5.6.2

Diabetes Mellitus

Diabetes Mellitus is a group of metabolic diseases characterized by high blood glucose. The high blood glucose is a result of the absence or not enough insulin or because cells do not respond to the insulin produced. Left untreated, diabetes can cause both acute (ketoacidosis -acidic blood pH) and chronic complications (cardiovascular disease, renal failure, blindness, infections, and nerve damage). There are three main types of diabetes mellitus: Type 1, Type 2, and gestational diabetes.

Diabetes Type I

Type 1 diabetes mellitus is the result of the loss of beta cells leading to severe insulin deficiency. Beta cell loss is caused by a T-cell-mediated autoimmune attack for reasons that are not yet understood. However, genetics and environmental factors appear to play definite roles. It is interesting to note that if one identical twin gets diabetes type I, the other twin will only get it about 50% of the time. This suggests that while genes are important, environmental factors have just as important of a role. Environmental factors probably “trigger” diabetes in genetically susceptible individuals. For example, scientists have shown that humans can experience as much as a 10 fold increase in the risk of diabetes type I just by moving to a different area that has a documented higher incidence of the disease. Perhaps it is diet. Some controversial claims suggest that wheat and wheat products can increase the risk of diabetes type I. Dairy milk (particularly the milk proteins) have also been blamed. The theory is that these dietary proteins are handled in the gut by bacteria that result in the production of antigens that look like beta cell antigens. The result is the production of antibodies and that accidental attack of beta cells. Lack of Vitamin D has also been blamed for development of the disease. Vitamin D is very important for proper and healthy immune function and a lack of Vitamin D can be associated with a host of abnormal immune responses. Viruses have also been blamed as triggering agents for the onset of diabetes type I. This theory suggests that certain viral diseases may stimulate a flurry of antibody production and in some cases these antibodies may accidentally attack beta cells. Studies that look at these type of environmental risk factors are usually correlative and lack the ability to show cause and effect. Thus, the actual contribution of environmental risk factors to diabetes type I risk is frequently controversial.

Type 1 diabetes accounts for about 10% of all cases of diabetes mellitus and usually affects the individual before 14 years of age. Even though the blood glucose levels are extremely high, without insulin, many cells cannot access the glucose, and as a result, they send signals requesting more glucose. Ironically, other hormones are released (cortisol, glucagon, epinephrine) in response to the signals requesting more glucose, which worsens the situation. If the body "thinks" that it doesn't have enough glucose then it breaks down other substances (proteins or lipids) to provide substrates for glucose production (gluconeogenesis). With an increase in substrates, the liver frantically works to convert them to glucose, and over time, the increased load overwhelms the liver enzymes and bi-products such as ketone bodies begin to accumulate. Ketone bodies re-enter the circulation and can create a condition called ketoacidosis (low blood pH). The constant breakdown of fats and proteins results in profound weight loss or wasting.

Acute symptoms include (*Note: these symptoms are manifested in both type I and II diabetics but type II is more chronic and takes longer to develop).

- **Polyuria** - (excessive urine production) because the increased plasma glucose exceeds the renal threshold for glucose reabsorption (kidney module)
- **Polydipsia** - (excessive thirst and drinking of water) due to the dehydration from excessive urine production
- **Polyphagia** - (excessive eating) due to the inability of the body's cells to utilize the nutrients in the blood.

- **Blurred vision** - The excess glucose in the extracellular fluids makes them hypertonic. In the lens of the eye this results in edema, an increase in extracellular fluid volume, and the lens swells. This swelling results in the blurred vision.
- **Fatigue** - If the glucose isn't able to enter the cells there isn't as much raw material to fuel the processes that make ATP. If the muscles cells can't produce sufficient amounts of ATP they will not be able to function properly resulting in fatigue.
- **Hypoglycemia** - With diabetics the most common cause of hypoglycemia is either taking too much insulin or taking insulin and then not eating enough.
- **Diabetic Ketoacidosis** - Diabetic Ketoacidosis (DKA) is a severe, acute complication of Diabetes. About 30% of the time an episode of DKA is the first sign that someone has type 1 diabetes. Although the condition can be easily prevented the occurrence is approximately 4.6-8 cases per 1000 type 1 diabetics annually.
    - **Cause**: Recall that when blood glucose levels are low several hormones are released to bring the levels back to normal. One of these hormones is glucagon. Glucagon raises blood sugar levels by stimulating the breakdown of glycogen to glucose in the liver. Another of its actions is to stimulate the oxidation of fatty acids in the liver to produce ATP. If those fatty acids are fully oxidized abundant ATP is produced. However, if they are only partially oxidized ketone bodies are produced. This process is called ketogenesis and provides an important role in healthy individuals. The neurons of the brain cannot metabolize fatty acids to make ATP but they can utilize ketone bodies for energy production. Therefore, when blood glucose levels are low the liver, under the direction of glucagon, partially oxidizes fatty acids to produce ketone bodies in order to supply energy to the cells of the nervous system. In healthy individual's low secretion of insulin moderates the actions of glucagon by inhibiting its secretion thus preventing production of large quantities of ketone bodies. Since type 1 diabetics do not produce any insulin there is nothing to keep glucagon in check, thus making them much more likely to develop DKA. With type 1 diabetics the usual cause of DKA is insufficient administration of insulin, triggering ketogenesis and hyperglycemia which leads to polyuria and dehydration.
- **Hyperglycemic, hyperosmotic, nonketotic coma (HHNC)** - Those at risk for this complication are typically elderly patients who are experiencing some other major medical event. The onset is slower than with DKA and the mortality rate is much higher (up to 15%). As the name implies, this condition is associated with hyperglycemia (blood glucose levels as high as 600-1200 g/dl) and hyperosmolarity of the extracellular fluids. HHNC is usually brought on by some major medical event such as a heart attack, stroke, an infection, or another acute illness. Because of the severity of the precipitating condition, HHNC often goes undiagnosed until it has progressed to a critical stage. The relative insulin deficiency with inadequate fluid intake seems to be the underlying causes of HHNC. Blood glucose levels are very high, 600-1200 g/dl, resulting in polyuria and dehydration. HHNC is more common in Type II diabetics (see below).

