

From Twiggy to Tubby: The Progression of Insulin Resistance and Type II Diabetes

by

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Part I – Glucose Digestion and Absorption

Timmy and His Fast Metabolism

Timmy had been way too skinny for as long as he could remember; he'd had a growth spurt early in high school but in spite of stopping at 6'2" he was teased unmercifully by his friends and family for being a twig, only weighing 160 lb. Although he didn't realize it at the time, his lean physique contributed to his achievement of the highest vertical leap of all the athletes in his high school district and he was extremely well coordinated. Timmy made the varsity basketball team as a freshman in high school and was a starter all four years, making first-team all-conference his junior and senior year.

In spite of his athletic success, mostly he just heard the name calling and jokes about being so thin, and he packed in as many calories as he possibly could. In fact, all through high school Timmy chose his foods based on the amount of carbohydrates they contained. He had at least four large energy drinks per day, ate a large pizza and a box of donuts for lunch, snacked on one or two family size bags of potato chips, and his nightly routine consisted of chocolate milk and Oreo cookies. While he was the all-star basketball player in high school, his height left him with just a few scholarship offers from smaller schools and junior colleges. However, Timmy's ultimate dream was to become a surgeon so he chose to turn down all the scholarship offers and attend a large university with an excellent pre-med program.

Glucose Digestion

At this point in Timmy's life, he is able to metabolize glucose efficiently. Due to the fact that Timmy is extremely active, the cells in his body use glucose to make energy at a relatively fast rate to keep up with his active lifestyle. Let's take a closer look at what happens to the glucose Timmy consumes while he's still young, active, and healthy.

While carbohydrates are important for energy production in the body, many of us consume far too many carbohydrates just like Timmy. There are two basic types of carbohydrates: simple carbohydrates, or monosaccharides and disaccharides, and complex carbohydrates, or polysaccharides.

The process by which carbohydrates are made available to cells in the body begins with the movement of food from the *mouth* through the *esophagus*, into the *stomach*, and lastly into the *small intestine* where the final steps for chemical digestion and absorption occur. *Digestion* is the chemical or mechanical breakdown of nutrients whereas *absorption* is movement of nutrients in their simplest form into the body, this primarily occurs in the small intestine but some absorption can also occur through oral mucosa.

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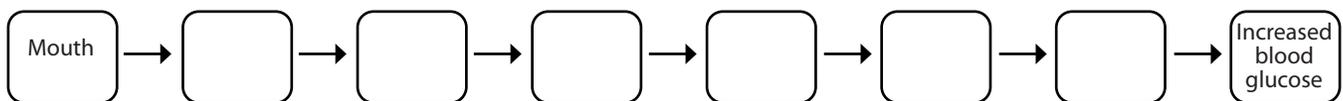
Mechanical breakdown is the physical breakdown of food, which involves grinding food with teeth or the muscular layers of the stomach. *Chemical breakdown* requires enzymes to break bonds, such as the breakdown of polysaccharides into monosaccharides and disaccharides. While most carbohydrates are chemically digested in the small intestine via enzymes secreted by the pancreas and intestinal mucosa, small amounts of chemical digestion also occur within the oral mucosa via salivary amylase. Effective carbohydrate digestion allows simple carbohydrates, such as the monosaccharide glucose, to be absorbed into intestinal epithelial cells called *enterocytes*.

Glucose is found in many, many foods, even those that do not taste sweet. Glucose is a large, polar, water-soluble molecule and therefore cannot passively diffuse across a cell membrane without transport membrane proteins. Once monosaccharides, like glucose, have passed through enterocytes, they will diffuse into the *extracellular fluid (ECF)* and finally into the blood via facilitated diffusion. Lastly, they will travel through the blood to the cells throughout the body, such as skeletal muscle cells to produce energy or energy stores, called *ATP* and *glycogen* respectively.

Activity 1

Fill in the flowchart (Figure 1) indicating where a polysaccharide travels through the GI tract beginning with oral ingestion and ending with monosaccharide and disaccharide absorption into the blood.

