MOLECULAR BASIS OF DIABETES

Diabetes mellitus

- **Diabetes mellitus** (**DM**), commonly referred to as **diabetes**, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period.
- Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications.
- Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma.
- Serious long-term complications include cardiovascular disease, stroke, chronic kidney failure, foot ulcers, and damage to the eyes.

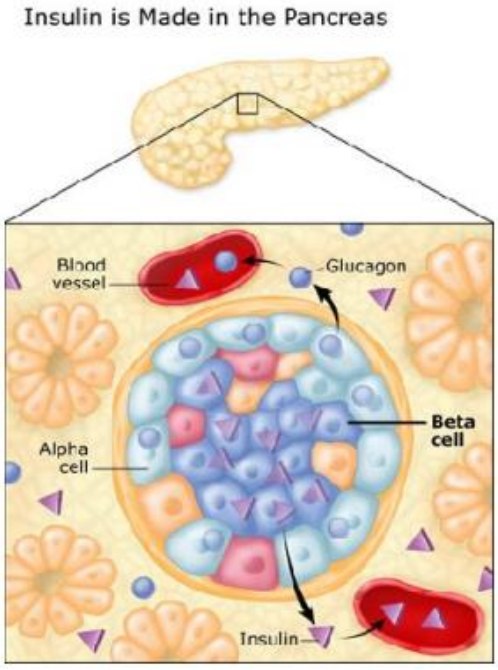
Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced.

There are three main types of diabetes mellitus:

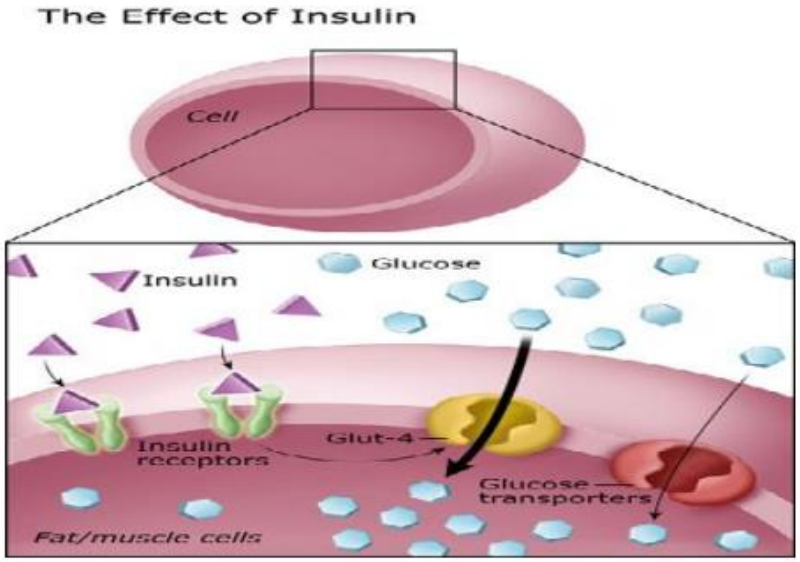
- Type 1 DM results from the pancreas's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown.
- Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise.
- Gestational diabetes, is the third main form and occurs when pregnant women without a previous history of diabetes develop high blood-sugar levels.

Insulin is the main regulator of sugar in the bloodstream.

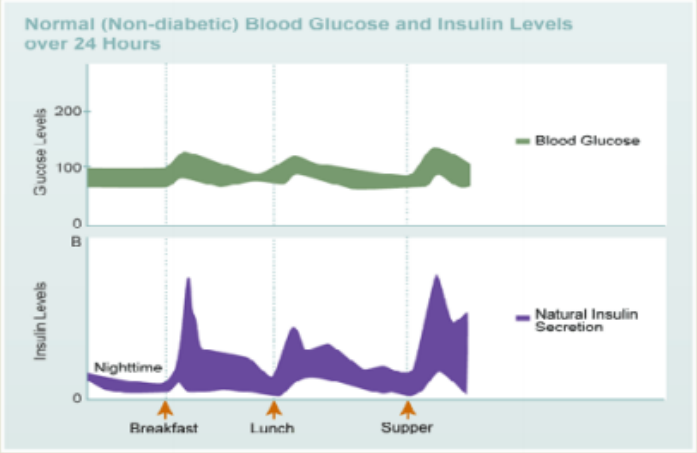
- This hormone is made by beta cells and is continuously released into the blood stream. Beta cells are found in the pancreas, which is an organ behind the stomach. Insulin levels in the blood stream are carefully calibrated to keep the blood glucose just right.
- High insulin levels drive sugar into muscle, fat and liver cells where it is stored for future use. Low insulin levels allow sugar and other fuels to be released into the blood stream.



- Overnight and between meals, insulin levels in the blood stream are low and relatively constant. These low levels of insulin allow the body to tap into its stored energy sources (namely glycogen and fat) and also to release sugar and other fuels from the liver. This overnight and between-meal insulin is referred to as **background or basal** insulin. When you haven't eaten for a while, your blood sugar level will be somewhere between 60 to 100 mg/dl.
- When eating, insulin is rapidly released from the pancreas. The burst of insulin that accompanies eating is called **bolus** insulin. After a meal, blood sugar levels peak at less than 140 mg/dl and then fall back to the baseline (pre-meal) range. The high levels of insulin help the sugar get out of the blood stream and be stored for future use.



Insulin levels throughout the day



- There are other hormones that work together with insulin to regulate blood sugar including incretins and glucocounterregulatory hormones, but insulin is the most important. It is important to know about glucagon, amylin, GIP, GLP-1, epinephrine, cortisol, and growth hormone.

Glucagon:

Made by islet cells (alpha cells) in the pancreas, controls the production of glucose and another fuel, ketones, in the liver.

Glucagon is released overnight and between meals and is important in maintaining the body's sugar and fuel balance. It signals the liver to break down its starch or glycogen stores and helps to form new glucose units and ketone units from other substances. It also promotes the breakdown of fat in fat cells.

In contrast, after a meal, when sugar from the ingested food rushes into your bloodstream, your liver doesn't need to make sugar. The consequence? Glucagon levels fall.

Unfortunately, in individuals with diabetes, the opposite occurs. While eating, their glucagon levels rise, which causes blood sugar levels to rise after the meal.

GLP-1 (glucagon-like peptide-1), GIP (glucose-dependent insulinotropic polypeptide) and amylin:

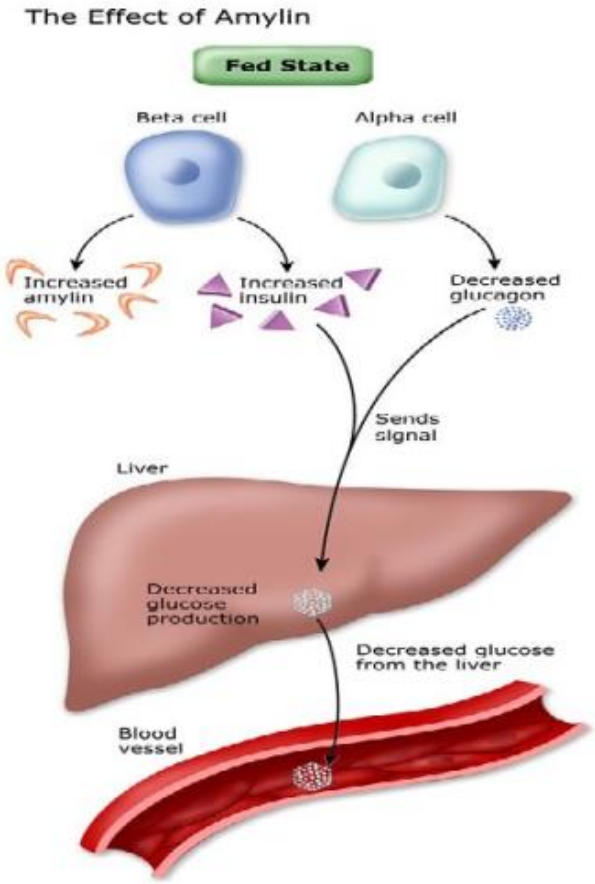
GLP-1 (glucagon-like peptide-1), GIP (glucose-dependent insulinotropic polypeptide) and amylin are other hormones that also regulate mealtime insulin. GLP-1 and GIP are incretin hormones. When released from your gut, they signal the beta cells to increase their insulin secretion and, at the same time, decrease the alpha cells' release of glucagon. GLP-1 also slows down the rate at which food empties from your stomach, and it acts on the brain to make you feel full and satisfied.