Chronic symptoms include:

- **Microvascular diseases** - Microvascular diseases associated with diabetes include **retinopathy**, **nephropathy**, and **neuropathy**. These diseases arise from the injury or destruction of small vessels and nervous tissue. In chronic hyperglycemia, some of the excess glucose combines with amino acids on circulating or tissue proteins. This process is called glycosylation. This process initially forms reversible early glycosylation products and later irreversible advanced glycosylation end products (AGEs). The formation and accumulation of AGEs leads to increased vessels permeability, procoagulant activity, and vasoconstriction. These results can, in turn, lead to the destruction of the microvascular structure or peripheral nervous tissue. This destruction may occur in the retina, kidneys, and the peripheral nervous system.
- **Macrovascular diseases** - The marcovascular systems consists of vessels that carry larger amounts of blood to and from major organs. These vessels are found in the heart (coronary arteries), the brain (cerebral arteries), and in the arms and legs (peripheral arteries). Alteration of the macrovascular structure can lead to life-threatening events such as stroke, myocardial infarction, and peripheral arterial disease. Diabetics are at increased risk for these life-threatening events because of macrovascular complications associated with diabetes. Diabetic arteriopathy (disease of the arteries) is a form of macrovascular disease that encompasses endothelial dysfunction, changes in blood flow, hypercoagulability (procoagulant activity), and platelet abnormalities. Each of these factors place the diabetic patient at increased risk for major, life-threatening cardiovascular events. As previously mentioned, AGEs are produced in patients with long-standing hyperglycemia. These AGEs increase the vessel's permeability, and in this increased permeability state, is more susceptible to accumulation of low density lipoproteins within the vessel wall. This accumulation will lead to fatty streaks and eventually plaque formation within the arterial wall. In addition to the increased permeability of the vessel, AGEs will also decrease the vessel's ability to dilate, placing the vessel in a fixed stage of vasoconstriction. These results alone will put the diabetic patient at an increased risk for a critical macrovascular event.
- **Hypercoagulability, Procoagulant Activity, and Platelet Abnormalities -** Due to accumulation of AGEs, platelets act inappropriately to increase hypercoagulability. This increased platelet activity increases the patient's risk of thrombus (clot) formation ultimately putting the patient at risk for critical, life-threatening events such as a myocardial infarction or cerebral vascular accident. If this hypercoagulable state leads to thrombus formation, these blood clots can be broken off it's original location and travel through the circulatory system. This 'traveling clot is considered an embolus. If the embolus lodges in a vessel, and obstructs the vessel, the patient suffers an embolism. Due to these macrovascular complications, there is indisputable evidence that diabetes increases one's risk of cardiovascular and cerebrovascular events. Cardiovascular disease is listed as a cause of death in approximately 65% of those with diabetes, and as expected, those with diabetes have a higher risk of atherosclerotic disease and worse prognosis when compared to non-diabetic patients. Diabetic patients 45-74 were found to have a two-fold increased death from cardiovascular disease and a two- to three-fold increase in stroke.

Treatment of type 1 diabetes is administration of insulin either by injection or via an indwelling catheter. If not treated, type 1 diabetes results in death.

