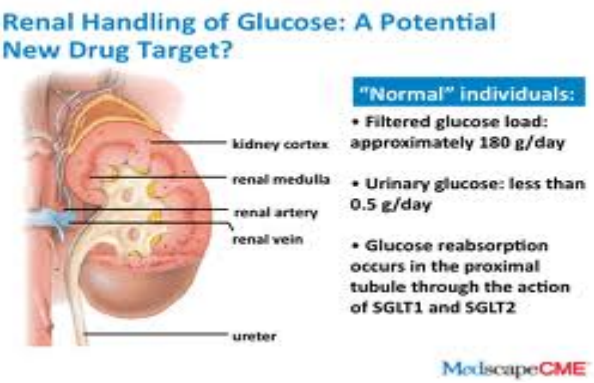
Module 15 – Drugs to Treat Diabetes

15.1 – Introduction to Diabetes

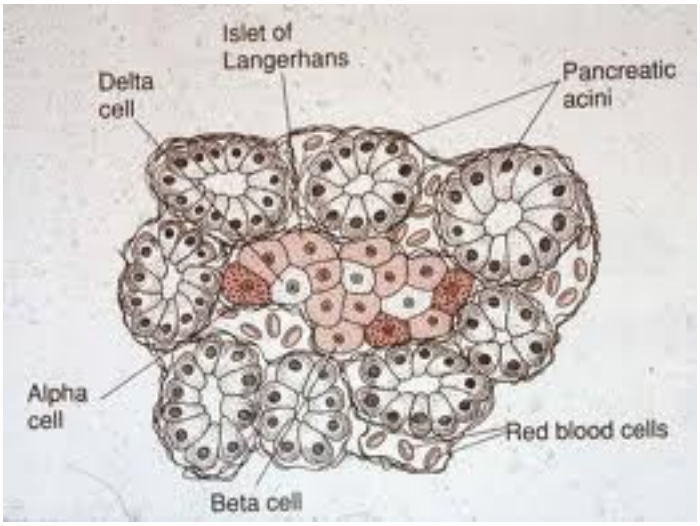
- Diabetes is a chronic disease characterized by elevated blood levels of glucose (i.e. sugar).
- Normally glucose is efficiently reabsorbed in the proximal tubule of the kidney so it is not found in the urine.
- In untreated diabetes, blood glucose rises so high that the transporters that reabsorb it are saturated and significant amounts of glucose are found in the urine.



- In fact, many years ago diabetes was diagnosed by the sweet smell AND TASTE of the urine!

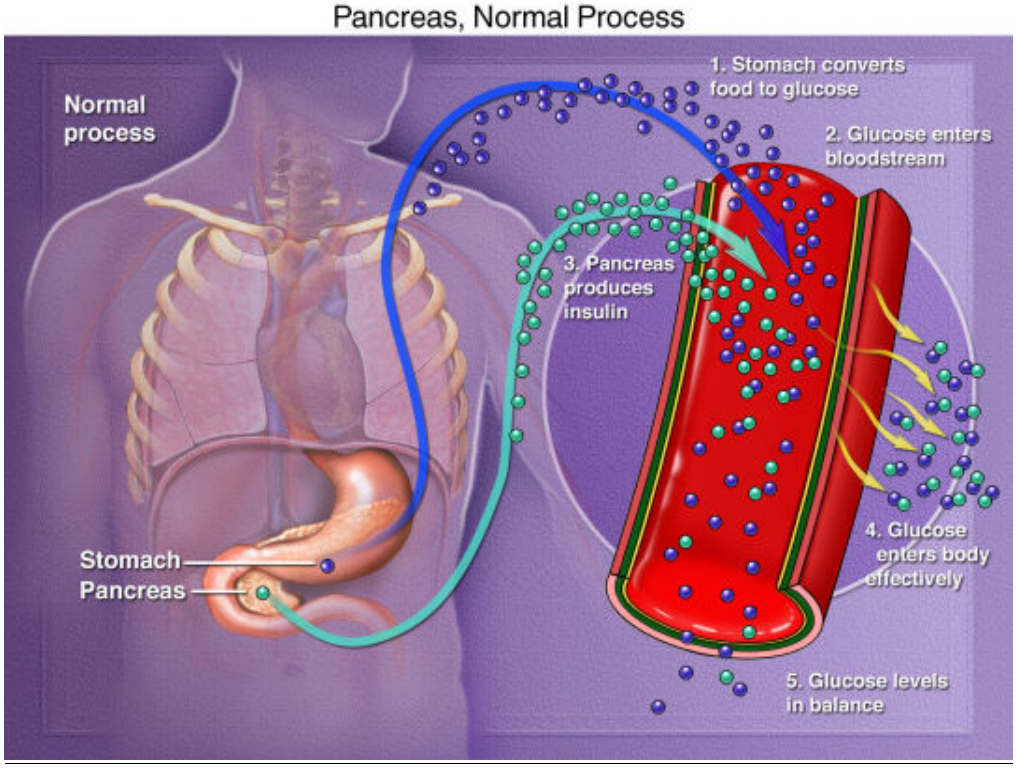
- High blood sugar in diabetes results from <u>either</u> not enough insulin produced in the body or because the body's cells do not respond to the insulin that is produced.
- The classic symptoms of diabetes are polyuria (increased urination), polydipsia (increased thirst), polyphagia (increased hunger) and weight loss.
- Insulin is a hormone produced by the pancreas that is involved in tightly regulating blood glucose.
- Diabetes occurs when insulin levels are too low or when the body's cells are resistant to the effects of insulin.

Insulin: The basics



- Insulin is a peptide hormone synthesized by the β (beta) cells of the islets of Langerhans of the pancreas.
- Insulin is rapidly released from the pancreas into the blood in response to increases in blood glucose.
- When insulin is secreted, it causes glucose uptake into muscle, liver, and fat cells.
- In liver cells, glucose uptake results in glycogen synthesis (*a storage form of glucose*).
- In muscle cells, glucose is used as energy and promotes protein synthesis.
- In fat cells, insulin causes increased synthesis of fatty acids, which results in increased triglyceride synthesis.
- Extracellular potassium is important in the action of insulin as it helps insulin to drive glucose into the cell.