People with type 1 diabetes have absent or malfunctioning beta cells so the hormones insulin and amylin are missing and the hormone GLP1 cannot work properly. This may explain, in part, why individuals with diabetes do not suppress glucagon during a meal and have high blood sugars after a meal.

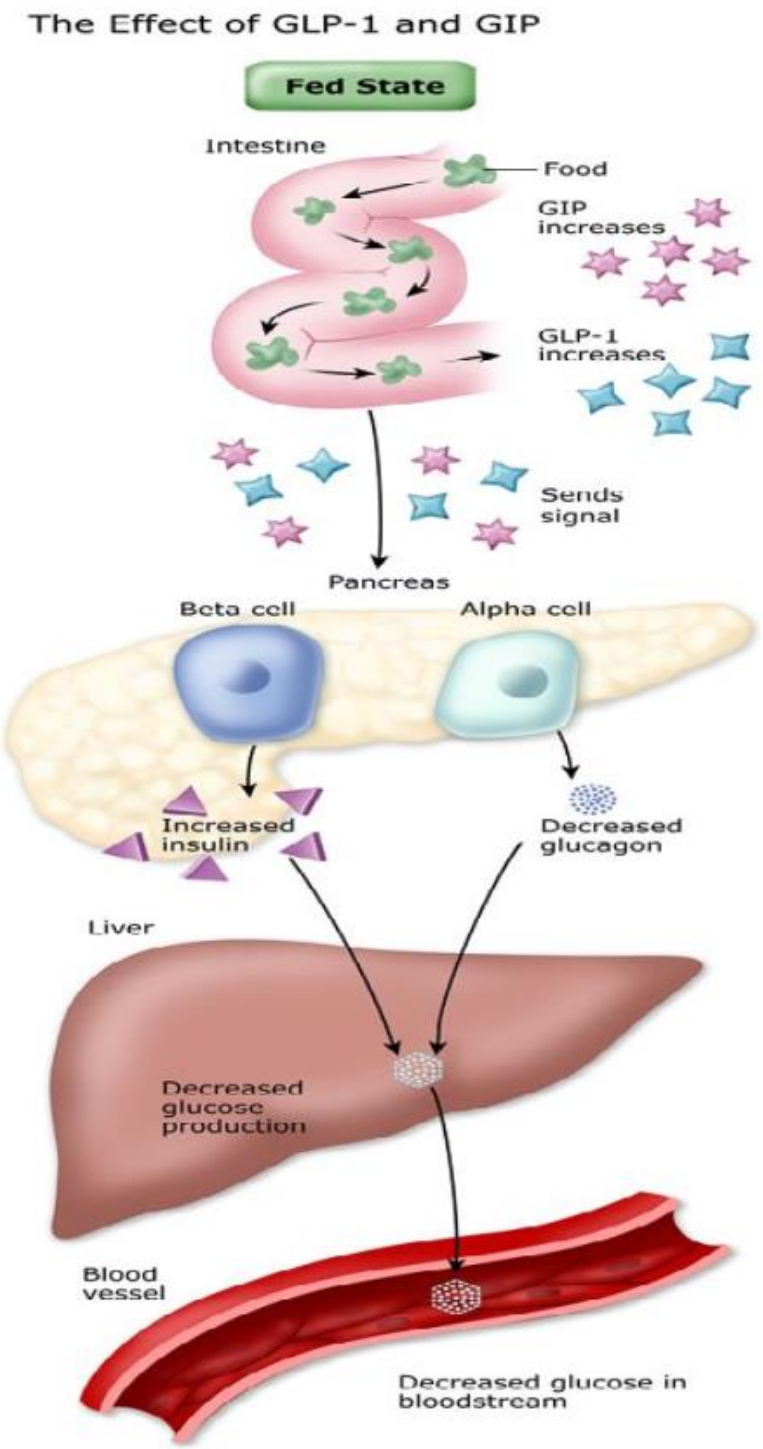
Amylin:

Amylin is released along with insulin from beta cells. It has much the same effect as GLP-1. It decreases glucagon levels, which will then decrease the liver's glucose production, slows the rate at which food empties from your stomach, and makes your brain feel that you have eaten a full and satisfying meal.

The overall effect of these hormones is to reduce the production of sugar by the liver during a meal to prevent it from getting too high.

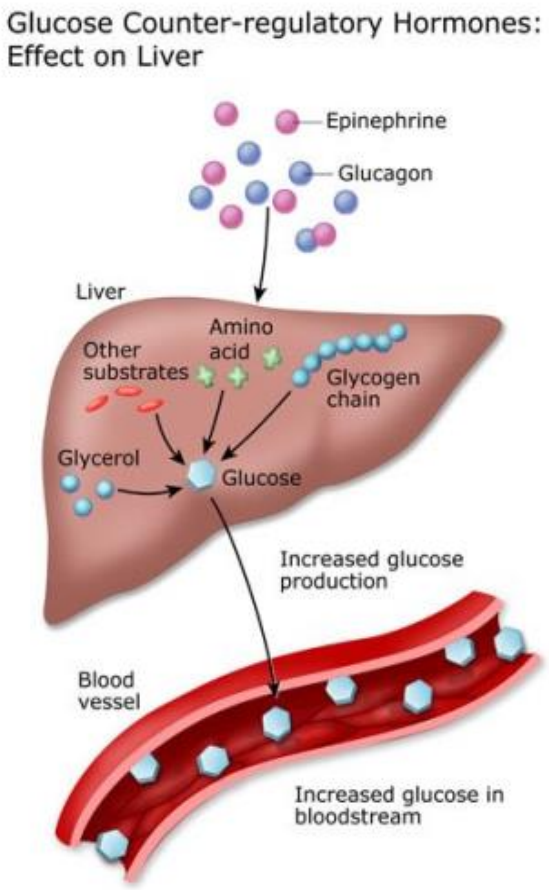


The good news is that amylin is now available as a medicine to control post-meal glucagon and blood sugar in individuals with type 1 diabetes. (GLP-1 also is available as a medicine but is not approved for use for people with type 1)



Epinephrine, cortisol, and growth hormone:

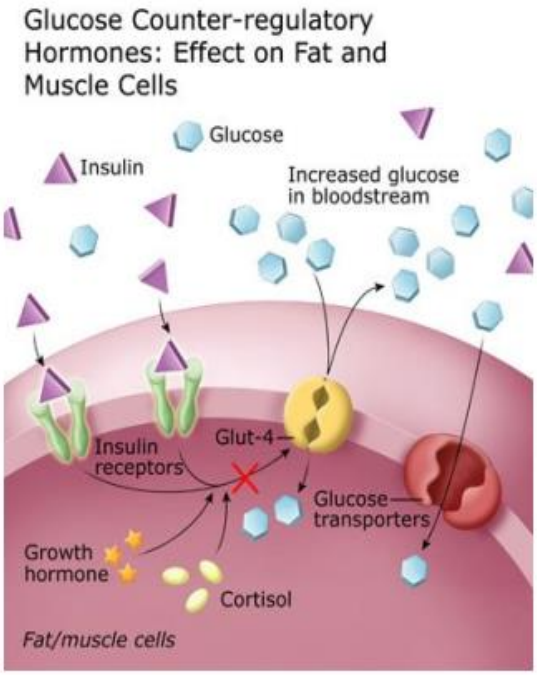
Epinephrine, cortisol, and growth hormone are other hormones that help maintain blood sugar levels. They, along with **glucagon** (see above) are called "stress" or "gluco-counter-regulatory" hormones – which means they make the blood sugar rise.



Epinephrine (adrenaline) is released from nerve endings and the adrenals, and acts directly on the liver to promote sugar production (via glycogenolysis). Epinephrine also promotes the breakdown and release of fat nutrients that travel to the liver where they are converted into sugar and ketones.

