

Diabetes Mellitus

WHAT IS A NORMAL BLOOD SUGAR?

Normal blood sugars typically run between 60 and 100 in the fasting state and may go as high as 140 to 180 after meals. The blood sugar goals that people with diabetes should try to achieve are 70 to 110 fasting and less than 120 before meals.

IS HOME BLOOD GLUCOSE MONITORING NECESSARY?

Absolutely! Would you drive a car if you couldn't see? How well could doctors adjust blood pressure medications if we didn't have blood pressure cuffs? How can we optimally adjust diabetic medications if we don't know what the blood sugars are doing from day to day? Virtually all diabetics in good control use a method of home blood glucose monitoring. Test strips typically are read directly using a small machine called a reflectance meter to arrive at a specific number that will be displayed on the screen. There are around 25 meters available in the U.S. marketplace. The ones with the longest track records are the Accu-Cheks, Freestyles, Glucometers, and One-Touch instruments. These all take blood samples from the fingertips. The newest innovation in meters is the Freestyle Libre continuous glucose monitor. The sensor pad is applied to the back of your upper arm once every 2 weeks, and blood sugar readings are taken every 5 minutes. The sensor is "read" each time you move the reader within 6" of the sensor. There are 2 other continuous glucose monitors, the Dexcom and the Minimed. The Dexcom unit reads out on a handheld meter, and the Minimed monitor reads out on the Minimed Insulin pump. To maintain optimal blood sugar control most studies have shown that blood testing needs to be done a minimum of 2 times a day. In some special situations, diabetics are monitoring their blood sugar levels up to 7 times a day--before and after each meal and at bedtime--in order to try to obtain the best possible diabetic control. These machines cost about \$100, and usually are covered by insurance policies. Many manufacturers will have discount programs for the meters or even give the meters away free. The reason is that selling the strips for testing is how the companies make their profits. The strips are expensive, running 25 to 50 cents each. Medicare and insurance companies typically will cover the costs of strips if they are obtained by prescription. For people who REGULARLY test 2 or more times per day, it is likely to be more cost-effective to use one of the continuous glucose monitors.

IS CAREFUL CONTROL OF DIABETES IMPORTANT?

For many years controversy existed as to whether or not careful control of the hyperglycemia of diabetes would result in better long-term outcomes of the disease--that is, fewer or less severe long-term complications. In the 1990s definitive studies were done showing that frequent blood sugar monitoring, exercise programs, dietary changes and proper medication

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adjustment can satisfactorily control everyone with diabetes. Furthermore, these studies showed that controlling the hyperglycemia of diabetes would reduce or eliminate the development, severity, and rate of progression of long-term diabetic complications such as eye disease, nerve involvement and kidney disease. Studies have shown that it is the hyperglycemia per se that is directly responsible for much of the damage done to various body tissues. Only by controlling that hyperglycemia can we hope to reduce these complications that have been devastating to so many people with diabetes in the past.

WHAT KIND OF A DIET SHOULD A DIABETIC FOLLOW?

Diabetic diet recommendations have been a controversial area for years. There are 4 important points to remember: **1)** Everyone agrees that diabetics should eat a well-balanced diet with adequate amounts of proteins, fats and carbohydrates. **2)** A diabetic diet should include at least 3 meals AND a bedtime snack daily. **3)** Those meals should be consistent from one day to the next, in terms of when the meals are eaten, the number of calories eaten at each meal, and the amount of carbohydrate eaten at each meal. **4)** Diabetics should avoid simple sugars, candies, etc. between meals as these foods cause rapid swings in blood sugar levels (causing poor control).

We really don't know if a high carbohydrate, low fat diet or a low carbohydrate, high fat diet is to be recommended or whether it even makes any difference (although the kind of fat in the diet does seem to make a difference). Studies suggest that regular table sugar may not be harmful to diabetic control as long as it is eaten in the context of a balanced meal (one that contains fat and protein so that it is absorbed through the stomach and intestine more slowly in order to delay any rapid swings in the blood sugar level.) Again, obviously, the key here is moderation and a balanced diet. A prudent diet is one that is low in cholesterol and large quantities of saturated fats. There is GOOD evidence that all "trans-fats" are harmful. Excessive intake of these foods predisposes to atherosclerosis (hardening of the arteries). All diabetic patients should have a good general understanding of diets--what proportions of nutrients (proteins, fats, carbohydrates) various foods contain, how to use exchange diets, how to select proper foods when eating out, what foods to avoid, etc. A reasonable diet for diabetics contains about 12% to 16% protein, 45% to 55% carbohydrate, and 30% to 40% fat. These percentages are somewhat flexible. Probably the carbohydrate should be in a complex form such as starch or that found in less than fully cooked vegetables. The use of vitamins is optional. Generally, anyone in the United States eating a balanced diet and consuming 1000 calories or more a day will get enough vitamins and minerals in the foods that they eat