The Healthy Pancreas



15.2 – Types of Diabetes

- Diabetes can be classified into one of three distinct groups:

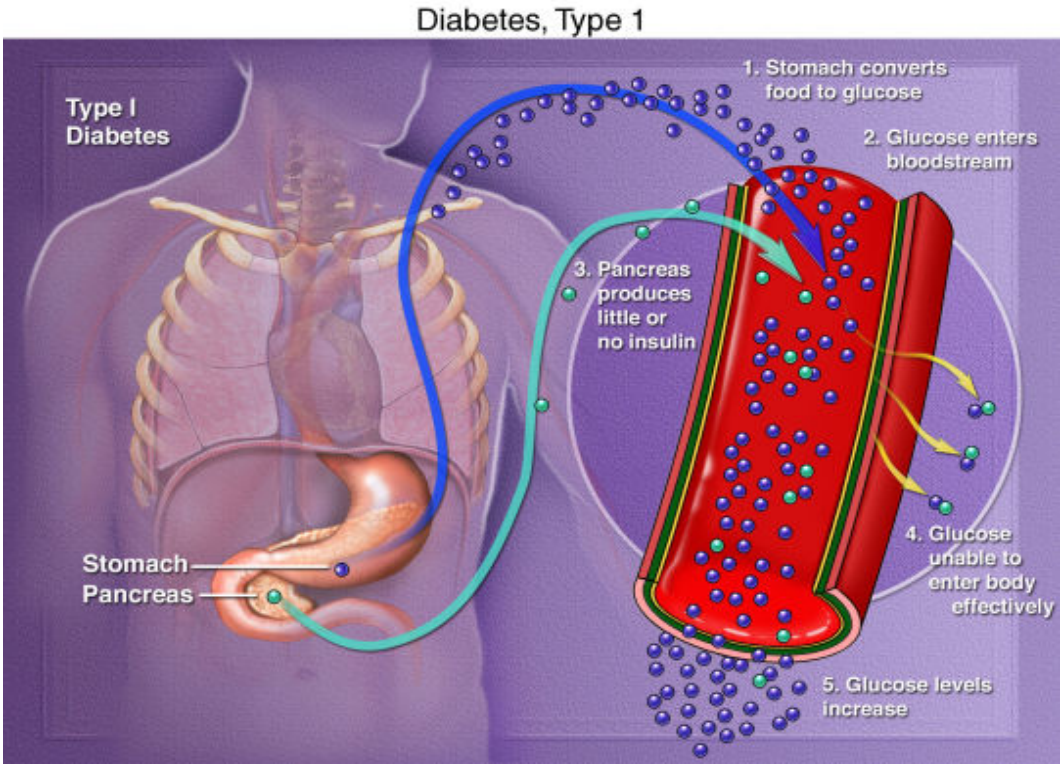
  1. **Type I diabetes** – Also called insulin dependent diabetes mellitus.

  2. **Type II diabetes** – Also called non-insulin dependent diabetes mellitus.

  3. **Gestational diabetes** – Diabetes that occurs in pregnancy.