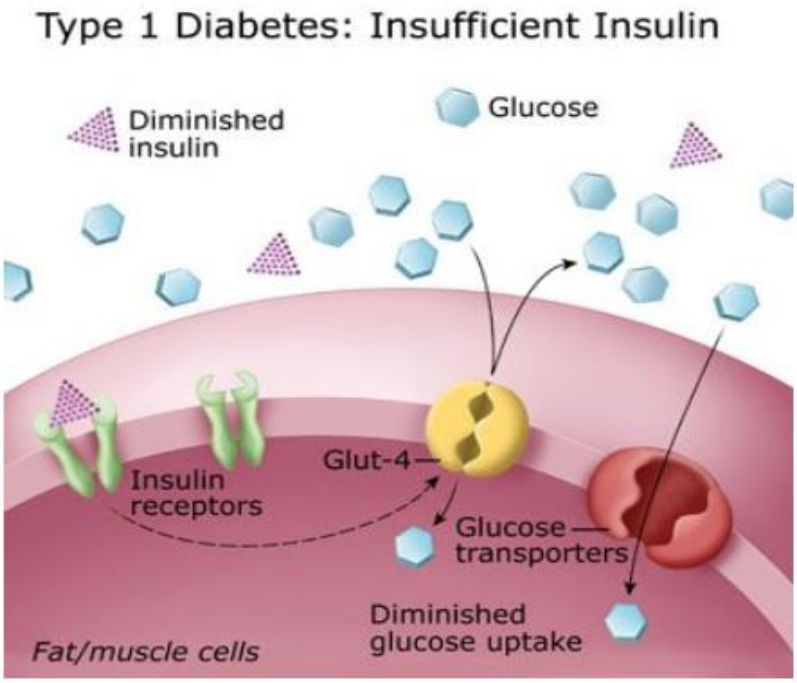
Cortisol is a steroid hormone also secreted from the adrenal gland. It makes fat and muscle cells resistant to the action of insulin, and enhances the production of glucose by the liver. Under normal circumstances, cortisol counterbalances the action of insulin. Under stress or if a synthetic cortisol is given as a medication (such as with prednisone therapy or cortisone injection), cortisol levels become elevated and you become insulin resistant. When you have Type 1 diabetes, this means your may need to take more insulin to keep your blood sugar under control.

Growth Hormone is released from the pituitary, which is a part of the brain. Like cortisol, growth hormone counterbalances the effect of insulin on muscle and fat cells. High levels of growth hormone cause resistance to the action of insulin.



Type 1 diabetes accounts for about 5-10% of diabetes worldwide.

- It is diagnosed in every ethnic group, but is most frequent in individuals of European ancestry.
- While type 1 diabetes is commonly diagnosed during adolescence and early adulthood, it can occur at any age. Older people who develop type 1 diabetes are often misdiagnosed as having Type 2 diabetes.
- Most people first diagnosed with type 1 diabetes are lean.
- 85-90% will have no known family history of the disease.
- There are many theories about what causes type 1 diabetes. Autoimmune disease, viral infection, genetic disposition, and environmental factors may all play a role.
- There is a hereditary component to type 1 diabetes; however, it is still difficult to predict who will develop it. Among identical twins (who presumably have the same genetic and environmental risk), it is traditionally reported that only about 40% will both have the disease. Recent research suggests that the number may be much higher.
- Markers in your blood and the presence of certain gene types, coupled with test results, can help predict who might develop diabetes.
- Diabetes researchers are seeking ways to identify both high-risk individuals and ways to protect them.



Sub categories of Type 1 diabetes

There are 2 sub categories of Type 1 diabetes:

- Type 1a including Latent Autoimmune Diabetes of Adults (LADA)
- Type 1b

You have Type 1a if:

Your immune system is so overactive that it is destroying normal beta cell tissue. The telltale signs of this destruction are detectable by a laboratory blood test. The test looks for markers. The list of markers includes glutamic acid decarboxylase antibodies (GADA), islet cell antibodies to membranous tyrosine phosphatase (ICA-512), islet cell antibodies (ICA), and insulin auto antibodies (IAA).

Some adults have a slowly progressive autoimmune destruction of their beta cells referred to as **Latent Autoimmune Diabetes of Adults or LADA**. Sometimes this is also known as diabetes type 1 ½. Individuals with LADA may be treated for years with diet and pills, and often are misdiagnosed as having Type 2 diabetes. Ultimately insulin replacement therapy is necessary to control the blood sugar. A diagnosis is made by confirming the presence of antibody markers.

You have Type 1b if:

You meet two criteria: the first, if there is no evidence in your blood that your immune system is attacking beta cells and the second, if you have alternating cycles where you need

and then don't need insulin replacement. This form of the disease is unusual and most often diagnosed in those of African or Asian heritage.

Liver and blood sugar:

The liver both stores and produces sugar…

The liver acts as the body's glucose (or fuel) reservoir, and helps to keep your circulating blood sugar levels and other body fuels steady and constant. The liver both stores and manufactures glucose depending upon the body's need. The need to store or release glucose is primarily signaled by the hormones insulin and glucagon.

During a meal, your liver will store sugar, or glucose, as glycogen for a later time when your body needs it. The high levels of insulin and suppressed levels of glucagon during a meal promote the storage of glucose as glycogen.

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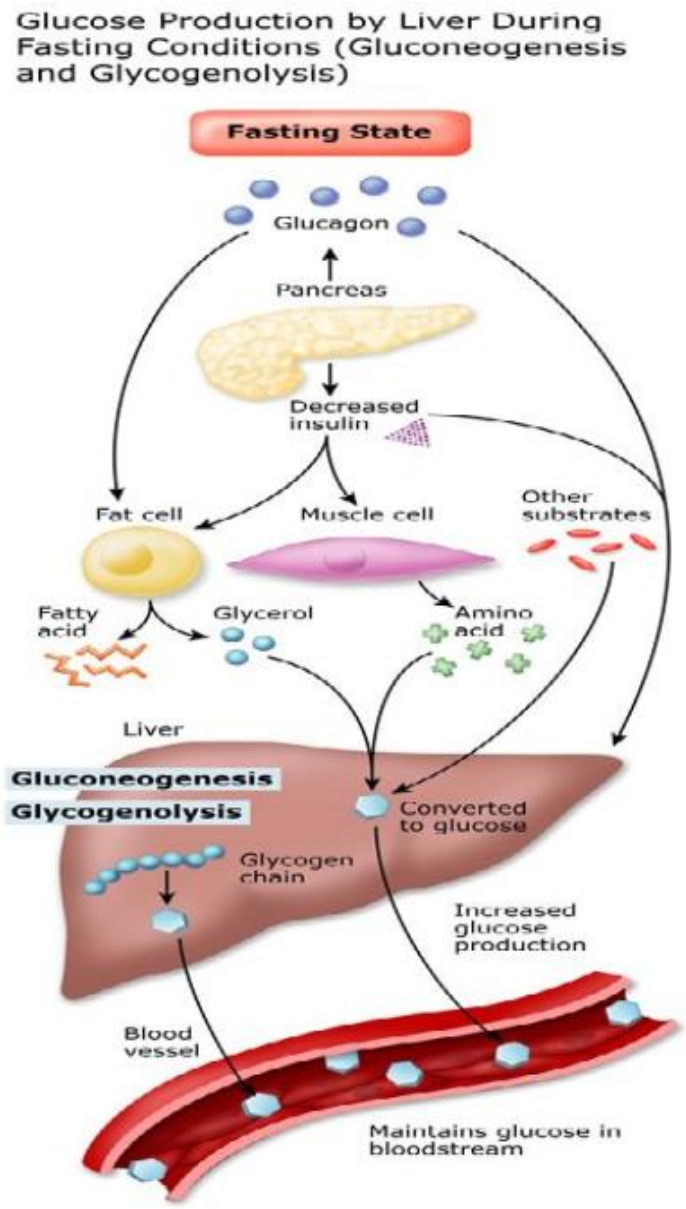
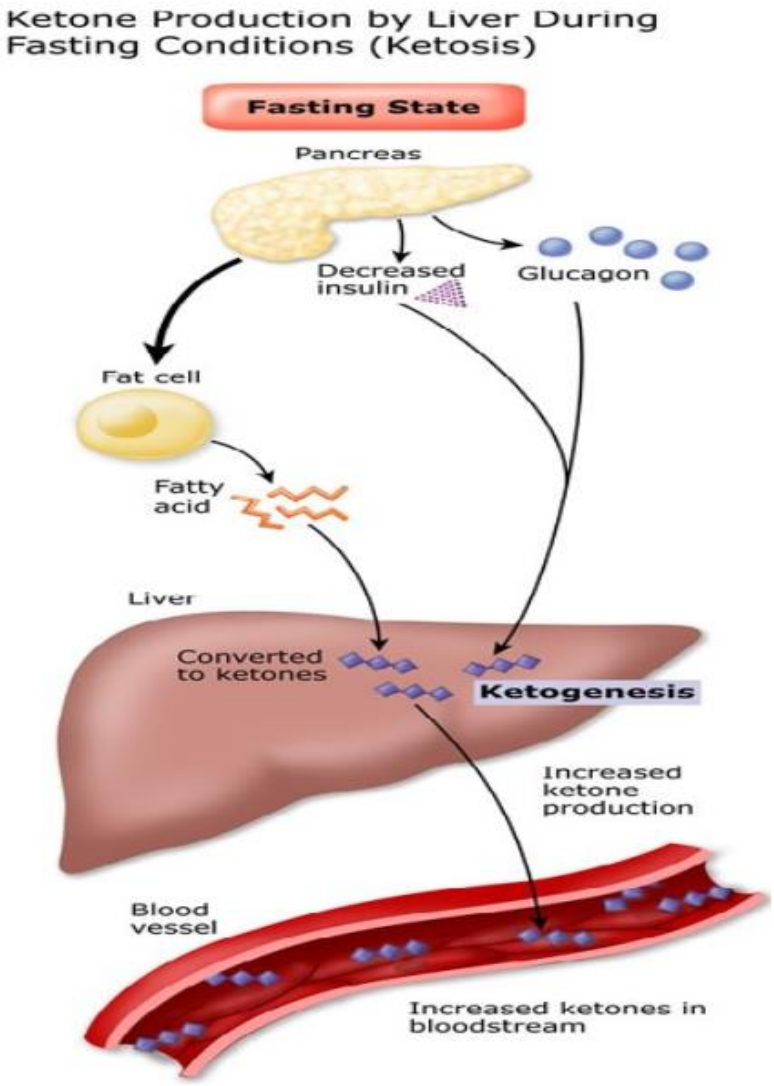
The liver makes sugar when you need it….