Diabetes Type II

The history of diabetes type II does not really start until the 1930s. It was not until diabetes type I began to be treated that doctors realized some people suffered high blood sugars with intact beta cells and plenty of insulin production. Some people seemed to have a problem with insulin sensitivity, not insulin quantity. This development of insulin insensitivity is usually slow and is usually found in adults rather than children. This disease is called **Diabetes Mellitus Type II**. It is also referred to as "adult onset diabetes" or "non-insulin dependent diabetes". Even though there is enough insulin, the insensitivity to the insulin creates a "relative" deficiency. The fat and muscle cells do not become permeable enough to glucose and blood sugars rise. Type II diabetes is NOT an autoimmune disease. There are no antibodies found to be directed toward the selective destruction of beta cells. Genetics does play an important role in this disease. However, it is not really possible to narrow the genetic problem down to one or two genes. There are likely a dozen or more genes that play a role in risk determination for this disease. Those with type II diabetes in their family have a much higher risk of developing the disease themselves. Identical twin studies show that if one twin gets the disease,

the other twin will get it 75% or more of the time. Our American Indian population suffers from very high incidences of diabetes type II (as much as double the incidence compared to other Americans). The theory is that Indian ancestors survived longer and were able to pass on genes that were highly efficient for glucose metabolism. The modern diet, high in sugar may be the environmental trigger to bring on diabetes type II in this genetically pre-disposed population. It appears that while there are certainly genes that can bias or predispose a person to becoming diabetic as an adult, we believe that it frequently requires an environmental trigger to fully manifest the disease.

Obesity, smoking, drinking, poor diet and lack of exercise are at the top of the list for triggering the onset of diabetes type II. Individually, each risk factor correlates with the development of diabetes, but the accumulative effect of more than one risk factor is thought to have a very large contribution to the onset of new diabetic cases each year. It is hard to ignore studies like the one done by Mozaffarian et al., 2009. This group suggested that the accumulated risk in life choices could increase the chance of new diabetes onset by more than 80%. Another study by Vasanti et al., 2010, suggested that sugary drinks could trigger diabetes in susceptible individuals and they mentioned that some appeared to get the disease even without any documented weight gain! Moreover, there are studies where people were sleep deprived and the results showed a profound insulin resistance in just a week of sleep deprivation https://pubmed.ncbi.nlm.nih.gov/10543671/.

Lack of enough exercise is another environmental factor that has a powerful impact to trigger diabetes type II. Exercise often proves to be a more powerful prevention of diabetes than even sugar lowering drugs.

Consider the top 10 reasons given to diabetic patients to exercise by the American Diabetes Association.

1. Improve blood glucose management. Activity makes your body more sensitive to the insulin you make. Activity also burns glucose (calories). Both actions lower blood glucose.
2. Lower blood pressure. Activity helps your heart pump stronger and slower.
3. Improve blood fats. Exercise can raise good cholesterol (HDL) and lower bad cholesterol (LDL) and triglycerides. These changes are heart healthy.
4. Take less insulin or diabetes pills. Activity can lower blood glucose and weight. Both of these may lower how much insulin or diabetes pills you need to take.
5. Lose weight and keep it off. Activity burns calories. If you burn enough calories, you'll trim a few pounds. Stay active and you'll keep the weight off.
6. Lower risk for other health problems. Reduce your risk of a heart attack or stroke, some cancers, and bone loss.
7. Gain more energy and sleep better. You'll get better sleep in less time and have more energy, too.
8. Reduce stress, anxiety, and depression. Work out or walk off daily stress.
9. Build stronger bones and muscles. Weight-bearing activities, such as walking, make bones stronger. Strength-training activities, such as lifting light weights (or even cans of beans), make muscles strong.
10. Be more flexible. Move easier when you are active.

The American Diabetes Association also recommends that diabetic patients get 150 minutes per week of moderate – to-vigorous aerobic exercise spread out across at least three days with no more than 2 consecutive days between bouts.

Sometimes the disease has advanced far enough that diet and exercise cannot control high blood sugars. In these cases, treatment will normally involve the use of medication. The physician will discuss medication choices with their patient and decide on one or more of the following options.

1. **Sulfonylureas**. Drugs that stimulate the beta cells to release more insulin. Glucotrol is the name of a common drug that does this. Stimulating the beta cells to release more insulin can help control blood sugar, but insulin sensitivity does not necessarily improve and may get worse.
2. **Biguanides**. Drugs that lower the amount of glucose produced by the liver. Metformin (Glucophage) is a name of a common drug that does this by inhibting complex I in the mitochondrial electron transport chain. Metformin is also commonly used because it appears to increase insulin sensitivity as well although the mechanism for how it does this is not clearly understood.
3. **Thiazolidinediones**. Drugs that increase sensitivity of fat and muscle cells to the actions of insulin. Avandia is a common name for a drug that does this. If the insulin receptors are more sensitive then there is likely to be a larger response of GLUT 4 channel exocytosis which will result in more sugar leaving the blood.
4. **Glucosidase Inhibitors**. Drugs that block the breakdown of sugars in the intestinal tract. Acarbose is a common name in this class of drug. If the gut is restricted from breaking sugars down to the monomeric form, absorption into the blood is inhibited. This helps decrease blood sugars from ingested food, but has the side effect of intestinal discomfort as the extra sugar allows for abnormal bacterial growth and metabolism in the digestive tract (think bloating , gas and pain).
5. **DPP-4 Inhibitors**. Drugs that block the enzymatic destruction of GLP-1. Januvia is the name of a common drug that does this. GLP-1 (Glucagon-Like Peptide-1) is a hormone produced in the gut that increases insulin release and inhibits glucagon release. The ability to inhibit the destruction of GLP-1 causes a potent antihyperglycemic effect. These drugs are still pretty new and long term effects of these drugs are not well known.