Figure 1. Movement of glucose from ingestion into systemic circulation.



Questions

1. Compare and contrast the processes of mechanical and chemical digestion in relation to the breakdown of polysaccharides. Where in the GI tract do each of these processes occur and what is involved in these processes?
2. How would a diet that includes more simple carbohydrates, rather than complex carbohydrates, impact glucose absorption from the GI and into enterocytes?
3. What might happen to glucose levels in the blood if carbohydrates could not be efficiently digested within the GI tract?

Cool Down and Recovery

After Timmy would play a hard game of basketball, he liked to cool down with a large chocolate milkshake. Every time he gulped down his post-workout milkshake he noticed that he soon felt ready for more basketball action, almost as though he had a renewed level of energy. His muscles felt good and he was ready for more. Considering Timmy's burst of energy after his ice cream ritual, we can conclude that he was able to ingest, absorb, and uptake glucose efficiently and utilize this glucose for energy within his skeletal muscle cells that provided him with the ability to run, dribble, and shoot basketball.

Glucose Absorption

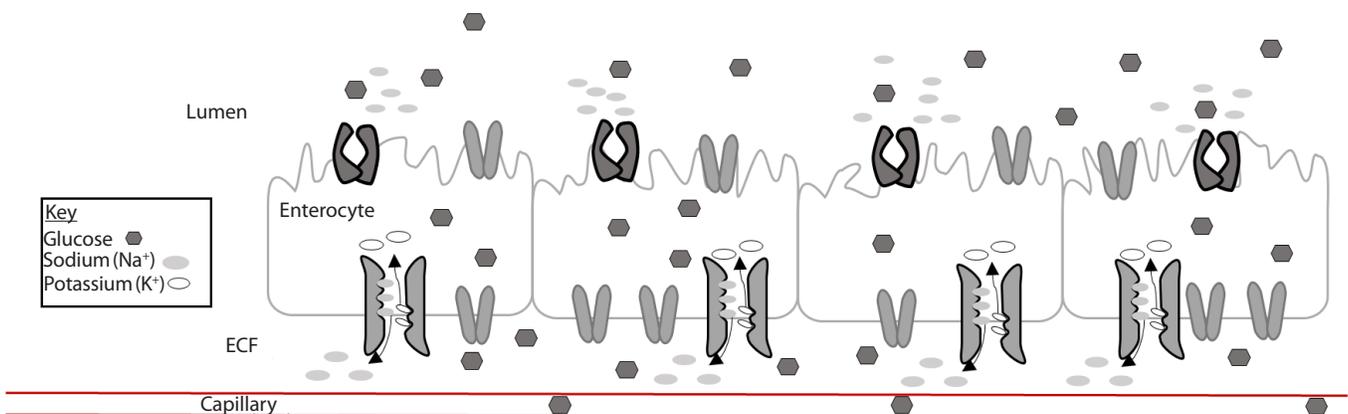
Once carbohydrates are broken down into their monomers, the process of absorption can begin. The *sodium glucose-linked transporter (SGLT-1)* is the primary transporter used for glucose absorption from the lumen of the small intestine into the intestinal epithelial cells called enterocytes. As indicated by its name, the SGLT-1 moves both sodium and glucose at the same time, making it a symporter. Like most symporters, the SGLT-1 relies on the work of Na^+/K^+ pumps to keep intracellular sodium levels low. These pumps are located along the basolateral membrane of enterocytes and use ATP to continuously pump sodium out of the cell while pumping K^+ into the cell. Once glucose enters the enterocyte via the SGLT-1 it will diffuse into the extracellular fluid (ECF) through a uniporter transport protein called *GLUT2* located on the basolateral membrane. GLUT2 also permits facilitated diffusion, as glucose moves from a high concentration to a low concentration.