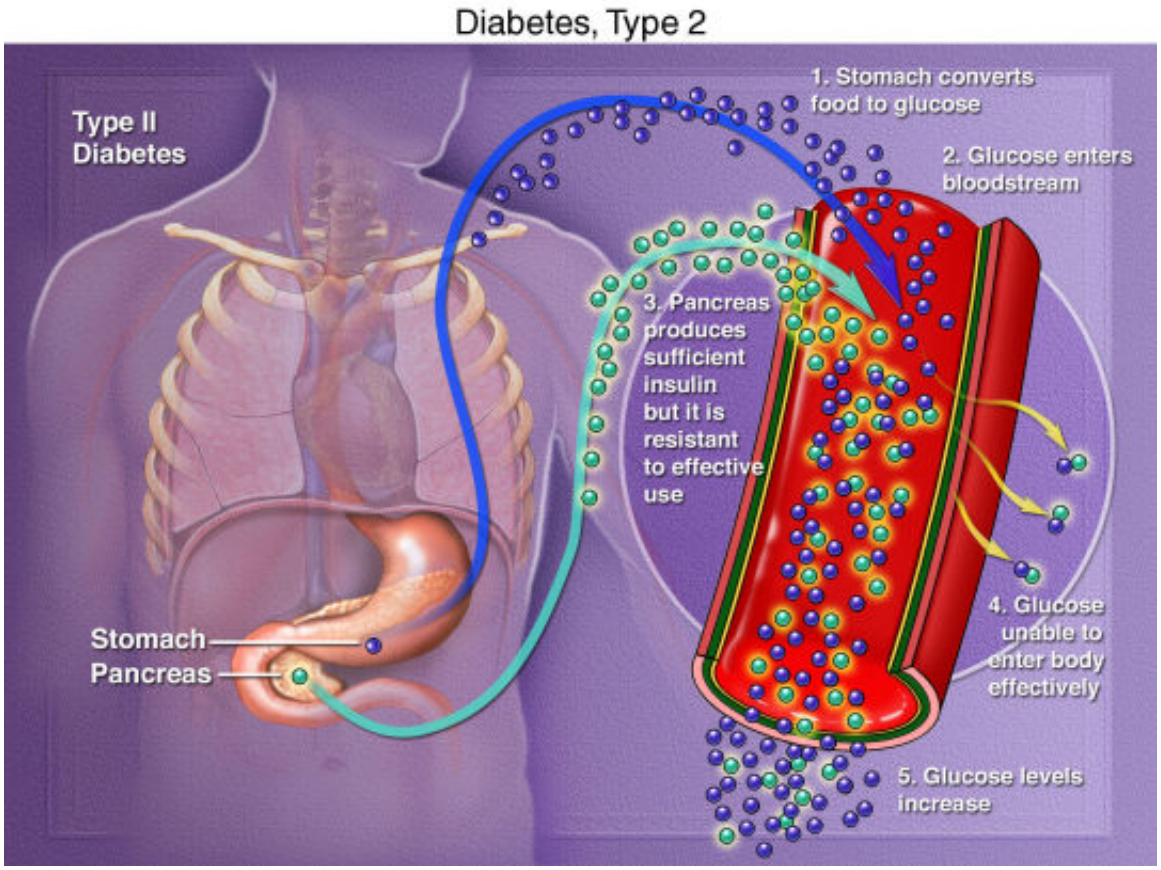
Type I Diabetes

- Approximately 10% of diabetics have type I diabetes.
- Type I diabetes is usually diagnosed in children or adolescents but symptoms may not appear until early adulthood.
- Type I diabetes is caused by an autoimmune reaction where the body's own immune cells attack and destroy the insulin secreting β cells.
- As a result, the body makes **too little or no insulin** at all and requires insulin replacement.
- Type I diabetes is not preventable and it is not caused by eating too much sugar.

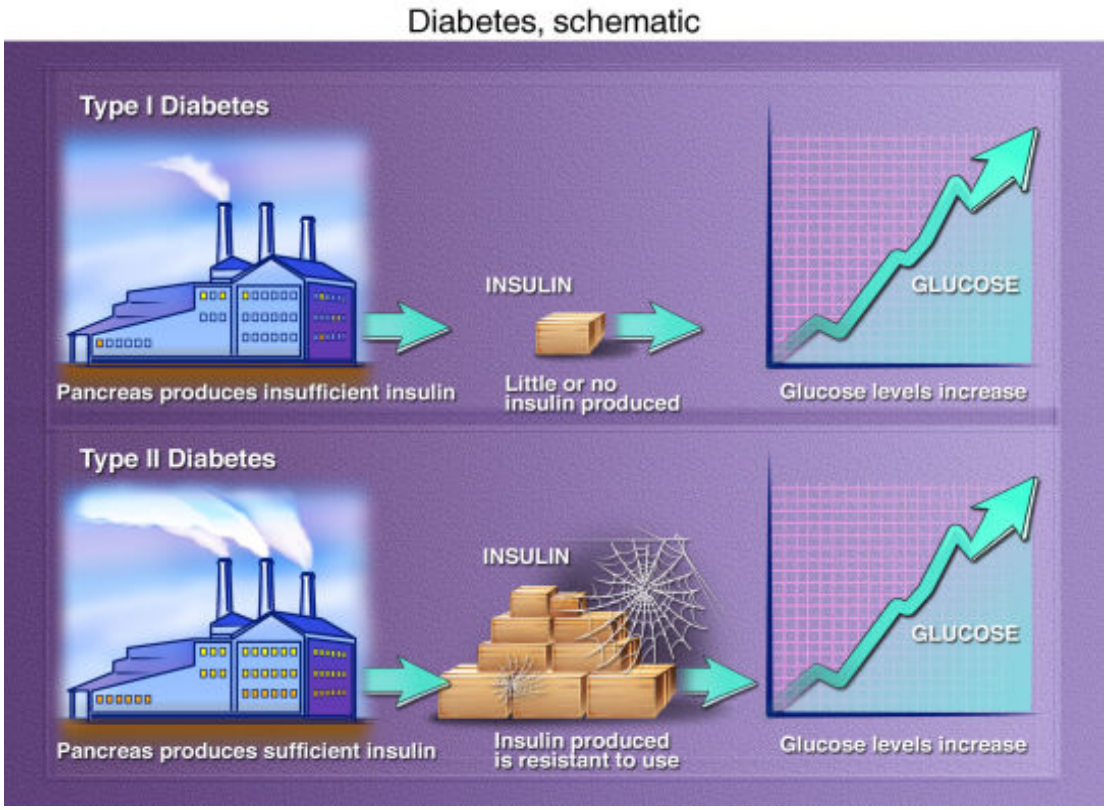


Type II Diabetes

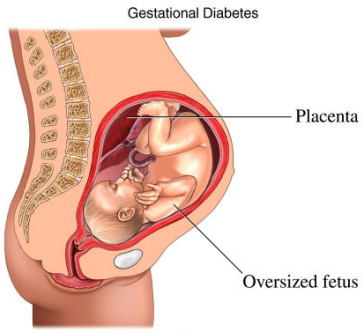
- Approximately 90% of all diabetics have type II diabetes.
- In type II diabetes the pancreas makes sufficient insulin, however, the **insulin produced is resistant to use**.
- Over the course of the disease, insulin synthesis may also decrease.
- There are many risk factors for developing type II diabetes including age, having a family member with diabetes, previous gestational diabetes, lack of exercise, heart disease, obesity, ethnicity (African and Native descent are at higher risk).
- It is important to note that in Canada, ~ 80% of all patients with type II diabetes are obese or overweight.
- Type II diabetes was typically diagnosed later in life but there is a trend towards younger people getting the disease.