When you're not eating – especially overnight or between meals, the body has to make its own sugar. The liver supplies sugar or glucose by turning glycogen into glucose in a process called **glycogenolysis.** The liver also can manufacture necessary sugar or glucose by harvesting amino acids, waste products and fat byproducts. This process is called **gluconeogenesis.**



The liver also makes another fuel, ketones, when sugar is in short supply….

When your body's glycogen storage is running low, the body starts to conserve the sugar supplies for the organs that always require sugar. These include: the brain, red blood cells and parts of the kidney. To supplement the limited sugar supply, the liver makes alternative fuels called ketones from fats. This process is called **ketogenesis**. The hormone signal for ketogenesis to begin is a low level of insulin. Ketones are burned as fuel by muscle and other body organs. And the sugar is saved for the organs that need it.



The terms "gluconeogenesis, glycogenolysis and ketogenesis" may seem like complicated concepts or words on a biology test. Take a moment to review the definitions and illustrations above. When you have diabetes, these processes can be thrown off balance, and if you fully understand what is happening, you can take steps to fix the problem.

Blood Sugar & Stress

Stress affects everyone…

During stressful situations, epinephrine (adrenaline), glucagon, growth hormone and cortisol play a role in blood sugar levels. Stressful situations include infections, serious illness or significant emotion stress.

When stressed, the body prepares itself by ensuring that enough sugar or energy is readily available. Insulin levels fall, glucagon and epinephrine (adrenaline) levels rise and more glucose is released from the liver. At the same time, growth hormone and cortisol levels rise, which causes body tissues (muscle and fat) to be less sensitive to insulin. As a result, more glucose is available in the blood stream.

When you have type 1 diabetes…

When you have type 1 diabetes, insulin reactions or low blood sugars are a common cause of stress. The hormonal response to a low blood sugar includes a rapid release of epinephrine (and glucagon for a year or so after diagnosis), followed by a slower release of cortisol and growth hormone. These hormonal responses to the low blood sugar may last for 6-8 hours – during that time the blood sugar may be difficult to control. The phenomena of a low blood sugar followed by a high blood sugar is called a "rebound" or "Somogyi" reaction.

When you have type 1 diabetes, stress may make your blood sugar go up and become more difficult to control – and you may need to take higher doses of insulin.

Ketones:

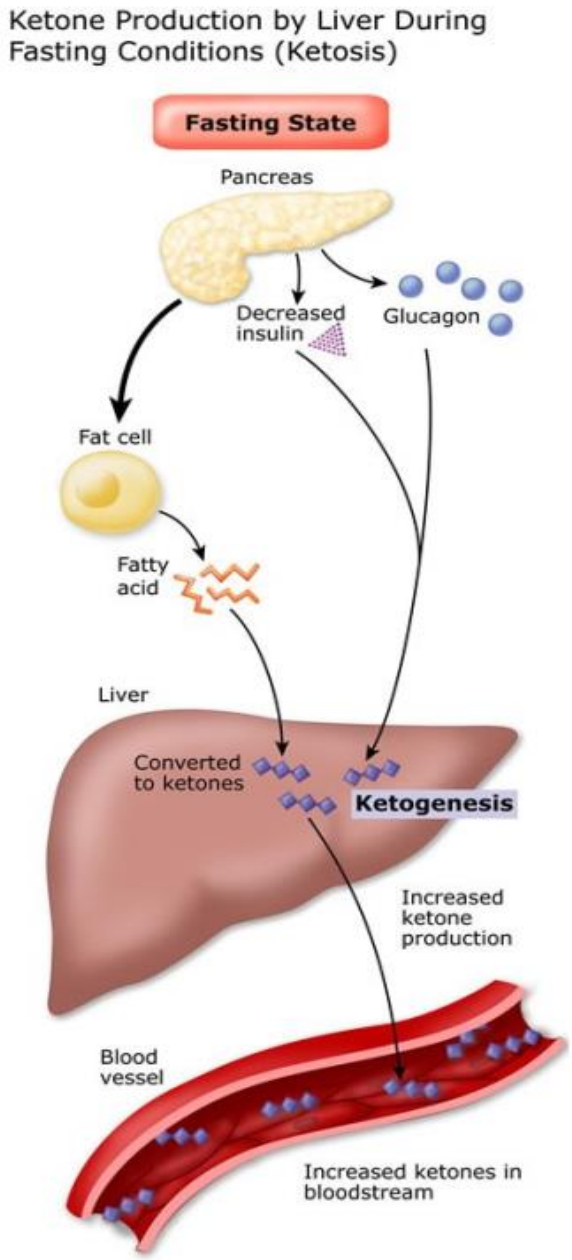
In a person without diabetes, ketone production is the body's normal adaptation to starvation. Blood sugar levels never get too high or too low, because the production is regulated by just the right balance of insulin, glucagon and other hormones. However, in an individual with diabetes, dangerous and life-threatening levels of ketones can develop.

What are ketones and why do I need to know about them?

Ketones and ketoacids are alternative fuels for the body that are made when glucose is in short supply. They are made in the liver from the breakdown of fats.

Ketones are formed when there is not enough sugar or glucose to supply the body's fuel needs. This occurs overnight, and during dieting or fasting. During these periods, insulin levels are low, but glucagon and epinephrine levels are relatively normal. This combination of low insulin, and relatively normal glucagon and epinephrine levels causes fat to be released from the fat cells.

The fats travel through the blood circulation to reach the liver where they are processed into ketone units. The ketone units then circulate back into the blood stream and are picked up by the muscle and other tissues to fuel your body's metabolism.



Autoimmunity:

- Type 1a diabetes develops because the body mistakenly identifies insulin-producing cells (beta cells) as being foreign, or "non-self." The immune system targets and ultimately destroys the beta cells, resulting in an absence of insulin and the subsequent diagnosis of diabetes. This autoimmune process is thought to smolder for

years, and there are individuals at risk of developing diabetes who do not yet have the diagnosis.

- During the "prodrome," or prior to the time of diagnosis, it is speculated that the regulatory T cells are unable to control cytotoxic T cells directed against self proteins.
- CD4 and CD8 T cells coordinate to attack and destroy insulin-producing cells (beta cells). At the same time, B cells are making antibodies against beta cell proteins.
- There may be some beta cell re-formation (by cell division or by new cell formation) that replaces the destroyed cells. But over the years, the net destruction is greater than the replacement. When the number of beta cells is reduced by approximately 80%, the body is unable to secrete enough insulin, the blood sugar rises and clinical diabetes is diagnosed. The diagnosis of diabetes is based on an elevated blood sugar.

Who Is At Risk?

ype 1 diabetes is diagnosed worldwide, and occurs in every race and nationality. The incidence (or frequency) of the disorder is increasing in every population.

Type 1 diabetes is most common in white people or individuals of Northern European heritage, in whom the incidence is 1 out of every 300 or 400 individuals. Finland and Sardinia are "hot spots" where the risk of type 1 diabetes is 1 out of every 100 to 200 people. The reasons for the geographical and racial differences are not understood.

The presence of antibodies directed against beta cell antigens or molecules is a significant risk factor for the development of type 1 diabetes. The antibodies are directed against proteins associated with the beta cells, such as glutamic acid decarboxylase, tyrosine phosphatase, insulin and heat shock proteins.

Commercial tests are available for:

- Glutamic acid decarboxylase (gadas)
- Islet cell antigen 512 (ICA512s or ICA IA-2s)
- Insulin auto-antibodies (iaas)
- Islet cell antibodies (icas)
- Zinc transporter 8 (znt8)

Up to 3-5% of the general population may test positive for one of these antibodies, but only about 20% of these individuals will develop diabetes. The presence of two antibodies, however, creates a more than 75% risk of developing type 1 diabetes within the next 10 years.