Gestational Diabetes

Gestational Diabetes (GDM) occurs in pregnant women (thus the name gestational). Nearly 18% of the time, previously non-diabetic women can have a sudden onset of high blood sugars during their pregnancy. The condition appears to be a problem of either insufficient insulin release or insufficient insulin sensitivity. Usually, it is the latter and so Gestational Diabetes presents clinically much like diabetes type II. However, Gestational Diabetes is temporary and the glucose control problems normally clear up after delivery. Rarely, the diabetic symptoms remain after delivery and the woman is diagnosed with an onset of diabetes type II (probably triggered by the pregnancy).

It would make sense to ask “what, really, is the difference between Gestational Diabetes and diabetes type II. The answer to this is the cause of the insulin insensitivity. In diabetes type II, the insulin insensitivity appears to be a result of complex metabolic interactions. Adipose tissue, poor diet and lack of activity appear to interact poorly with hormonal regulatory mechanisms that control cellular metabolism. In Gestation Diabetes, the metabolic problems come from the interactions of the hormones of pregnancy. Several placental hormones appear to affect metabolism in ways that decrease insulin sensitivity. Up to a point, this is actually a normal thing and even helpful to a developing fetus as more sugar would become available in the mother’s blood to feed the growing tissues of the baby. However, there is a threshold at which increased blood sugar in the mother becomes excessive and actually damages healthy growth processes of the fetus rather than benefit it. Therefore, a mother who responds in excessive ways to the hormones of pregnancy can experience diabetic problems until the pregnancy is concluded. We know that this tendency to over-react to pregnancy hormones can be influenced by certain genes. Several genes have been identified that increase risk of this condition if they are inherited. So, the chances that a woman will suffer Gestational Diabetes are certainly higher if any of her immediate family members suffered the condition.

It is thought that many women have some genetic bias to lose control of blood sugar regulation, but the manifestation of this problem only surfaces when this genetic bias meets poor life choices. Lack of exercise, poor diet, and obesity have all been shown to increase the chances of Gestational Diabetes onset. One recent and interesting study showed that more than 4 servings of sugar sweetened cola per week resulted in a 22% increase in the risk of developing Gestational Diabetes. A woman may not know what genes she was born with and she may not be aware of how her body will respond to the hormones of pregnancy, but the following are reasons that would seem to make ANY woman wanting to try hard make good life choices to minimize the chances of Gestational Diabetes onset.

- A woman who experiences Gestational Diabetes has a higher risk of acquiring Diabetes Type II later in life.
- A woman who experiences Gestational Diabetes has a higher risk of complications during pregnancy including health damage to the baby
- A woman who experiences Gestational Diabetes has a much higher risk of Gestational Diabetes again with future children.
- A child who is born from a mother who suffered Gestational Diabetes has a higher risk of being overweight and acquiring Diabetes Type II later in life.
- A female child who is born from a mother who suffered Gestational Diabetes has a higher risk of Gestational Diabetes onset when she herself gets pregnant.
- Studies show that there is an increased prevalence of Diabetes Type I among offspring of mothers who suffered Gestational Diabetes.

If a woman is diagnosed with Gestational Diabetes during her pregnancy, she should work closely with her doctor to use diet, exercise, and medication if necessary to control blood sugar. The complications of Gestational Diabetes are greatly reduced if blood sugars can be controlled during the pregnancy.

Diabetes Insipidus

There is one other type of diabetes. It is called Diabetes Insipidus. Other than the name, this condition has very little in common with the other types of diabetes. This condition occurs when the kidneys are unable to conserve water. Normally, the conservation of water in our kidneys is regulated by a hormone Anti Diuretic Hormone (ADH). If the Kidney fails to respond to ADH or if ADH fails to be released in sufficient quantities, the quantity of water in the urine will increase and cause polyuria. The progressive loss of water in the urine will of course lead to polydipsia. These symptoms are similar to the symptoms seen in other types of Diabetes but the cause is very different. Diabetes Insipidus will not be a focus of this class as it is not dependent on any metabolic problems and sugar regulation is not a part of this disease. Life style choice has very little impact on the onset of this condition.