When luminal glucose levels are very high, for example, after finishing a meal, GLUT2 can also assist the SGLT-1 transporters on the apical side of the enterocytes. The *translocation*, or movement between cellular compartments, of some GLUT2 transporters from the *basolateral* membrane to the *apical* membrane of the enterocyte helps increase glucose absorption. When glucose levels within the enterocyte are low, glucose will still diffuse into the cell because the Na^+/K^+ ATPase pumps continually pump sodium out of the enterocyte to drive sodium into the cell, and thus pull glucose and sodium through the SGLT-1.

Activity 2

In the figure below, use arrows to label the *Na^+/K^+ pumps*, *SGLT-1 transporters*, and *GLUT2 transporters*. Then, indicate the *direction* in which glucose and sodium are moving through the SGLT-1 and GLUT2 transporters using arrows.

Figure 2. Glucose absorption in the jejunum of the small intestine.



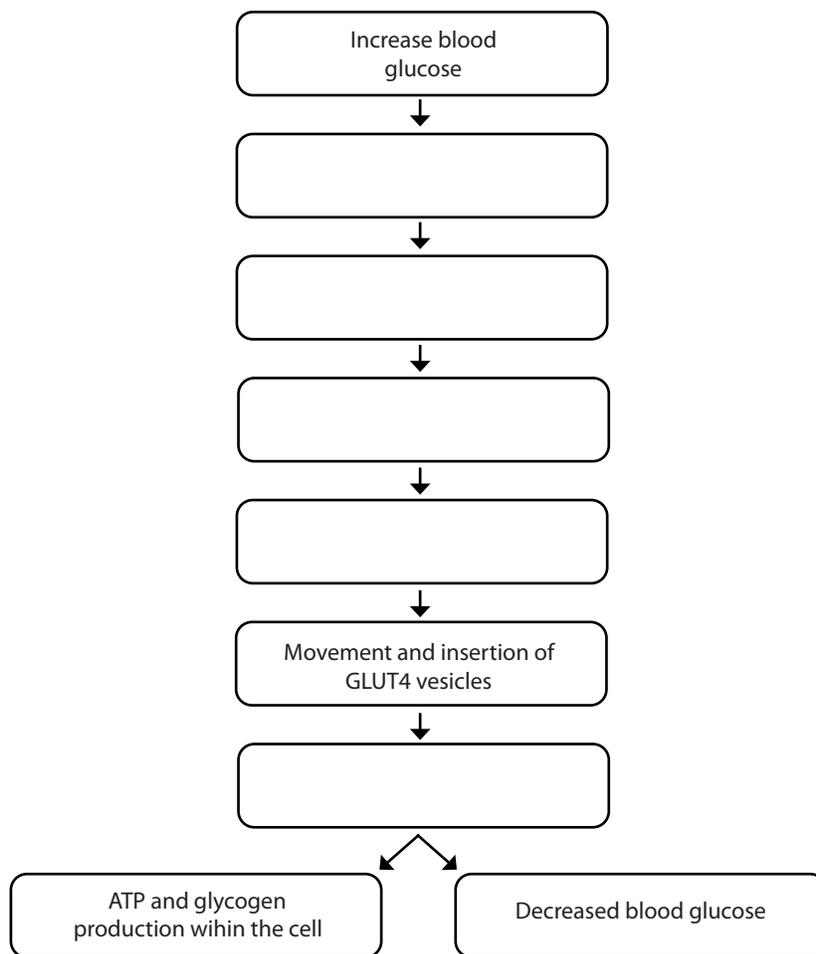
Recall that after Timmy absorbs the glucose from his chocolate milkshake, he gets a burst of energy and is ready to play another round of basketball. As long as Timmy is able to absorb glucose from his diet efficiently it will enter his blood stream and will travel to his body's cells, including *pancreatic beta cells*. When pancreatic beta cells receive glucose from the blood they respond by releasing *insulin*. This hormone travels in the blood and signals any cell possessing an *insulin receptor* to take up glucose from the blood. Insulin is required for glucose uptake in some cells; these are referred to as *insulin dependent* cells and include resting skeletal muscle cells and adipocytes, or fat cells. *Insulin independent* tissues can absorb glucose without insulin; these include exercising skeletal muscle cells, neurons and glial cells, and hepatocytes, or liver cells. We will use a *skeletal muscle cell* as our model for understanding how this process occurs.