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that a supplement is not necessary. A good diet is a way to achieve Ideal Body Weight and minimize rapid or wide swings in the blood sugar levels. When exercise and a reasonable diet alone cannot control blood sugar, then medication is needed.

If you are overweight, you should work on losing weight down towards Ideal Body Weight. You can look up "Ideal Body Weight tables" on the internet. Even a 15 or 20 pound weight loss can make a marked difference for many people. Diet pills do not have proven long term safety. The effective ones are related to amphetamines, which are stimulants with strong addiction potential. They tend to increase blood pressure and increase the workload of the heart. Several drugs had to be taken off the market in the late 1990s because of very serious potential long-term complications. When diet pills are used to help people lose weight, they must be taken indefinitely. There is no safety data that indicates they are safe to use for such long periods. But we know when people stop such medications, they gain the weight they've lost right back. We do not recommend fad diets. Diets such as all protein diets, liquid diets, or all fruit diets, are not balanced in terms of nutrients, may not have adequate vitamins so that a supplement will be necessary, and are not sustainable over the long term. Once a person loses some weight on one of these diets, what happens when they go back to their normal diet? What has changed so that the weight will stay off? Studies have shown that seesawing body weight by losing weight and then gaining it back is *more* unhealthy for people that not losing weight at all! Only by changing your normal everyday diet "**FOR LIFE**" will you be able to change your body weight on the long term. That's what a prudent diabetic diet is meant to accomplish.

INSULIN PREPARATIONS

Insulin was first extracted from animal pancreases in 1921 by a team of physicians at the University of Toronto. Its use was immediately recognized as a life-saving treatment for Type 1 diabetes. The University patented this preparation but because of its life-saving effect in diabetes in 1923 gave the patent freely to drug companies to manufacture it worldwide along with the subsequent right to patent any improvements. That is exactly what the pharmaceutical industry did. Insulin became widely available for treatment of Type 1 diabetes. Over time it was made purer. A longer acting insulin (protamine) was introduced in 1946 followed by other longer acting insulins and then insulin combinations. Synthetic insulin made by recombinant DNA technology appeared in the market in 1982. Insulin analogues (insulin molecules that were genetically altered) first appeared in the market in 1996. Pharmaceutical companies continue to make changes to the insulin molecule that improves efficacy, absorption characteristics, duration of

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action, and side effect profiles of these products on a regular basis. As the pharma industry develops these improvements, they create new patents regularly. This practice of stringing one patent after another on the same product is called “evergreening” in the pharmaceutical industry.

Manufacturers who made the older, generic versions of insulin eventually stopped producing them after the turn of the millennium, presumably because of lower profits. All this has led to the situation in which we have NO generic insulins in the market, only BRAND NAMES, and higher prices (\$100 to \$500/month). In the US, historically import restrictions made it difficult to obtain insulins from other countries. However, recently US customs import restrictions on foreign made drugs have been relaxed somewhat and many foreign made medicines can now be sourced on the internet. In 2019, the US market has 7 categories of insulins: 1) Rapid-acting (analog insulins that work faster than traditional regular insulin), 2) Short-acting (what previously was known as regular human insulin), 3) intermediate-acting (NPH insulin), 4) basal analogue, 5) long-acting basal analogue, 6) Premixed (70/30, 75/25, 50/50), and 7) inhaled.

In general, the rapid, sort-acting, and basal insulins are available as clear solutions, and the protamine insulins and mixtures are cloudy suspensions that need to be mixed before injection. The table on the following page lists current insulins.