Summary: Type I vs. Type II Diabetes

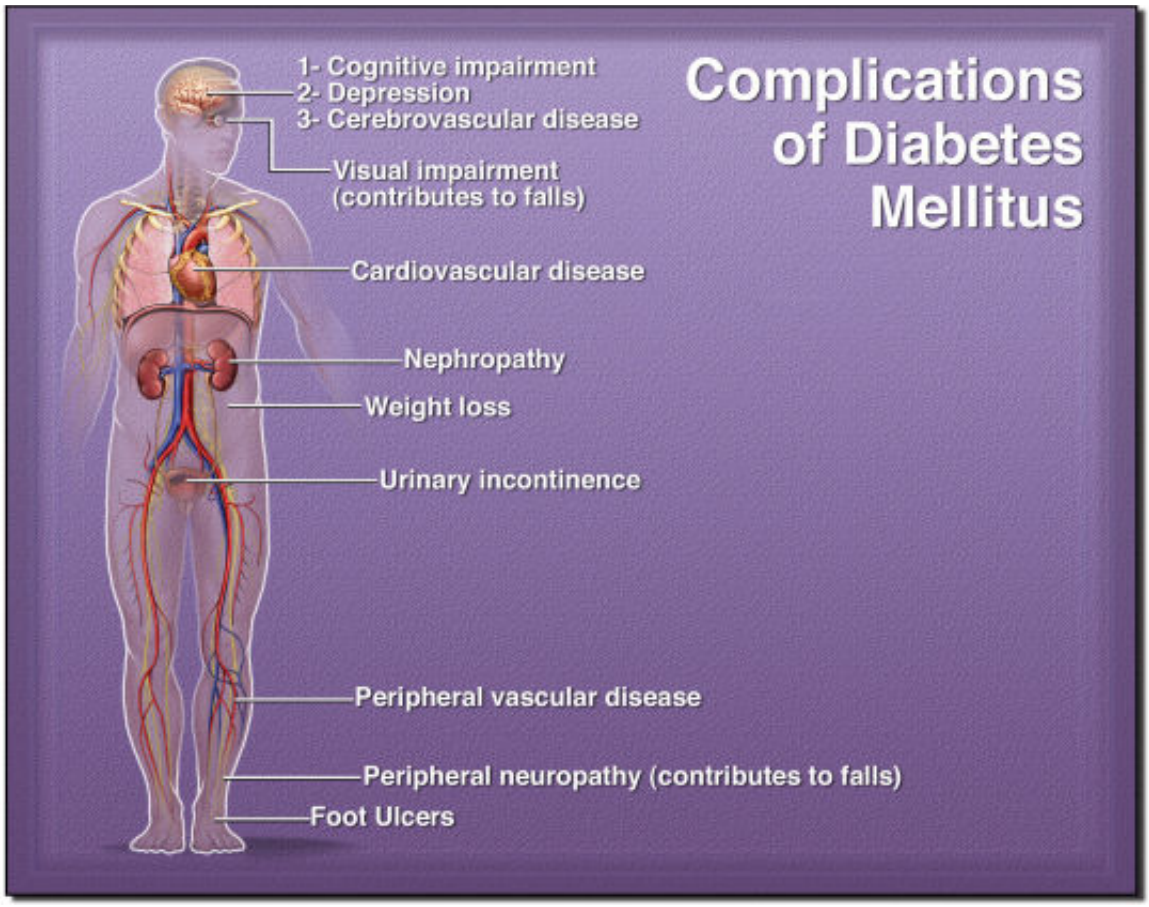


Gestational Diabetes



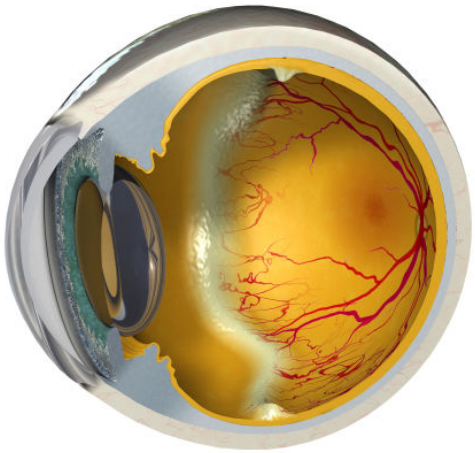
- Gestational diabetes is diabetes that first starts during pregnancy.
- Usually begins ~ halfway through pregnancy.
- All women should have an oral glucose tolerance test between weeks 24-28 of pregnancy to test for gestational diabetes.
- Usually diet and exercise are sufficient to keep blood glucose levels within normal ranges.
- Pregnant women with gestational diabetes tend to have larger babies and babies with hypoglycemia in the first few days of life.
- After birth, the blood sugar of the mother usually returns to normal however; blood glucose should be continually monitored as many patients develop diabetes 5 – 10 years later.

15.3 – Complications and Diagnosis of Diabetes



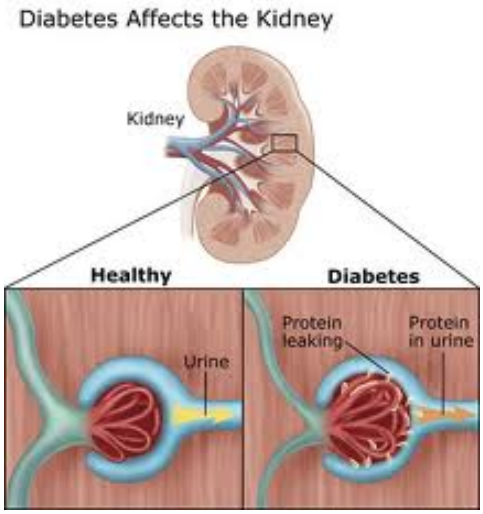
Diabetic Retinopathy

- Diabetic retinopathy is the most common cause of blindness in people under the age of 65.
- Hyperglycemia causes damage to retinal capillaries.
- Tightly controlling blood sugar minimizes the risk of retinopathy.
- Patients with type I or type II diabetes should have an eye exam once a year.