Among identical twins, it is traditionally reported that only about 40% will both have the disease. Recent research suggests that the number may be much higher. And if one identical twin is positive for antibodies directed against the beta cell, and the other has type 1 diabetes, it is almost certain that both will eventually have diabetes.

A predictive test used in research – the intravenous glucose tolerance test :

Another predictive test, called an intravenous glucose tolerance test (IVGTT), evaluates "first phase" insulin secretion. "First phase" refers to the amount of insulin secreted within the first few minutes after the administration of the intravenous glucose. When someone has a low first phase insulin secretion and two or more antibody tests are positive, there is at least a 90% risk of developing clinical diabetes within the next few years.

Genetics of Type 1a:

ype 1 diabetes is a complex genetic disorder. It occurs more frequently in families in which there are other relatives with type 1 diabetes and other autoimmune conditions.

Children have a 5% to 6% chance of developing diabetes if their father has type 1 diabetes, and a 3% to 4% chance if their mother has type 1 diabetes. It is thought that some of the mother's chromosomal material, or DNA, gets inactivated when passed on to the child, thereby accounting for the difference in the children's diabetes risk.

If a sibling has type 1 diabetes, the risk is 5-6%; however, if the sibling has identical MHC (Major Histocompatibility Complex) haplotypes, the risk increases. When one identical twin has diabetes, the risk of the other twin developing diabetes traditionally has been thought to be about 40%. Recent research suggests that the number may be much higher.

A number of genes have been identified that are associated with the development of diabetes. The chromosomal locations of these "diabetes genes" are called inherited susceptibility loci.

There are now at least 20 insulin-dependent diabetes mellitus (IDDM) susceptibility loci.

The most important are:

- IDDM 1 (the major histocompatibility complex on chromosome 6)
- IDDM 2 (the insulin gene locus on chromosome 11)
- PTPN 22 (the protein tyrosine phosphatase gene) with a mutation at LYP (the lymphocyte-specific phosphatase gene) on chromosome 1 associated with susceptibility to multiple autoimmune disorders

IDDM 1

It is estimated that about 40-50% of the risk for type 1 diabetes is associated with the MHC complex or IDDM 1 loci. The MHC genes most associated with diabetes in white people are known as the human leukocyte antigens HLA DR3 and HLA DR4. Other racial groups are less well studied and may have different MHC gene profiles. More than 90% of European ancestry individuals with type 1 diabetes will have one or the other of these DR3 or DR4 haplotypes, but about 40% of the general population has one of these gene locations as well. The presence of high-risk haplotypes and evidence of positive antibodies, however, strongly predict the development of diabetes.

Specific high-risk genotypes are:

- DR4 DQB1*0302
- DR4 DQA1*0301
- DR3 DQA1*0501 and
- DR3 DQB1*0201

Interestingly, some MHC genes, such as HLA-DR2 DQB1*0602 and DR4 DRB1*1401, seem to be protective, and less than 1% of individuals with diabetes will have this gene type. The reason for the increased risk or protection is unknown, but it is thought to be related to which antigens or protein snippets the MHC protein can most easily bind and present to the immune cells. It has to be emphasized that there are multiple "at-risk" as well as protective haplotypes, and that calculating risk of diabetes based on HLA types is difficult.

IDDM 2

The IDDM 2 susceptibility locus confers approximately 10% of the familial risk for type 1 diabetes. This site refers to an area flanking the insulin gene that includes a variable number of tandem repeating (VNTR) nucleotide sequences. An increased risk of type 1 diabetes is associated with short sequences. These short repeating sequences appear to cause the thymus to under-express the insulin gene and thereby allow T cells with a T cell receptor that targets insulin to survive.

PTPN 22

A variation in the PTPN 22 gene locus may account for a little less than 10% of the genetic chance of developing type 1 diabetes. This variation – called a functional polymorphism – also increases the risk of someone developing rheumatoid arthritis and systemic lupus erythematosis.

Type 1 diabetes is associated with a number of other autoimmune conditions. The strongest association is with:

- Celiac disease
- Hashimoto's disease, or hypothyroidism
- Graves' disease, or hyperthyroidism
- Addison's disease, or adrenal failure, and
- Pernicious anemia

Treatment Of Type 1 Diabetes:

his section focuses on the medical management of type 1 diabetes. And as the term "medical management" implies, this management is done with the guidance of your medical provider and medical team. **The key principles of medical management are**:

- Regular blood sugar (and ketone) self monitoring as a part of daily living
- Taking insulin
- Problem solving how and when to make adjustments in your food and insulin doses to prevent high or low blood sugars
- Understanding complications and how to screen for, prevent and treat them

Good management requires all of these elements. All the elements are intertwined.

For example, you need to monitor your blood sugar to know if your treatment is successful. You need to problem solve if the self blood sugar monitoring shows your treatment is not successful. The self blood sugar monitoring will indicate if you need to adjust the dose of insulin. Regular screening for diabetes-related complications may pick up a complication that is in the early stages, and early treatment usually gives the best results.

Goals Of Diabetes Treatment

- To keep the blood sugar as normal as possible without serious high or low blood sugars
- To prevent tissue damage caused by too much sugar in the blood stream

Normal ranges for blood sugar

People who don't have diabetes keep their blood sugars between 60 – 100 mg/dl overnight and before meals, and less than 140 mg/dl after meals. Although the ultimate goal of diabetes management is to return the blood sugar to the natural or non-diabetic level, this may be difficult without excessive low blood sugars or hypoglycemia.

What are the blood sugar (glucose) targets for diabetes?

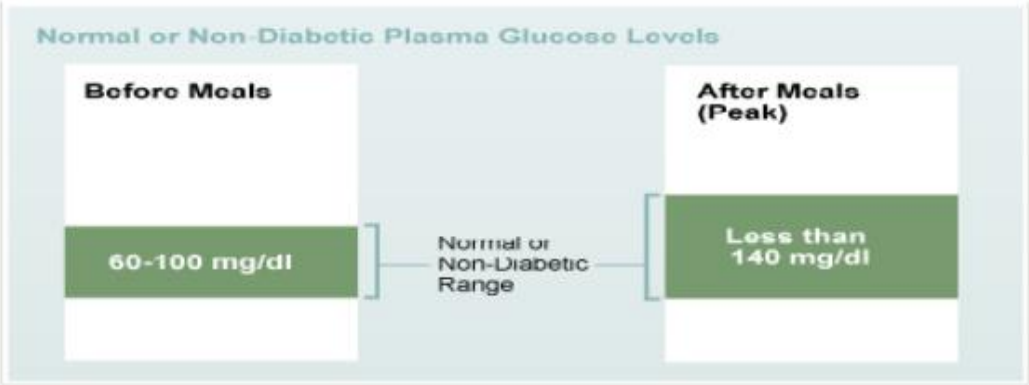
The ultimate treatment goal for Type 1 diabetes is to re-create normal (non-diabetic) or NEARLY normal blood sugar levels – without causing low blood sugars.

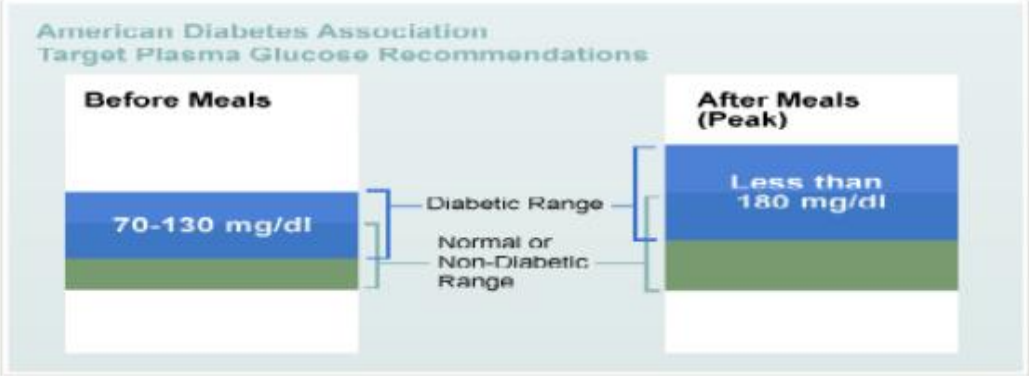
Good blood sugar control requires that you know and understand a few general numbers. The numbers measure how much glucose is in your blood at certain times of the day and represent what the American Diabetic Association believes are the best ranges to prevent complications.

