes has just been found and it is not clear whether type 1 diabetes or type 2 diabetes is present. A person whose pancreas is deficient in insulin production (type 1 diabetes) will have a low level of blood insulin and C-peptide. A person with type 2 diabetes can have a normal or high level of C-peptide.

History: Cindy Mallon, an 8-year-old girl in previously good health, has noticed that, in the past month, she is increasingly thirsty. She gets up several times a night to urinate, and finds herself gulping down large amounts of water. At the dinner table, she seems to be eating twice as much as she used to, yet she has lost 5 pounds in the past month. In the past three days, she has become nauseated, vomiting on three occasions, prompting a visit to her pediatrician.

Lab Work: At the doctor’s office, blood and urine samples are taken showing the following lab results:

- Fasting blood glucose level = 445 mg/dl (normal = 70 - 100 mg/dl)
- Blood pH level = 7.23 (normal = 7.35 - 7.45)
- Hb A1C = 9.5% (normal = 4 – 5.6%)
- C-Peptide Test = 0.4 ng/ml (normal = 1.0 – 4.3 ng/ml)
- Urine tested positive for glucose and for acetone / acetoacetate / beta-hydroxybutyric acid (i.e. ketone bodies) (normally urine is free of glucose and ketone bodies)
A. Based on the above lab results you determine that Cindy has diabetes. What specific type does she have and what test(s) support your conclusion?

The blood tests support the diagnoses that Cindy has Type I or insulin-dependent diabetes mellitus. The low levels of C-peptide narrow the diagnosis to type I and not type II. C-peptide is generally found in amounts equal to insulin because insulin and C-peptide are linked when first made by the pancreas. The level of C-peptide in the blood can show how much insulin is being made by the pancreas. A person with type 2 diabetes can have a normal or high level of C-peptide.

B. Explain why her blood-glucose level is elevated?

Her pancreas is not making a sufficient amount of the hormone insulin. Insulin normally helps lower blood-glucose levels by stimulating the uptake of blood glucose into skeletal muscle, adipose tissue, and other tissues. Thus, a deficiency of insulin will raise the blood glucose level. Furthermore, an insulin deficiency enhances the effects of those counter-regulatory hormones which raise blood glucose levels (e.g. glucagon, epinephrine, and cortisol). Some organs, such as the brain, kidneys, and liver, actually do not require insulin in order to take up glucose from the bloodstream.

C. Why is her blood pH level decreased?

Insulin normally stimulates the uptake of blood lipids into adipose tissue (i.e. it helps the body store away excess energy in the form of fat). The hormone glucagon has the opposite effect in the body - it stimulates fat breakdown ("lipolysis") and the release of lipids from adipose tissue into the bloodstream. In Cindy's condition, glucagon's effects are enhanced while insulin's action is decreased. Since her insulin levels are so low her skeletal muscle and many other tissues cannot utilize glucose as an energy source, they must rely on lipids. Increased glucagon activity and decreased insulin activity cause blood lipid levels to rise. The liver metabolizes these lipids and produces ketone bodies as by-products. The three major ketone bodies produced during this exaggerated fat metabolism are acetone, acetoacetic acid, and beta-hydroxybutyric acid. As levels of the latter two ketone bodies rise in the bloodstream, the pH of the blood falls. This condition is called diabetic ketoacidosis.
D. Cindy’s blood test is found to have a glycosylated hemoglobin level (Hb A1C) of 9.5%. What is the basis for this test? What additional information does this test provide that a one-time direct measurement of blood glucose doesn’t? What is the normal range for glycosylated hemoglobin?