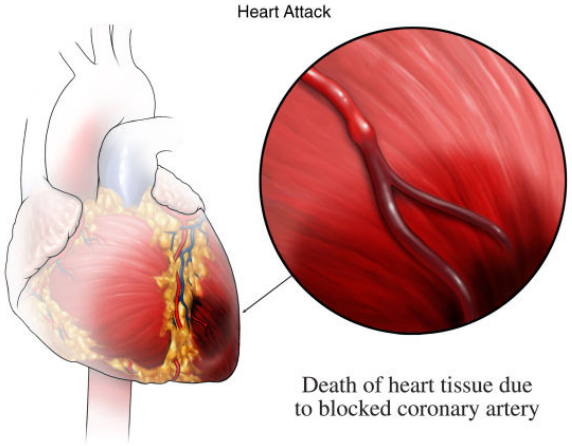
Diabetic Nephropathy

- Diabetic nephropathy is characterized by proteinuria (protein in the urine), decreased glomerular filtration and increased blood pressure.
- Proteinuria is the earliest sign of diabetic nephropathy.
- Diabetic nephropathy is the leading cause of morbidity and mortality in patients with type I diabetes.
- Tight control of blood glucose both delays and reduces the severity of diabetic nephropathy.
- ACE inhibitors and ARBs are useful in preventing diabetic nephropathy. Experts suggest patients with type I diabetes take an ACE inhibitor or ARB regardless of their blood pressure.



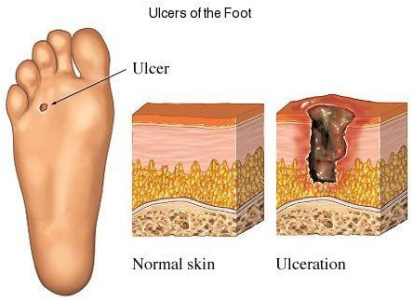
Cardiovascular Disease (CVD)

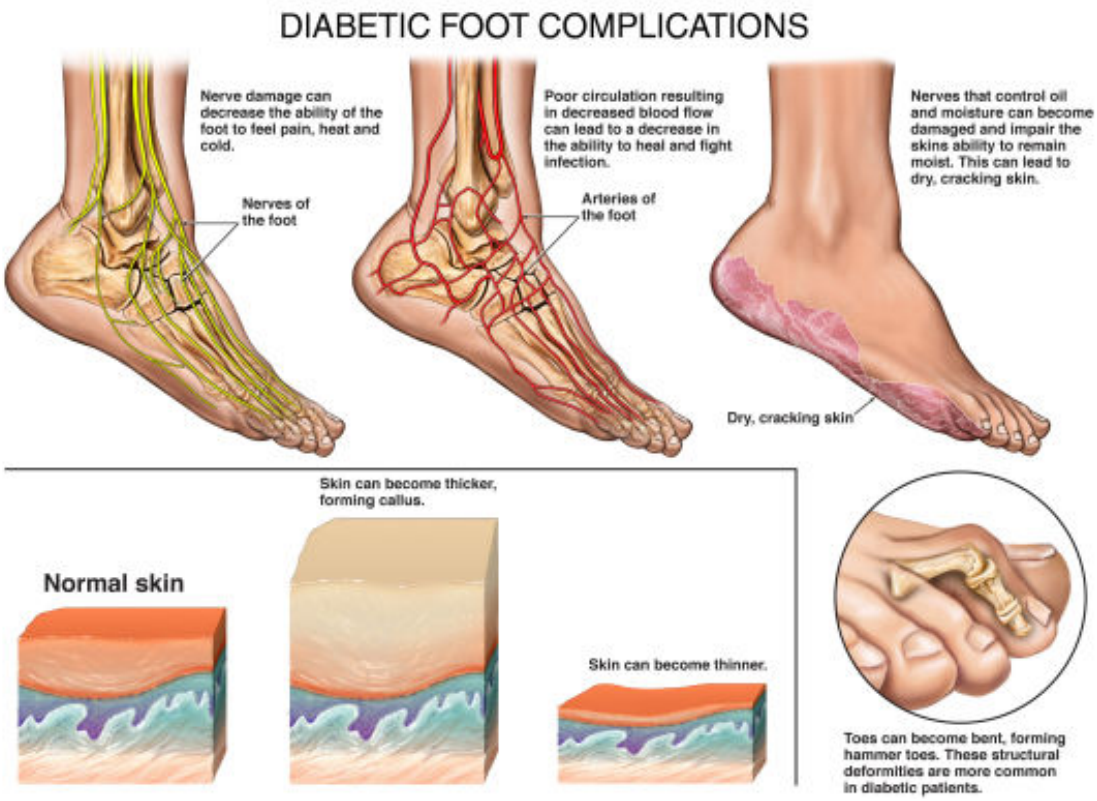
- CVD including heart attack and stroke are the leading causes of morbidity and mortality in type II diabetics.
- Atherosclerosis develops much earlier in diabetic patients than in non-diabetics.
- CVD in diabetes results from a combination of hyperglycemia and altered lipid metabolism.
- Statins reduce cardiovascular events in diabetic patients, regardless of their LDL cholesterol levels.



Diabetic Foot Ulcers

- Are the most common cause of hospitalization for diabetic patients.
- Diabetes accounts for approximately half of all lower limb amputations every year due to infection.
- All diabetic patients should have regular foot exams.





Diagnosis of Diabetes

- Diabetes is diagnosed when plasma glucose levels are elevated.
- There are three tests used to diagnose diabetes:

1. Fasting Plasma Glucose Test
2. Casual Plasma Glucose Test
3. Oral Glucose Tolerance Test (OGTT)

1. Fasting Plasma Glucose Test

- Patients fast for at least 8 hours and then have a blood sample drawn to measure blood glucose.
- If the fasting plasma glucose is $\geq$ 7.0 mmol/L then diabetes is diagnosed.
- The fasting plasma glucose test is the preferred test for diagnosing diabetes.

2. Casual Plasma Glucose Test

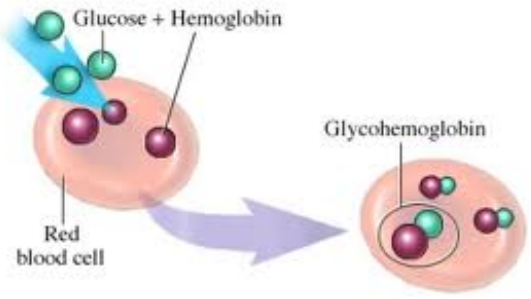
- Blood can be drawn at any time no matter what the interval was since the last meal.
- For a diagnosis of diabetes, the casual plasma glucose is $\geq$ 11.1 mmol/L AND the patient displays classic signs of diabetes including polyuria, polydipsia and weight loss.
- If an initial casual plasma glucose test suggests diabetes, it is often followed up by a fasting plasma glucose test.