NPH insulin was originally formulated so that a shot in the morning would last all day (through lunch) and a shot in the evening would last until the next morning. Lantus insulin (insulin glargine, approved by the FDA in 2000) and Levemir are newer synthetic insulin preparations that were specially formulated to be absorbed more slowly and uniformly throughout the 24 hour day. Unlike NPH insulin, they have no peak effect after injection (this means fewer low sugar reactions) and **DO** last close to 24 hours for about 85% of people who take them, so that one shot a day is all that is necessary. For a few individuals, though, 2 shots of basal insulin daily seems to give a more uniform insulin delivery curve. Insulin Toujeo and Tresiba are ultra-long acting basal insulins and are given once daily.

Rapid-acting	Onset of Action	Peak	Duration of Action
Insulin aspart	10-20 min	1.5-2.5 hr	3-6 hr
Insulin lispro	10-20 min	1.5-2.5 hr	3-6 hr
Insulin glulisine	20 min	1.5-2.5 hr	3-6 hr

Short-acting

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Humulin R	30-60 min	2-4 hr	6-10 hr
Novolin R	30-60 min	2-4 hr	6-10 hr
ReliOn R	30-60 min	2-4 hr	6-10 hr

Intermediate

Humulin N	1-3 hr	4-9 hr	14-20 hr
Novolin N	1-3 hr	4-9 hr	14-20 hr
ReliOn N	1-3 hr	4-9 hr	14-20 hr

Basal analogue

Insulin Lantus	1-2 hr	6 hr, minimal	18-26 hr
Insulin Basaglar	1-2 hr	6 hr, minimal	18-26 hr
Insulin Levemir	1-2 hr	8 hr, minimal	18-26 hr

Long-acting basal

Insulin Toujeo	6 hr	Minimal	24-36 hr
Insulin Tresiba	1-4 hr	Minimal	42 hr

Premixed

75/25 lispro protamine/lispro	30-60 min	2-12 hr	15 hr
50/50 lispro protamine/lispro	30-60 min	2-12 hr	15 hr
75/25 lispro protamine/aspart	30-60 min	2-12 hr	15 hr
70/30 NPH/regular (Humulin, Novolin, ReliOn)	30-60 min	2-12 hr	15 hr
70/30 degludec/aspart	30-60 min	2-12 hr	15 hr

Inhaled

Afrezza	<15 min	50 min	2-3 hrs
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SHOULD I CONSIDER GETTING AN INSULIN PUMP?

Insulin pumps are simply mechanical devices that allow for continuous subcutaneous injection of regular or lispro insulin 24 hour per day. They are an alternative to multiple daily injections of insulin and may help to better control diabetes. They are not a substitute for careful blood sugar monitoring and may not be any better than 3 or 4 shots of insulin a day for many people. But in certain cases they clearly can improve blood glucose control. Insulin pumps are expensive, selling for between \$2000 and \$3000 and require careful attention and upkeep. Infusion sets (needles and tubing) have to be changed every 2-3 days, and the pump disconnected when showering, bathing or swimming. The first generation glucose sensing insulin pumps came to the market in 2007. They still require the user to do daily finger stick blood sugars to calibrate the equipment. They also require more user time to monitor their function. Currently, insurance companies often WILL cover the costs of insulin pumps and their supplies.

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WHAT IS A GLYCOSYLATED HEMOGLOBIN (GLYCOHEMOGLOBIN)?

This is a test to assess diabetic control over the 2 to 3 months immediately prior to the date of the blood draw. A glycosylated hemoglobin level measures the per cent (%) of hemoglobin molecules in the blood that have sugar molecules attached. Hemoglobin is the red pigment in red blood cells that helps to transport oxygen. The level of hemoglobin in the blood is constant, but new red blood cells are being continually created and old red blood cells are being continually destroyed. On average, the half-life of any hemoglobin molecule in the bloodstream is about 60 days. Sugar molecules in the blood can attach to hemoglobin molecules in such a way that they can't detach themselves, and this is called glycosylated hemoglobin. All of us have a few percent of the hemoglobin molecules in our blood with sugar molecules attached. This normal range for glycosylated hemoglobin varies from lab to lab but in general is about 4% to 6%. Diabetics, however, who have on average higher than normal blood sugar levels over the last 2 to 3 months (the life span of hemoglobin in the bloodstream) will have more sugar molecules attached to the hemoglobin molecules and therefore have higher glycosylated hemoglobin levels (anywhere from 6% up to about 14%). Diabetics in good control, on the other hand, will have more normal glycosylated hemoglobin levels. The American Diabetes Association has stated that the goal for glycohemoglobins for diabetics in good control should be 7% or less. Excellent control is about 6.5% or less. This is now the currently recommended goal from the American College of Endocrinology.