In skeletal muscle cells, insulin receptors are located on the sarcolemma and t-tubules. Once insulin binds to its receptor, a *second messenger pathway* is activated which involves intracellular signaling that results in the translocation of *GLUT4* to the *sarcolemma* or *t-tubules*. GLUT4 is a transport protein that is stored and moves within the cell via *storage vesicles*. The storage vesicle will *fuse* to the sarcolemma or t-tubule to provide GLUT4 transporters and will allow a way for glucose to enter the skeletal muscle cell. The expression of GLUT4 within the sarcolemma or t-tubule is triggered by both insulin and muscle contraction. Thus, skeletal muscle cells can be considered as both insulin dependent and insulin independent. Regardless of what activates GLUT4 translocation to the sarcolemma and t-tubules, glucose will enter the skeletal muscle cell and be used for ATP or glycogen production.

Activity 3

Fill in the flow chart below indicating what will happen to resting skeletal muscle cells when insulin is released from the pancreatic beta cells.

Figure 3. Insulin release and glucose uptake.



Questions

4. The flow chart you have just filled out (Figure 3) represents a resting skeletal muscle cell. Will the rate of glucose uptake change in an exercising skeletal muscle cell? If so, how?

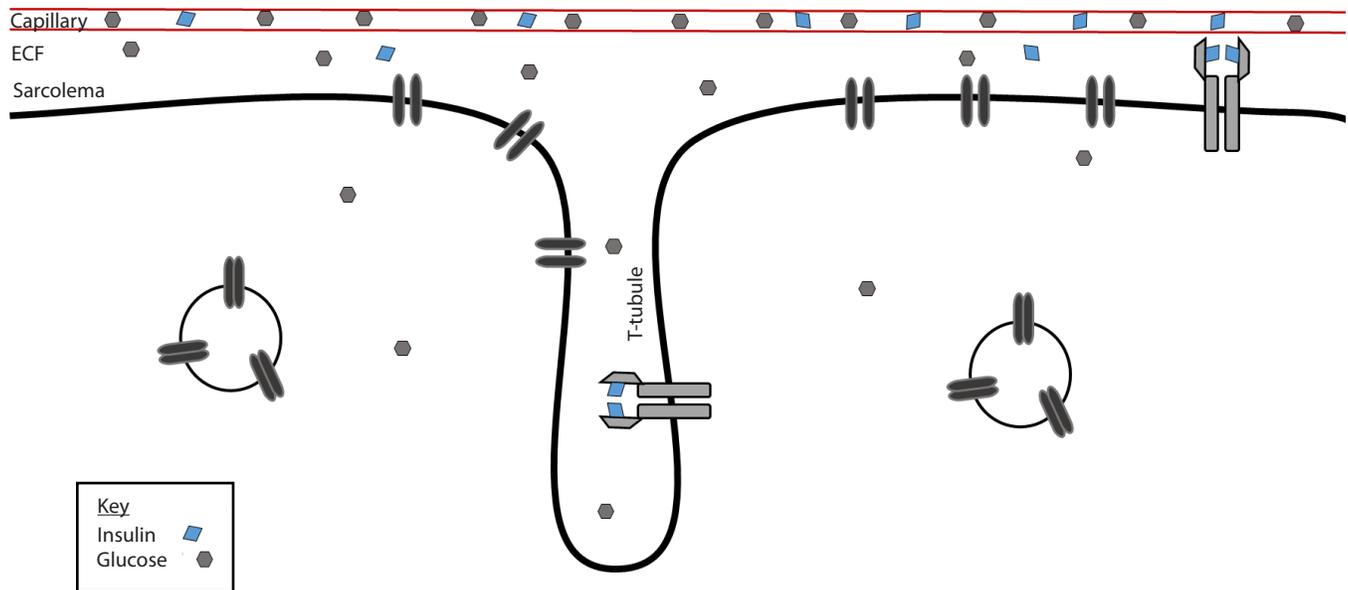
5. If insulin cannot properly interact with its receptor, how might this affect glucose uptake into the resting skeletal muscle?