3. Oral Glucose Tolerance Test (OGTT)

- This test is used when the other tests are unable to definitively diagnose diabetes.
- Patients are given an oral 75 gram dose of glucose and plasma glucose is measured 2 hours later.
- If plasma glucose is $\geq$ 11.1 mmol/L then the patients will be diagnosed with diabetes.

Glycosylated Hemoglobin

- Upon prolonged exposure in the blood, glucose interacts with hemoglobin to form glycosylated derivatives, mostly HbA_{1C}.
- Glycosylated hemoglobin is a poor diagnostic test for diabetes but is useful in providing an index of the average blood glucose levels over the previous 2-3 months.



- Measuring glycosylated hemoglobin is a good determinant of how well a patient is responding to therapy.
- The target for management of diabetes is to maintain $HbA_{1C} < 7\%$ of total hemoglobin.

15.4 – Treatment Goals and Lifestyle Modifications

- The complications of diabetes arise from prolonged elevations of plasma glucose.
- Therefore, the primary goal of diabetes therapy is to maintain tight control of plasma glucose levels.
- "Tight control" means keeping plasma glucose levels in the normal range for the entire day.
- The targets for plasma glucose are:
    - Pre-meal plasma glucose 4.0 - 7.0 mmol/L
    - Peak post-meal glucose 5.0 - 10 mmol/L
    - HbA_{1C} < 7%

Other Treatment Goals

- As diabetes is closely associated with cardiovascular disease and nephropathy, it is also crucial to decrease these risk factors:

Cardiovascular Risk

- Blood pressure – systolic < 130, diastolic < 80
- Lipids – LDL < 2.6 mmol/L, triglycerides < 1.7 mmol/L, HDL (men) > 1.0 mmol/L, HDL (women) > 1.3 mmol/L.

Kidney Function

- Urine albumin to creatinine ratio < 30 mg/g (albumin/creatinine).

Lifestyle Modifications – Type I Diabetes

Diet

- Most patients with type I diabetes are thin, therefore the goal is to maintain weight, not lose it.
- Total caloric intake should be split throughout the day with meals 4-5 hours apart.

Exercise

- Exercise increases the cellular response to insulin and increases glucose tolerance so patients should be encouraged to exercise.
- Strenuous exercise may cause hypoglycemia so close patient oversight is required.

Insulin

- Survival requires insulin.
- Blood glucose levels must be monitored 3 or more times per day.

Lifestyle Modifications – Type II Diabetes

Diet

- Diet is a crucial component of treatment in type II diabetes.
- Dietary modifications alone (i.e. caloric restriction) often normalize insulin release and decrease insulin resistance.
- Patients with type II diabetes are often obese so losing weight is a treatment goal.

Exercise

- Exercise stimulates glucose uptake and should be encouraged in patients with type II diabetes.

15.5 – Insulin

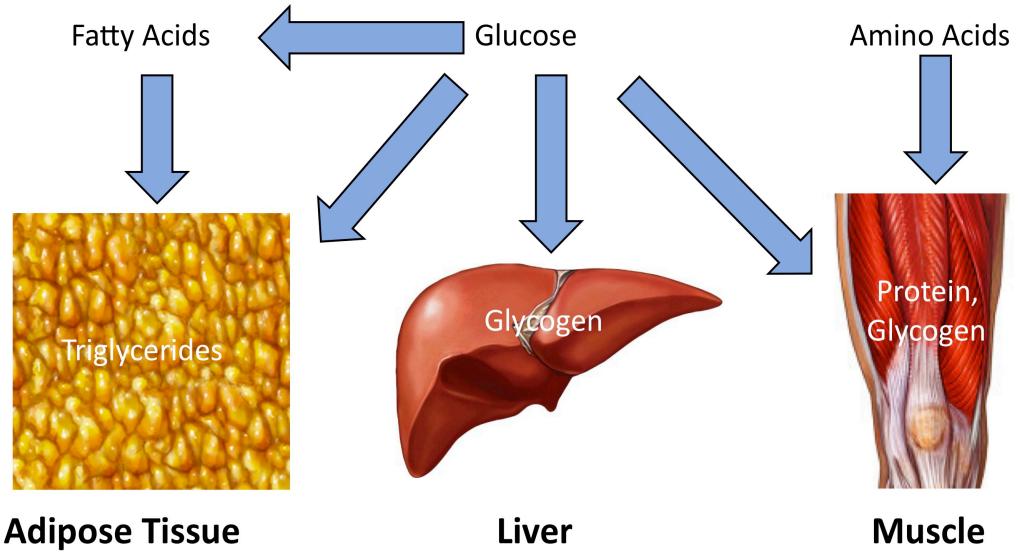
- The effects of insulin were discovered by Sir Frederick Banting, a Canadian!
- Banting along with colleagues in Toronto won the 1923 Nobel prize in Physiology/Medicine for this incredible discovery.
- Before the discovery of insulin, patients diagnosed with diabetes would die within 2-3 years of diagnosis.

Sir Frederick Banting

Metabolic Actions

- Insulin can be thought of as anabolic (i.e. "building up" or conservative).
- This means that the actions of insulin promote energy storage and conservation.
- Insulin's anabolic actions include:

    - Cellular uptake of glucose into liver, muscle, and fat.
    - Glucose uptake results in the formation of glycogen (liver and muscle) and triglycerides (adipose tissue).
    - Decreased hepatic gluconeogenesis (i.e. glucose synthesis).
    - Cellular uptake of amino acids (mostly into muscle).
    - Amino acid uptake results in increased protein synthesis.