American Diabetes Association Recommendations

A1c*	< 7.0%
Before Meal Glucose Level	70-130 mg/dl
After Meal Glucose Level	< 180 mg/dl

**Hemoglobin (A1c) is a measure of your average blood glucose control over the previous 3 months. Think of the A1c as a long-term blood glucose measure that changes very gradually.*





Of course, these are general standards for everyone with diabetes – both type 1 as well as type 2. Ask your diabetes team for personalized goals and blood sugar (blood glucose) monitoring schedules.

For example:

When you have type 1 diabetes you are treated with insulin replacement therapy. The goal is to replace the insulin in the right amount and at the right time. Sometimes, more insulin than needed is taken and this will cause hypoglycemia.

To minimize this risk, many providers will recommend that individuals treated with insulin target a pre-meal blood sugar (plasma glucose) of 90-130 mg/dl and post meal blood sugar (plasma glucose) of less than 180 mg/dl.

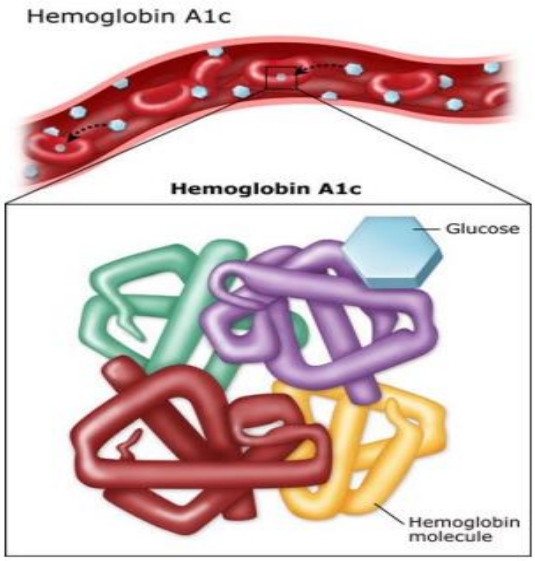
Also, if you are experiencing a lot of hypoglycemia or have hypoglycemic unawareness your provider may suggest you target higher blood sugar levels.

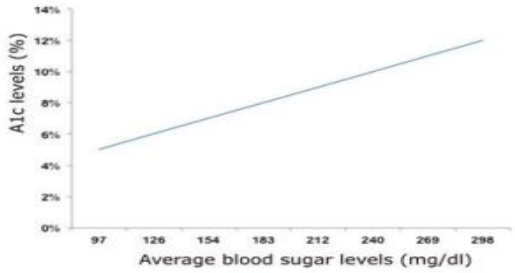
In contrast, pregnant women or women thinking about getting pregnant will have lower blood glucose targets.

Understanding Your Average Blood Sugar:

Glysolated Hemoglobin (or A1c) is a measure of your average blood glucose control over the previous three months.

Glucose attaches to hemoglobin the oxygen carrying molecule in red blood cells. The glucose-hemoglobin unit is called glycosolated hemoglobin. As red blood cells live an average of three months, the glycosolated hemoglobin reflects the sugar exposure to the cells over that time.





The higher the amount of glucose in the blood, the higher the percentage of hemoglobin molecules that will have glucose attached. Think of the A1c as a long-term blood glucose measure that changes very gradually as red blood cells die and are replaced by new cells.

The A1c doesn't replace self blood-glucose monitoring. Because the A1c is an **average of all your blood sugars**, it does not tell you your blood sugar patterns. For example, one person with frequent highs and lows can have the same A1c as another person with very stable blood sugars that don't vary too much.

So what's the point?

A1c is yet another indicator of how well you're doing.

- An A1c measurement between 4-6% is considered the range that someone ***without*** diabetes will have.

- The American Diabetes Association goal is an A1c less than 7%. Research has shown that an A1c less than 7% lowers risk for complications.
- The American College of Endocrinology goal is an A1c less than 6.5%.
- For some people with diabetes an A1c goal of less than 6% is appropriate.
- Talk with your doctor about your A1c goal.

Use this chart to view A1c values and comparable blood glucose values:

A1c	Estimated Average Glucose mg/dL
5%	97
6%	126
7%	154
8%	183
9%	212
10%	240
11%	269
12%	298

A note of caution: the A1c measurement is not always accurate. For example, if someone has certain type of hemoglobin mutations (variation in the hemoglobin structure), is severely anemic (low red blood cell count), iron deficient or is being treated blood transfusions or medications to increase the production of new red blood cells, the A1c test may not be accurate.

If your finger-stick blood tests give an average blood sugar that is much higher or lower than your A1c test, ask your doctor if the A1c is the right test for you. An alternative test to the A1c is a fructosamine test. Unfortunately, the fructosamine test and the A1c are not interchangeable because they are measuring different things. The fructosamine test reflects the average blood sugars only over a 2-3 week period.

Checking for Ketones

Check your urine or blood for ketones if you are sick or have symptoms of ketoacidosis. If the test is positive, you need immediate medical care.

There are two ways to test your body for ketones.

- Urine Test
- Blood Test

How to Check for Urine Ketones

Urine Ketones: Examples: Ketostixs® or Chemstrips®
Urine is applied to reagent strip and the color change shows the level of ketones.

- **Advantages:**
  - Easy to use
  - Portable
  - Reasonably priced
- **Disadvantages:**
  - Results are not current; they may lag by as many as three hours
  - Color changes are categorized as trace, small, medium, and large only
  - Dehydration can affect results

CAUTION: Be sure to get individually foil wrapped urine ketone test strips! Test strips rapidly loose their accuracy once they are exposed to the air. By using individually foil wrapped strips, only the strip you are using is exposed to the atmosphere.

How to Check for Blood Ketones

Blood Ketones: Example: Abbott Precision Xtra®

Quantitative ketone (beta-hydroxybutyrate) is measured. The normal level is less than 0.6 mmol/l. Check the manufacturer's package insert for an explanation of results and more information. CardioChek, BioScanner 2000, and other blood ketone testing devices are also available.

- **Advantages:**
  - Results are more accurate and reflect ketone levels at the time the test is done vs. lag time found with the urine testing
- **Disadvantages**:
  - The blood ketone test strips are expensive
  - May not be covered by medical insurance
  - Test requires a meter

Medications And Therapies

Type 1 diabetes:

When you have type 1 diabetes, your body no longer makes enough insulin, and it needs to be replaced. This insulin replacement is known as insulin therapy which your medical provider will prescribe for you. It is important to understand how insulin replacement therapy works in your body so that you can control you blood sugar more easily.

- Insulin Therapy:
  Injections that raise your insulin level and replace the insulin that you are missing
- Non-insulin Treatment for Type 1 Diabetes – Amylin analogs:
  Injections that reduce sugar production in the liver and slow the absorption of food
- **Insulin pump therapy**:
  Insulin delivery via a continuous subcutaneous insulin infusion device

Type 2 Diabetes

You have Type 2 diabetes if your tissues are resistant to insulin, and if you lack enough insulin to overcome this resistance. Type 2 diabetes is the most common form of diabetes of diabetes worldwide and accounts for 90-95% of cases.

Risk Factors

Your risk of type 2 diabetes typically increases when you are:

- **Older**
- **Less active**
- **Overweight or obese**

Other risk factors are:

- Family history of diabetes in close relatives
- Being of African, Asian, Native American, Latino, or Pacific Islander ancestry
- High blood pressure
- High blood levels of fats, known as triglycerides, coupled with low levels of high-density lipoprotein, known as HDL, in the blood stream
- Prior diagnosis of pre-diabetes such as glucose intolerance or elevated blood sugar
- In women, a history of giving birth to large babies (over 9 lbs) and/or diabetes during pregnancy

Type 2 diabetes is strongly inherited

These are some of the statistics:

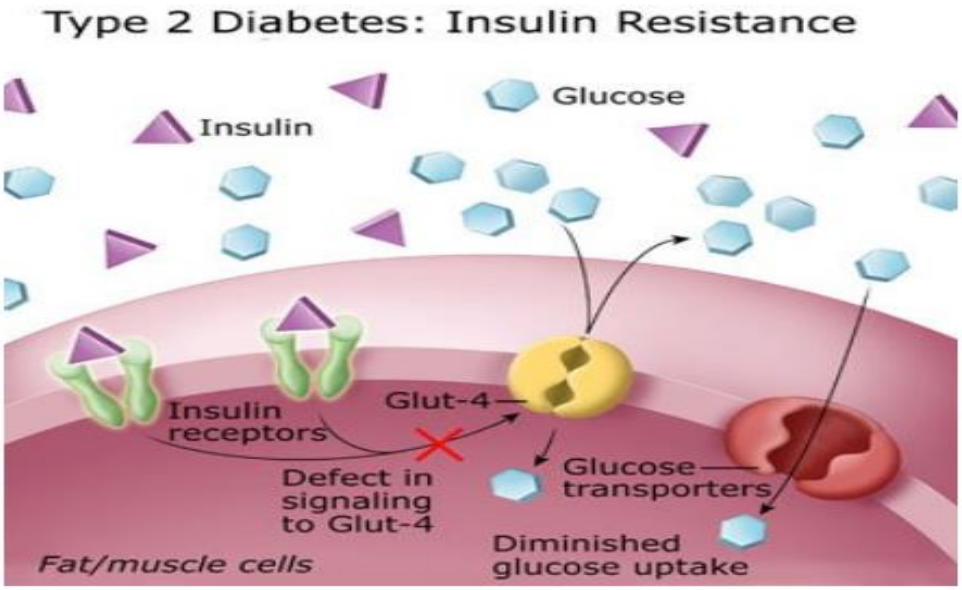
- 80-90% of people with Type 2 diabetes have other family members with diabetes.
- 10-15% of children of a diabetic parent will develop diabetes.