6. Suppose glucose in the blood cannot be detected by pancreatic beta cells. Refer to your flowchart above and explain how this will affect glucose levels in the blood. Will this influence energy production among insulin dependent cells?

Activity 4

In Figure 4 below, use arrows to label the following: insulin in the extracellular fluid (ECF), glucose in the ECF, insulin receptor, GLUT4 storage vesicle, GLUT4, and GLUT4 fusion into the sarcolemma and t-tubule. Then indicate the direction in which glucose is moving through the GLUT4 transporter.

Figure 4. Glucose uptake into skeletal muscle cell.



Part II – Insulin Resistance

Testing Timmy

“Mom! You’re washing my jeans in hot water and they’re getting too tight!” said Timmy as he was preparing to return to college after spring break. In spite of being several pounds overweight herself, Timmy’s mom replied, “Nope, the water heater is broken. Timmy, I’m afraid you’ve gained some weight. It looks like we’ll be doing some clothes shopping before you go back to school!”

When Timmy began college he soon realized it would be the best time of his life. And while he lost all interest in playing sports, he thoroughly enjoyed attending all of the university sporting events. His favorite activity was tailgating at college football games. Over lunch with his best friend Ashlyn at the college dining center, Timmy sat down with his usual pizza, potato chips, Coke, and his favorite self-serve ice cream.

Ashlyn took a deep sigh and said, “Timmy, do you ever eat anything green? You know, food with nutrient value...”

Timmy replied, “HA! I hate anything green, all healthy food tastes horrible.”

Ashlyn looked at him disturbed. “Timmy, I’m only concerned about your eating habits because you’ve gained quite a bit of weight since we met the first week of school in the dorms.” Timmy looked at his plate and sighed; he suddenly started to feel anxious.

The following summer, Timmy had a yearly check-up appointment at his family doctor. Dr. Wilson noticed that Timmy’s weight had increased to 203 lb and immediately began to question Timmy’s weight gain and lifestyle. After evaluating Timmy’s dietary lifestyle, she decided that he would need to return the next day at 8:00AM to complete a number of blood tests. Timmy’s eyes widened and his mouth dropped when Dr. Wilson informed him that he had to fast before the test and could neither eat nor drink anything but water after midnight.

The first test performed on Timmy was an A1C, which measures average blood glucose for the past two to three months. The second test was a fasting plasma glucose (FPG) test that includes drawing a sample of blood after fasting for at least eight hours. Blood is drawn again every 30-60 minutes for up to three hours, this test is often repeated on a different day.

Once Dr. Wilson reviewed Timmy’s lab results, she empathetically approached Timmy with serious concerns about his health.

Table 1 below includes cut-off ranges and diagnoses for average blood glucose percentages (A1C) and fasting plasma glucose (FPG). The A1C test is based on the attachment of glucose to hemoglobin proteins located on red blood cells (RBC). Considering the average lifespan of a RBC is about three months, this test indicates an average of blood glucose levels over time. FPG tests requires a patient to be fasted for at least eight hours which will indicate the amount of glucose in the blood without food consumption. These tests are both helpful in diagnosing diabetes because if glucose levels in the blood are elevated on average over the course of three months and/or after an eight hour fast, we can conclude that glucose is not being taken up effectively by the cells in the body, such as skeletal muscle cells.

Table 1. Blood glucose tests.