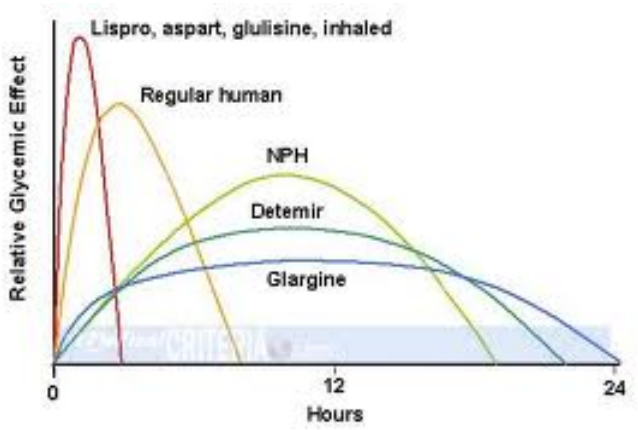
Insulin Deficiency

- Insulin deficiency puts the body into a catabolic ("breaking down") state.
- This means the body favours the breakdown of complex molecules into simpler substances.
- The catabolic effects seen in insulin deficiency include:

    - Glycogenolysis – conversion of glycogen to glucose.
    - Gluconeogenesis – new glucose synthesis.
    - Decreased glucose utilization.
- All of these effects contribute to the signs and symptoms of diabetes.
- Notice that these catabolic effects all act to raise blood glucose!

Insulin Therapy

- There are 7 main types of insulin available to treat diabetes.
- The different types of insulin differ in their appearance, time course of action, and route of administration.
- The insulins can be separated based on time course of actions:
    - Short duration-rapid acting
    - Short duration-slower acting
    - Intermediate duration
    - Long duration



Short Duration Rapid Acting Insulin

- This class includes three different types of insulin:
    - Insulin lispro
    - Insulin aspart
    - Insulin glulisine

- This class of insulin is administered in association with meals to control the postprandial (i.e. after eating) rise in glucose.
- The route of administration is subcutaneous, although they may be used IV if required.
- All three types are supplied as a clear solution.

Short Duration Slower Acting Insulin

- The only type of short duration slower acting insulin is unmodified human insulin.
- Short duration slower acting insulins can be injected before meals to control postprandial rises in glucose or infused to provide basal control of blood glucose.
- They can be administered subcutaneously or IM (rare).
- Following subcutaneous injection, the insulin molecules form small aggregates (i.e. dimers), which slows absorption.
- Supplied as a clear solution.

Intermediate Duration Insulin

- There are two intermediate duration insulins:
    - Neutral Protamine Hormone (NPH) insulin
    - Insulin Detemir
- The onset of action of both of these are delayed, so they may not be used at mealtime to control postprandial rises in blood glucose.
- Instead they are injected once or twice daily to control blood glucose between meals and in the evening.
- Why are the actions delayed?
    - NPH insulin – is insulin conjugated to protamine (a large protein). The protamine makes the molecule less soluble and decreases the absorption.
    - Insulin Detemir – Insulin detemir molecules bind strongly to each other which delays absorption. *(remember Module 2?)*
- Both NPH insulin and insulin detemir are administered by subcutaneous injection.
- NPH insulin is supplied as a cloudy suspension and insulin detemir is a clear solution.

Long Acting Insulin

- Insulin glargine is the only type of long acting insulin.
- The main advantage of insulin glargine is its long duration of action therefore, it is administered by subcutaneous injection once daily at bedtime.
- The long duration of action of insulin glargine is attributed to its low solubility at physiological pH. When it's injected, it forms microprecipitates that slowly dissolve and therefore release insulin glargine in small amounts over an extended time.
- Insulin glargine is supplied as a clear solution.

Mixing Insulins

- Sometimes insulin therapy calls for combining a short acting insulin with a longer duration insulin.
- It is optimal to be able to mix these insulins into a single syringe to avoid having to take two injections.
- Some rules for mixing insulins include:

    - Only NPH insulin can be mixed with short acting insulins.
    - When the mixture is prepared, the short acting insulin should be drawn into the syringe first.
    - Mixtures are stable for 28 days.

Complications of Insulin Therapy

- The primary complication of insulin treatment is hypoglycemia (blood glucose $\leq$ 3mmol/L).
- Rapid decreases in blood glucose, such as in overdose, result in activation of the sympathetic nervous system which causes:

    - Tachycardia
    - Palpitations
    - Sweating
    - Nervousness

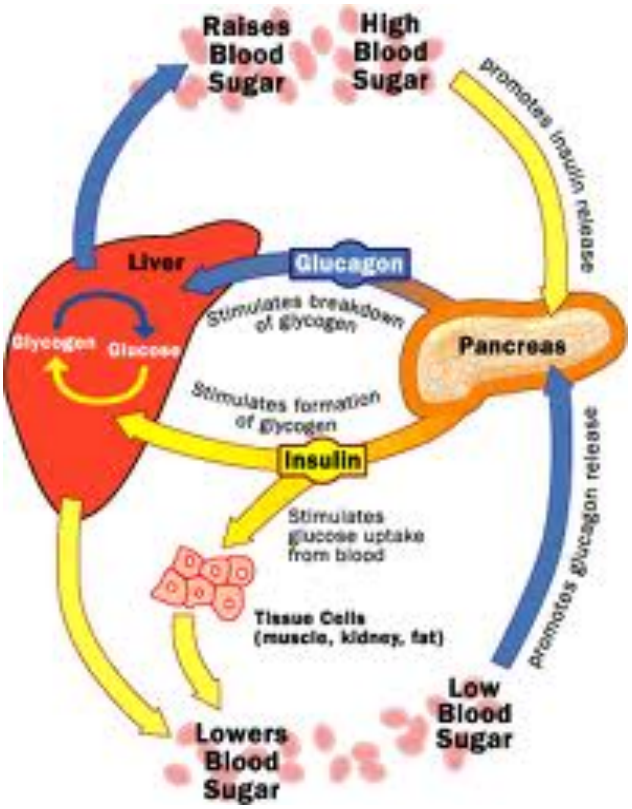
- When blood glucose levels decrease more gradually, CNS symptoms such as headache, confusion, drowsiness, and fatigue occur.
- If hypoglycemia is severe coma, convulsions, or even death may occur.