SHOULD I REGULATE MY OWN INSULIN DOSAGES?

Ideally, all patients taking insulin should be able to understand how to adjust their own insulin doses and how to routinely make small adjustments in their insulin regimens to control minor variations in their day-to-day blood sugar levels. Insulin needs change frequently enough that this is the only way we can hope to maintain really good control of a person's diabetes. To be able to do this, you need to know how your own body responds to insulin, meals and activity. This is why home blood sugar monitoring is done. Everyone is a little different, but typically regular insulin preparations have their maximum blood sugar lowering effect in about 3 to 6 hours and their effects last 6 to 10 hours. NPH insulin (and Lente insulin) typically have their maximum effects in about 8 to 12 hours and their effects last 18 to 28 hours. Lantus insulin doesn't even begin to appear in the blood stream until 4 hours after injection, has no peak of activity, and lasts about 24 hours. On average, we want to maintain our patients' blood sugar levels essentially

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normal (between 60 and 140 mg/dl). Blood sugar levels 1 hour after a meal should on average be less than 160 mg/dl. Knowing this information, you can begin to see some of the reasons for changing insulin doses. ***It takes several days to equilibrate to a new insulin dose so changes to an insulin regimen should not be made more often than every 3 days*** unless reactions are occurring or the blood sugar is very high (over 300-400). Insulin dose changes in general should be made slowly, only 2-4 units change at a time. I am not suggesting that you start to make changes in your own insulin dose or doses at this time, but as you learn more about this by talking with physicians or reading about diabetes, you may feel more comfortable helping us to determine what dose of insulin your body needs. When we both agree that you're becoming competent in making these assessments, then you will be able to start making some small changes on your own.

CAN MY DIABETES BE CONTROLLED BY ORAL AGENTS?

Diet and exercise can have a tremendous impact on controlling diabetes. A modest weight reduction not only decreases the amount of tissue that the pancreas has to produce insulin for, but also increases the efficacy of the insulin that is produced. Exercise can dramatically increase the efficacy of insulin action. Vigorous exercise can increase glucose utilization for a given concentration of insulin by 10 or 15 times! It will have dramatic impacts on blood sugar levels. Some determined people can and do change their lifestyles, lose weight and exercise every day and totally control their diabetes without having to use medications. Most people have a difficult time putting that much will power and energy into a new lifestyle: they need some help from medications.

Type 2 diabetes (what used to be known as Adult-Onset diabetes or Insulin Independent diabetes) is characterized by 3 primary defects: 1) The body is resistant to the action of insulin. Muscle and fat tissues simply require more insulin, sometimes much more insulin, to do the same job of getting sugar into the cells where it's used for fuel. 2) At the same time the liver is not responding to the presence of insulin and is producing excessive amounts of sugar. This is particularly a problem at night. 3) As time goes by, the pancreas seems to "get exhausted" and gradually loses its ability to produce large quantities of insulin. As insulin production declines, blood sugars rise further.

Fortunately, we now have medications that target each of the 3 primary defects seen in Type 2 diabetes. Early in the course of diabetes, just taking one or two of these medications may be adequate to control blood sugar levels. But a large number of people, perhaps the majority, will require medications that target all 3 defects to effectively lower blood sugars into a

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good range. Metformin (Glucophage) is a drug that suppresses liver output of sugar. It's usually associated with some weight loss and for that reason is often chosen as the first medication to use in overweight people. Its most common side effect is stomach upset and diarrhea, which can be minimized by starting with a small dose and every 2 weeks increasing the dose of the medication slowly up to a good therapeutic dose. Metformin cannot be used in people with significant liver or kidney disease, and should be stopped for 24 hours prior to IV contrast studies or surgery. Thiazolidinediones like pioglitazone (Actos) directly act on tissues to increase their sensitivity to the action of insulin. Thiazolidinediones also have positive effects on blood fats, blood pressure, the risk of blood clotting, and hardening of the arteries. For these reasons, many people with diabetes should be on them. They act very slowly, typically taking weeks to build up significant effects. And they can cause some fluid retention and weight gain. But because they are so effective, most of the time they should not be stopped for these relatively minor side effects. Sulfonylurea drugs (glyburide, glipizide, glimepiride) stimulate insulin production from the pancreas. These drugs are the oral agents most often associated with some weight gain and the risk of low blood sugar (hypoglycemic) reactions. When used in combination, 3 drug regimens for treating Type 2 diabetes are extremely potent.