<i>Test</i>	<i>Normal/Average</i>	<i>Prediabetes</i>	<i>Diabetes</i>
<i>A1C (%)</i>	Less than 5.7%	5.7-6.4%	6.5% or greater
<i>FPG (mg/dL)</i>	100 mg/dL	100-125 mg/dL	126 mg/dL or greater

Question

7. Predict Timmy's A1C and FPG values as an inactive college student. Explain your reasoning for these values and how you believe Timmy has been placed in this category.

A1C:

FPG:

In healthy people, such as high school Timmy, blood glucose is a tightly regulated physiological variable requiring constant communication, interaction, and feedback between many body systems. If any of these components are disrupted or fail, blood glucose levels will become difficult to control and wide fluctuations begin to occur.

As we have seen with Timmy, the inability to regulate blood glucose has led to chronically elevated blood glucose levels, a condition known as hyperglycemia. If allowed to persist, hyperglycemia can lead to elevated levels of insulin in the blood, a condition known as hyperinsulinemia. However, despite the fact that additional insulin is continuously being released, the body's cells become less and less able to respond. This decreased responsiveness to insulin is termed insulin resistance (IR). IR further contributes to hyperglycemia as the signal for blood glucose uptake by insulin-dependent cells becomes less effective perhaps due to changes in the conformation of the insulin receptor or changes in the second messenger pathway leading to a decrease in expression of GLUT4 transporters within cell membranes. Regardless of the cause, the result is often the same: insulin regulated glucose uptake into cells drastically declines while blood glucose levels increase. If this problem persists, the beta cells in the pancreas that produce insulin begin to fail, resulting in hypoinsulinemia although hyperglycemia remains. At this point, insulin resistance is diagnosed as prediabetes or diabetes, depending on the severity of the hyperglycemia.

Let's take a moment to recap the sequence of events that occurs over time with insulin resistance, prediabetes, and type II diabetes: chronically elevated blood glucose levels leading to hyperglycemia, increased insulin release from beta cells of the pancreas, hyperinsulinemia, downregulation or changes to insulin receptors present within cell membranes, decreased glucose diffusion into cells, continued hyperglycemia, exhaustion of beta cells.

Part III – Type II Diabetes

Twenty-Five Years Later

Timmy graduated college, got married, and had two kids. Although he originally was interested in becoming a surgeon, he switched his major to teaching high school science. He now taught biology and coached basketball at the high school in his home town. His lifestyle had not changed much since college; he still refused to eat his greens, and consumed large amounts of soda pop and potato chips. Timmy was required to have blood tests every one to two years since being diagnosed with prediabetes back in college.

"Hello Timmy! According to your chart, it appears that you've gained some weight since your last visit with us," Dr. Wilson stated as she walked into the patient room where Timmy had plopped down on the examination table.

"Yeah, I'm *still* struggling with this whole dieting thing Dr. Wilson," Timmy said with his head down in embarrassment. "I just love the food I eat so much, it's like I'm addicted to it!"

Dr. Wilson contemplated the situation and asked how often he exercised. Timmy replied, "Dr. Wilson, I couldn't tell you the last time I participated in any exercise. I don't even enjoy playing basketball anymore! I'm dog-tired every day and don't have the energy to keep up with my two kids."

Dr. Wilson replied, “It appears you have also been experiencing aches all over your body and loss of sensation in your feet?”

“Yes doctor; I didn’t even feel the giant splinter I got in my foot last weekend and my entire body just seems to ache every day.”

Dr. Wilson looked down at Timmy’s blood results from earlier that morning and took a deep breath. “Timmy, it’s time to make some serious lifestyle changes. According to your results this morning, you have officially developed type II diabetes. Previously we diagnosed you with prediabetes as your body became resistant to insulin; that means your body was not able to utilize glucose efficiently. At that point your body was still able to make sufficient amounts of insulin, which is a hormone that permits glucose to enter into your body’s cells to make energy. But now your body is not making enough insulin to support your energy needs. Now, all we can do is consider disease management options. You *must* start paying close attention to your diet, stay away from fast foods and processed carbohydrates. Also, you absolutely *need* to exercise for at least 30 minutes every day. Ask your wife or kids to hold you accountable for these things. We should also consider the use of metformin, a diabetic medication that will assist in lowering your blood glucose levels, or insulin injections. Also, we have a diabetes educator here at the clinic I encourage you to make an appointment with.”