- If one identical twin has type 2 diabetes, there is up to a 75% chance that the other will also be diabetic.
- There are many genetic or molecular causes of type 2 diabetes, all of which result in a high blood sugar.
- As yet, there is no single genetic test to determine who is at risk for type 2 diabetes.
- To develop type 2 diabetes, you must be born with the genetic traits for diabetes.
- Because there is a wide range of genetic causes, there is also a wide range in how you will respond to treatment. You may be easily treated with just a change in diet or you may need multiple types of medication.

Insulin resistance and insufficient insulin production

Insulin resistance in type 2 diabetes means the signal insulin gives to a cell is weakened. This results in less glucose uptake by muscle and fat cells and a reduction in insulin mediated activities inside cells. Compounding this problem of resistance, there is additional defect in insulin production and secretion by the insulin producing cells, the beta cells in the pancreas.

As a group, everyone with with type 2 diabetes has both insulin resistance and an inability to overcome the resistance by secreting more insulin. But any given individual with type 2 may have more resistance than insulin insufficiency or the opposite, more insulin insufficiency than resistance. And the problems may be mild or severe. It is believed that the wide range of clinical presentation is because there are many, many genetic causes – and combinations of genetic causes – of type 2 diabetes. At present there is no single genetic test for type 2 diabetes. The diagnosis is made on the basis of the individual having clinical features consistent with type 2 diabetes, and by excluding other forms of diabetes.



The amount of insulin resistance and beta cell impairment differs between individuals with type 2 diabetes

Assumptions About Type 2 Diabetes: Genetics and Environment

People are born with the genetic risk for type 2 diabetes

Caused by:

1. A genetic inability of the tissues to respond normally to insulin (or insulin resistance); and
2. A genetic inability of the insulin producing cells to secrete enough insulin to overcome the insulin resistance.

Type 2 diabetes has many genetic causes

There is NO single genetic test to identify type 2 diabetes or individuals "at risk" for type 2 diabetes

The genetic risk for diabetes can be modified by environmental factors

Pro-Diabetes Factors:

- Obesity
- Sedentary life style
- Pro-diabetes medications
- Aging
- Other medical diagnoses

Anti-Diabetes Factors:

- Balanced diet
- Lean
- Active
- Anti-diabetes Rx

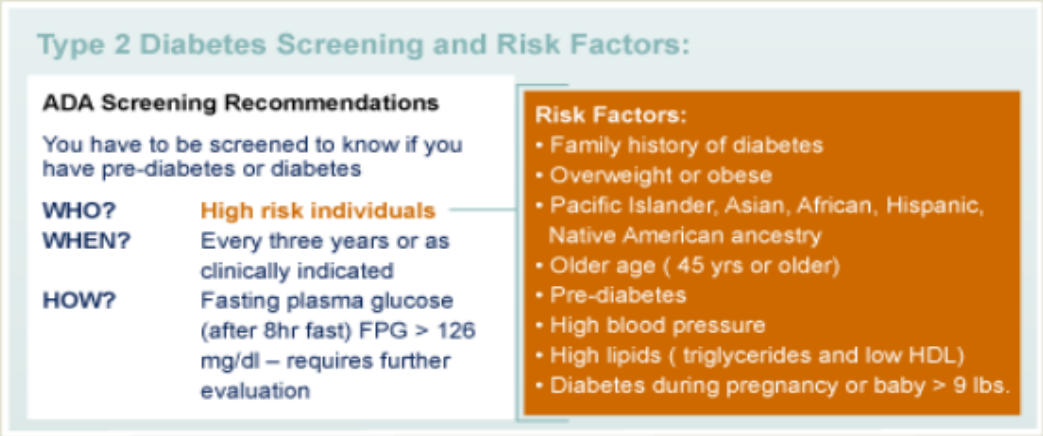
The progression from having a genetic predisposition to type 2 diabetes and the development of an elevated blood sugar or overt diabetes is affected by environmental factors

Development of type 2 diabetes

The development of type 2 diabetes is thought to be a progression from normal blood sugars to pre-diabetes to a diagnosis of overt diabetes. These stages are defined by blood sugar levels.

The timeline to developing an elevated blood sugar depends on many environmental factors (such as being overweight, physical activity, age, diet, illness, pregnancy, and medication) and also on how strong the gene traits are for diabetes. Ultimately, pre-diabetes and diabetes occur when the pancreas cannot make enough insulin to overcome the insulin resistance. Historically pre-diabetes and type 2 diabetes has been diagnosed when individuals are older;

however, because of a wide-spread epidemic of obesity which causes insulin resistance, the diagnosis of type 2 diabetes is occurring more frequently at younger and younger ages.

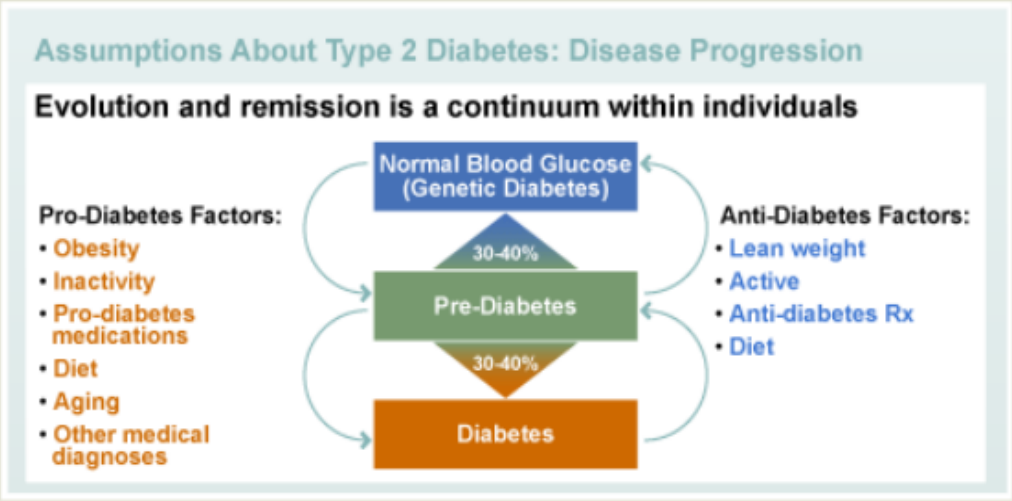


People born with the genetic traits for diabetes are considered to be pre-disposed. Genetically predisposed people may have normal blood sugar levels, but many will have other markers of insulin resistance such, as elevated triglycerides and hypertension. When environmental factors are introduced, such as weight gain, lack of physical activity, or pregnancy, they are likely to develop diabetes.

Some individuals with other types of diabetes may be misdiagnosed as having type 2 diabetes. Up to 10% of individuals who are initially diagnosed with type 2 diabetes may actually have an adult onset of type 1 diabetes also known as LADA or Latent Autoimmune Diabetes of Adults.

Pre-diabetes

Pre-diabetes is a stage between not having diabetes and having type 2 diabetes. You have pre-diabetes when your blood sugars are above normal, but not so high as to meet the diagnostic criteria for type 2 diabetes. One in three people with pre-diabetes will go on to develop type 2 diabetes; however, with the correct lifestyle changes, including exercise, weight loss, a healthy diet, and the correct medications, the odds decrease so that only one in nine pre-diabetic people develop type 2 diabetes. In some cases, your blood sugar levels can return to normal. However, even if blood sugar levels return to normal, the genetic risk for type 2 diabetes remains unchanged – you must continue positive lifestyle changes, and medication or risk the return of elevated blood sugar levels.