There are other classes of diabetic drugs that can also be used. These include alpha-1 glucosidase inhibitors, glucagon-like peptide molecules and dipeptidyl peptidase IV inhibitors. The chemistry behind their mechanisms of action is somewhat complicated, and will not be discussed here. The drug names you might recognize are Precose (acarbose), Glyset (miglitol), Byetta (exenatide), Januvia (sitagliptin) and Galvus (vidagliptin). These drugs are generally less potent than the drugs targeting the 3 primary defects seen in Type 2 DM, and because they are newer on the market tend to be more expensive. Byetta (a GLP-1 analogue) initially drew more attention with its release on the market because in about 1/3 of patients it was associated with a significant weight loss. In a few individuals the weight loss could be substantial, on the order of 20-40 pounds. Now a number of newer drugs in that category have come to market, including liraglutide (Victoza), dulaglutide (Trulicity) and semaglutide (Ozempic). Another drug related to these agents tirzepatide (Mounjaro) has just come to market. These drugs work well like the sulfonylureas to stimulate insulin release from the pancreas, and slow glucose absorption. But more importantly, they work on the hypothalamus to reduce appetite and have been found to be VERY effective in helping to lose weight. They will become major players with other drugs to control diabetes in the future. The most recent class of new agents for diabetes treatment are SGLUT-2 inhibitors (sodium-glucose cotransporter 2 inhibitors) which induce excess blood glucose loss through the kidneys (Invokana, Farxiga, Jardiance). Careful studies show that they

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lower blood sugar levels, help protect the kidneys from damage due to diabetes, lower the risk of heart failure and increase life span for people with diabetes and heart disease. Currently they are underutilized (in part because they are all brand name and expensive to purchase) but will become much more commonly used in the future.

WHY DO I NEED TO SEE THE DOCTOR SO OFTEN?

We usually recommend to our diabetic patients that they come in to the office every 3 months for follow up. This is an American Diabetes Association recommendation. Diabetes is a chronic disease that needs to be monitored over time. People with diabetes need to be encouraged to watch their diet, to exercise regularly, and their medications need regular adjustments to optimally control their blood sugars. Smokers need to quit cigarettes.* People with diabetes need annual eye examinations. Diabetes is a leading cause of blindness in the United States, and this complication of diabetes is totally preventable - **IF** the developing eye problems are treated early. Other signs of complications such as peripheral neuropathy and coronary artery disease need to be identified and the problems treated before they create more serious complications. Blood pressure needs to be tightly controlled. Doing so will dramatically decrease the risk of certain diabetic complications. Lipid levels also need to be tightly controlled. Kidney function should be monitored yearly and warning signs of developing problems (leakage of protein into the urine) should prompt treatment to prevent further progression of the damage done to the kidneys. Glycohemoglobins and blood sugars should be monitored every 3 months. In summary, we have effective treatments for many of the problems associated with diabetes that lead to diabetic complications. These treatments are most effective when started early and used aggressively. People with diabetes can live long, healthy and productive lives when they take good care of themselves and help their doctors address problems early, before they become a major illness.

*Cigarette smoking increases the risk of hardening of the arteries, such as heart attack, stroke and leg amputations 3-5 times that present in the non-smoking population. Likewise, people with diabetes have 3-5 times the risk of hardening of the arteries (those same complications) compared to the non-diabetic population. But, if you both have diabetes **and** you smoke, those risk factors do **not** add up, they **multiply** each other. That means ***you have 9-25 times the risk*** of having such complications as a heart attack or an amputation compared to someone who neither has diabetes nor smokes. These odds are so bad that you are virtually guaranteeing yourself of developing one of those complications if nothing

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changes. So far we can't cure diabetes. But ***you can make a very big difference in your life***, and markedly reduce your risk of such problems. **Quit smoking now!**

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