While Timmy’s case involves the development of type II diabetes through poor diet and lack of exercise, lifestyle choices are one of many causes linked to this multifaceted disease. Type II diabetes can also result from a genetic predisposition, fat distribution throughout the body, age, sex, hormones, infection, and/or race/ethnicity. Insulin resistance and type II diabetes is still not entirely understood and is an active area of research and investigation.

Questions

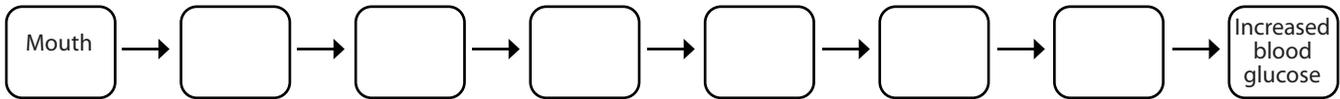
8. During the early stages of IR, Timmy did not need insulin injections, however Dr. Wilson explains that at this point in Timmy’s diagnosis, insulin injections may be necessary for his health. Why do you think Timmy did not need insulin injections when he was insulin resistant, but now that he has type II diabetes he does?
9. Explain how the ingestion of fast food, such as French fries, can cause a more dramatic change in the blood glucose concentrations in a type II diabetic as compared to a normal individual. Be sure to include any transporters necessary for glucose uptake in enterocytes and absorption into resting skeletal muscle cells, or lack thereof.
10. If you were working in a lab that studied IR and type II diabetes and needed to develop a drug to help treat type II diabetes, what would you want your drug to do and where would it be useful for it to interact? Explain why a drug with this mechanism of action would be helpful.

In this last section, we'll begin to pull together many of the concepts investigated in this case study and gain a more in-depth understanding of the complex web that exists between lifestyle choices and the development of IR.

Activity 5

Copy your previous flow charts (Figures 1 and 3) into the combined graphic on this page (Figure 5). When shown together, these flow charts illustrate the sequence of events that should occur after the consumption of carbohydrates and ending with the use of glucose by a cell. However, in a person who is suffering from IR and on their way to becoming diabetic, these sequences break down and in doing so begin to reveal the complex web of events that exist between the digestive system and the cells which rely on insulin for glucose uptake. Keep in mind that the sequences you have created so far represent the ideal. Now, let's see how IR and diabetes impact these by working through the following.

Figure 5. Linking diet, exercise, and insulin resistance together: impacts on a skeletal muscle cell.



- During the end stages of IR and the beginning of diabetes, pancreatic beta cells no longer produce adequate amounts of insulin due to exhaustion. Put an *X* over the one box in your flow chart that best represents this specific disruption and note how many subsequent steps are negatively impacted.
- Draw a line between the box you just put an *X* over to the box describing the resulting effects on blood glucose levels.
- Suppose Timmy continued to eat simple carbohydrates despite his diagnosis of IR or even diabetes. Draw lines indicating areas along the digestive tract where glucose, as a simple carbohydrate, can be absorbed from his food to the box describing the effects on blood glucose levels.
- While changes are occurring within the blood, changes are also occurring within resting skeletal muscle cells that leaves them without adequate fuel for contracting. Shade in the box that identifies these fuel sources to indicate a diminishing supply.
- If these fuel sources within skeletal muscle cells cannot be created, what impact would this have on blood glucose levels? Draw a line from the box you were just directed to shade in above to the resulting impact on blood glucose levels.
- Suppose you were asked to design a drug to help reduce blood glucose levels in a person with insulin resistance after they had eaten simple carbohydrates. Using asterisks, mark the boxes within your flowcharts that would be good targets for this blood glucose-reducing drug. Keep in mind there are several ways to reduce blood glucose levels.