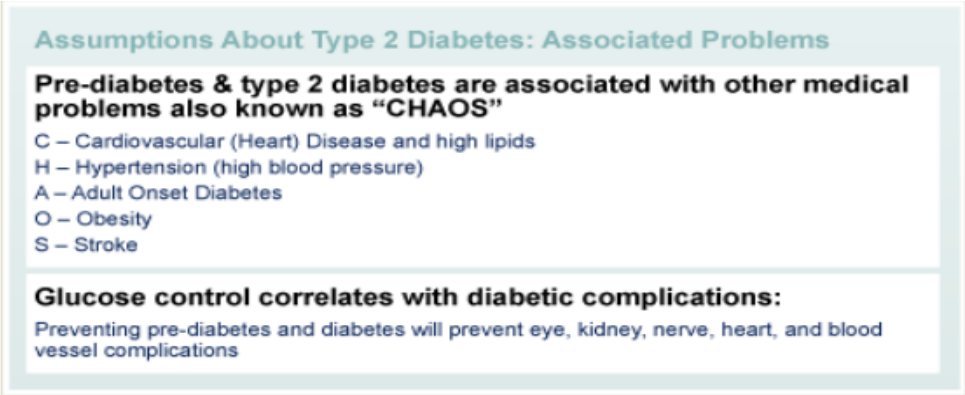
Is Type 2 diabetes increasing?

Type 2 diabetes is increasing at an epidemic rate, and is being diagnosed at younger and younger ages. The most likely reason for this increase is that individuals with a genetic susceptibility to type 2 diabetes are developing the disease due to lifestyle changes – namely less physical activity, weight gain, and longer life span.

Other conditions associated with type 2 diabetes

The insulin resistance syndrome

Individuals with type 2 diabetes are more likely to be diagnosed with other medical problems such as atherosclerosis, coronary artery disease, hypertension, obesity and dyslipidemia. Insulin resistance is thought to worsen and possibly directly cause these problems. The optimal medical care of type 2 diabetes includes not only controlling the blood glucose but also treating high blood pressure, high cholesterol or triglycerides, reducing excess weight and staying physically fit.



Gestational Diabetes

Gestational diabetes refers to diabetes diagnosed during pregnancy. About 4% of pregnant women will develop gestational diabetes.

Gestational diabetes requires specialized treatment for the rest of the pregnancy. After the pregnancy is over, most women will have normal blood sugars again; however, they remain at risk for diabetes. 20-50 % will be diagnosed with diabetes over the next 5-10 years and gestational diabetes is likely to recur during subsequent pregnancies.

What is Gestational Diabetes?

Pregnant women who have never had diabetes before but who have high blood glucose (sugar) levels during pregnancy are said to have gestational diabetes. According to a 2014 analysis by the Centers for Disease Control and Prevention, the prevalence of gestational diabetes is as high as 9.2%.

We don't know what causes gestational diabetes, but we have some clues. The placenta supports the baby as it grows. Hormones from the placenta help the baby develop. But these hormones also block the action of the mother's insulin in her body. This problem is called insulin resistance. Insulin resistance makes it hard for the mother's body to use insulin. She may need up to three times as much insulin.

Gestational diabetes starts when your body is not able to make and use all the insulin it needs for pregnancy. Without enough insulin, glucose cannot leave the blood and be changed to energy. Glucose builds up in the blood to high levels. This is called hyperglycemia. You may also be interested in our book, *Diabetes & Pregnancy: A Guide to a Healthy Pregnancy*.

How Gestational Diabetes Can Affect Your Baby

Gestational diabetes affects the mother in late pregnancy, after the baby's body has been formed, but while the baby is busy growing. Because of this, gestational diabetes does not cause the kinds of birth defects sometimes seen in babies whose mothers had diabetes before pregnancy.

However, untreated or poorly controlled gestational diabetes can hurt your baby. When you have gestational diabetes, your pancreas works overtime to produce insulin, but the insulin does not lower your blood glucose levels. Although insulin does not cross the placenta, glucose and other nutrients do. So extra blood glucose goes through the placenta, giving the baby high blood glucose levels. This causes the baby's pancreas to make extra insulin to get rid of the blood glucose. Since the baby is getting more energy than it needs to grow and develop, the extra energy is stored as fat.

This can lead to macrosomia, or a "fat" baby. Babies with macrosomia face health problems of their own, including damage to their shoulders during birth. Because of the extra insulin made by the baby's pancreas, newborns may have very low blood glucose levels at birth and are also at higher risk for breathing problems. Babies with excess insulin become children who are at risk for obesity and adults who are at risk for type 2 diabetes.

- See more at: http://www.diabetes.org/diabetes-basics/gestational/what-is-gestational-diabetes.html#sthash.TMuhnW7U.dpuf

How to Treat Gestational Diabetes

Because gestational diabetes can hurt mother and baby, **mother need to start treatment quickly**.

Treatment for gestational diabetes aims to keep blood glucose levels equal to those of pregnant women who don't have gestational diabetes. Treatment for gestational diabetes always includes **special meal plans and scheduled physical activity**. It may also include daily blood glucose testing and insulin injections.

If you're testing your blood glucose, the American Diabetes Association suggests the following targets for women who develop gestational diabetes during pregnancy. More or less stringent glycemic goals may be appropriate for each individual.

- Before a meal (preprandial): 95 mg/dl or less
- 1-hour after a meal (postprandial): 140 mg/dl or less
- 2-hours after a meal (postprandial): 120 mg/dl or less

You will need help from your doctor, nurse educator, and other members of your health care team so that your treatment for gestational diabetes can be changed as needed. For you as the mother-to-be, treatment for gestational diabetes helps **lower the risk of a cesarean section birth** that very large babies may require.

Sticking with your treatment for gestational diabetes will give you a healthy pregnancy and birth, and may help your baby avoid future poor health.

Etiologic classification of diabetes mellitus –based on American Diabetes Association criteria

I. Type 1 diabetes (ß-cell destruction, usually leading to absolute insulin deficiency)
   A. Immune mediated
   B. Idiopathic
II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
III. Other specific types
   A. Genetic defects of ß-cell function
      1. Chromosome 12, HNF-1∝ (MODY3)
      2. Chromosome 7, glucokinase (MODY2)
      3. Chromosome 20, HNF-4 (MODY1)
      4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
      5. Chromosome 17, HNF-1ß (MODY5)
      6. Chromosome 2, NeuroD1 (MODY6)
      7. Mitochondrial DNA
      8. Others
   B. Genetic defects in insulin action
      1. Type A insulin resistance
      2. Leprechaunism
      3. Rabson-Mendenhall syndrome
      4. Lipoatrophic diabetes
      5. Others
   C. Diseases of the exocrine pancreas
      1. Pancreatitis
      2. Trauma/pancreatectomy
      3. Neoplasia
      4. Cystic fibrosis
      5. Hemochromatosis
      6. Fibrocalculous pancreatopathy
      7. Others
   D. Endocrinopathies
      1. Acromegaly
      2. Cushing's syndrome
      3. Glucagonoma
      4. Pheochromocytoma
      5. Hyperthyroidism
      6. Somatostatinoma
      7. Aldosteronoma
      8. Others

E. Drug- or chemical-induced
   1. Vacor
   2. Pentamidine
   3. Nicotinic acid
   4. Glucocorticoids
   5. Thyroid hormone
   6. Diazoxide
   7. ß-adrenergic agonists
   8. Thiazides
   9. Dilantin
   10. ∝-Interferon
   11. Others

F. Infections
   1. Congenital rubella
   2. Cytomegalovirus
   3. Others

G. Uncommon forms of immune-mediated diabetes
   1. "Stiff-man" syndrome
   2. Anti–insulin receptor antibodies
   3. Others

H. Other genetic syndromes sometimes associated with diabetes
   1. Down's syndrome
   2. Klinefelter's syndrome
   3. Turner's syndrome
   4. Wolfram's syndrome
   5. Friedreich's ataxia
   6. Huntington's chorea
   7. Laurence-Moon-Biedl syndrome
   8. Myotonic dystrophy
   9. Porphyria
   10. Prader-Willi syndrome
   11. Others

IV. Gestational diabetes mellitus (GDM)

Patients with any form of diabetes may require insulin treatment at some stage of their disease. The use of insulin does not, of itself, classify the diabetes.

Common symptoms include:

- Unexplained weight loss
- Excessive thirst or hunger
- Fatigue
- Frequent urination
- Blurred vision
- Nausea and/or vomiting

The onset of these symptoms may be gradual or sudden. Generally over time, they persist to the point that the patient seeks medical advice. It is then that diabetes is diagnosed.