Hemoglobin A1c provides an average of a person’s blood sugar over the past 3 months. It measures what percentage of your hemoglobin is coated with sugar (glycated). As glucose circulates in the blood, some of it spontaneously binds to hemoglobin. The hemoglobin molecules with attached glucose are called glycated hemoglobin. The higher the concentration of glucose in the blood, the more glycated hemoglobin is formed. Once the glucose binds to the hemoglobin, it remains there for the life of the red blood cell – normally about 4 months (120 days). Glycated Hemoglobin is normal at low amounts; however when blood glucose levels are abnormally high as in the case of uncontrolled diabetes mellitus, high amounts of blood glucose combines with hemoglobin. Therefore, the average amount of sugar in your blood can be determined by measuring a hemoglobin A1c level. If your glucose levels have been high over recent weeks, your hemoglobin A1c test will be higher.

Hemoglobin A1c Test Results: For people without diabetes, the normal range for the hemoglobin A1c test is between 4% and 5.6%. Hemoglobin A1c levels between 5.7% and 6.4% indicate increased risk of diabetes, and levels of 6.5% or higher indicate diabetes mellitus.

E. At the office, Cindy is breathing rapidly and taking deep breaths. What physiological purpose does this serve?

Cindy’s breathing pattern, referred to as Kussmaul’s respirations, is a form of hyperventilation. By hyperventilating, Cindy reduces the level of carbon dioxide in the bloodstream. Carbon dioxide (CO2), carbonic acid (H2CO3), and bicarbonate ions (HCO3-) in the bloodstream can be interconverted by the enzyme carbonic anhydrase, which catalyzes the following reversible chemical reaction:

\[ \text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^- \]

As Cindy hyperventilates, carbon dioxide is removed from the bloodstream at a faster rate, lowering the level of CO2 in the bloodstream. Because CO2, H2CO3, and HCO3- are in a state of dynamic chemical equilibrium, lowering the CO2 level will enhance the leftward direction of this reversible chemical equation, causing more HCO3- and H+ to bind together to form H2CO3, which will be converted to CO2 and H2O. This effectively removes more H+ ions from the bloodstream, thus raising the pH of the blood and partially compensating for Cindy’s metabolic acidosis.
F. Cindy has a fruity odor to her breath. Explain why.

The ketone body acetone has a fruity odor. It moves easily from the bloodstream through the respiratory membrane into the alveolar air spaces. Cindy’s blood acetone level is increased, and as acetone passes through the respiratory membrane, her breath attains a fruity odor.

G. Explain why Cindy is urinating so frequently.

Because Cindy’s blood-glucose level is elevated, glucose is filtered out of the blood and into the proximal convoluted tubules of her kidney’s nephrons at a greatly increased rate. The transport mechanism that reabsorbs this glucose from the proximal convoluted tubule back into the bloodstream is being "flooded" with glucose. The active transport pumps are saturated with glucose, and the excess glucose that is not reabsorbed remains in the renal tubules, drawing water from the bloodstream into the renal tubules by osmosis. This condition, known as osmotic diuresis, increases Cindy’s urinary output and can cause her to become dehydrated, triggering her thirst mechanism.

H. How is Cindy’s condition like that of starvation? Address the role of glucagon in your answer.

Both starvation and uncontrolled insulin-dependent diabetes mellitus are conditions in which glucagon activity far outweighs insulin activity. During starvation, increased glucagon activity is entirely appropriate because this hormone raises blood-glucose levels by stimulating glycogen breakdown ("glycogenolysis") and new glucose production ("gluconeogenesis") in the liver. Glucagon also increases blood-lipid levels by stimulating fat breakdown ("lipolysis"). Thus, when no food is ingested for an extended period of time, the body insure that the blood contains energy-rich nutrients that can serve as an important fuel source for organs and tissues. In addition, the low levels of insulin in the bloodstream insure that skeletal muscle and other tissues can take up these nutrients from the bloodstream.

In uncontrolled insulin-dependent diabetes mellitus, enhanced glucagon activity helps raise blood-glucose and blood-lipid levels. However, there are not sufficient levels of insulin to allow skeletal muscle, adipose tissue, and other organs to take up these nutrients from the bloodstream and use them as an energy source. Therefore, those tissues that rely on insulin to stimulate nutrient uptake are essentially "starving."