Management of Hypoglycemia

- Rapid treatment of hypoglycemia is crucial to prevent irreversible brain damage.
- If patients are conscious, fast acting oral sugar should be used. Good examples are glucose tablets, orange juice, corn syrup, honey and pop (not diet).
- If the patient is unconscious, IV glucose may be required.
- Diabetic patients are also recommended to keep the hormone glucagon on hand.

Glucagon

- Glucagon is another hormone produced by the pancreas.
- Glucagon causes the conversion of glycogen to glucose (opposite action to insulin), and is therefore effective in treating hypoglycemia.
- It is most often used in the community when a hypoglycemic patient is unconscious. Once the patient regains consciousness, oral sugar solutions should be used.
- For unconscious patients, IV glucose is preferred to glucagon but is impractical outside of medical supervision.
- Glucagon is ineffective in starving or malnourished patients. Why? Malnourished or starving patients often do not have any glycogen stores to begin with.



15.6 – Oral Antidiabetic Drugs

- Oral antidiabetic drugs are used to treat **type II diabetes** and are for the most part ineffective in type I diabetes.
- There are six classes of oral antidiabetic drugs:

1. Biguanides
2. Sulfonylureas
3. Meglitinides
4. Thiazolidinediones (glitazones)
5. Alpha-glucosidase inhibitors
6. Gliptins

1. Biguanides

- Biguanides are often the drug of choice for treating type II diabetes.
- Biguanides lower blood glucose in three separate ways:

    1. Increases the sensitivity and number of insulin receptors.
    2. Decreases hepatic gluconeogenesis.
    3. Reduces intestinal glucose absorption.

- The major advantage of biguanides is that they don't increase insulin levels, so they pose no risk of hypoglycemia.

Adverse Effects

- Nausea
- Decreased appetite
- Diarrhea
- Decreased absorption of vitamin B_{12} and folic acid.
- Lactic acidosis is rare but serious (mortality in ~ 50% of patients that get it).

2. Sulfonylureas

- Act primarily by stimulating release of insulin from the pancreas.
- They also inhibit glycogenolysis (the breakdown of glycogen to glucose).
- There are "1st generation" and "2nd generation" sulfonylureas.
- The major difference between the two generations is that second generation sulfonylureas are much more potent and cause fewer drug interactions.
- The major adverse effect of sulfonylureas is hypoglycemia.
- Prolonged use may cause pancreatic burnout (i.e. the pancreas has a reduced capacity to synthesize insulin).

3. Meglitinides

- Meglitinides have the same mechanism of action as sulfonylureas, as they stimulate insulin release from the pancreas.
- Meglitinides differ from sulfonylureas in that they:

    - Have a short half life so they are effective for treating postprandial rises in glucose.
    - Less likely to cause hypoglycemia.
    - Less likely to cause pancreatic burnout.

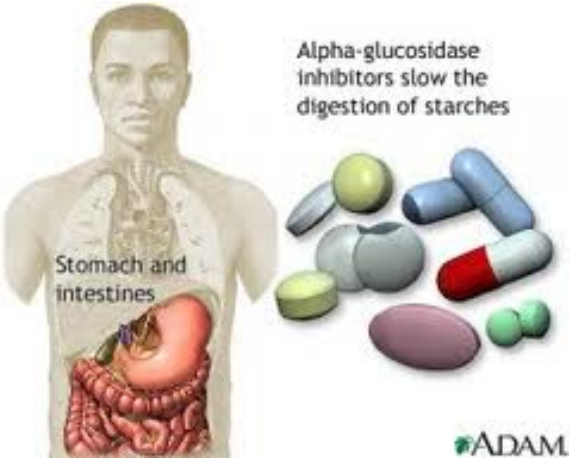
4. Thiazolidinediones (Glitazones)

- Glitazones act by increasing insulin sensitivity in target tissues and decreasing hepatic gluconeogenesis.
- Glitazones activate the PPARγ (gamma) receptor, which is an intracellular receptor.
- Activation of PPARγ turns on genes that regulate carbohydrate metabolism.
- The result is increased sensitivity to insulin by increases in the number of glucose transporters.
- Glitazones also increase HDL and decrease triglyceride levels via activation of PPARα *(remember Module 12?).*
- The adverse effects of glitazones include:

    - Fluid retention/edema
    - Headache
    - Myalgia

5. Alpha-Glucosidase Inhibitors

- Act at the intestine to delay carbohydrate absorption.
- In order to be absorbed, the complex carbohydrates in our diet must be broken down into monosaccharides (single sugar molecules). This process is mediated by alpha-glucosidase, an enzyme in the intestine.
- Alpha-glucosidase inhibitors block the enzyme and therefore cause a decrease in complex carbohydrate metabolism. This reduces the postprandial rise in glucose.
- Adverse effects are limited to the intestine since alpha-glucosidase inhibitors are poorly absorbed.
- Adverse effects include:



    - Flatulence
    - Cramps
    - Abdominal distention
    - Diarrhea
    - Decreased iron absorption

6. Gliptins

- Gliptins act to inhibit an enzyme called dipeptidyl peptidase 4 (DPP-4).
- DPP-4 breaks down the incretin hormones GLP-1 and GIP.
- Incretin hormones, such as GLP-1 and GIP, are released from the GI tract after a meal. GLP-1 and GIP cause:

    1. Increased release of insulin
    2. Decreased release of glucagon

- By inhibiting DPP-4, gliptins allow more GLP-1 and GIP to reach the pancreas therefore causing increased insulin release and suppression of glucagon release.
- Gliptins have no known major adverse effects.

Incretin Mimetics

- Incretin mimetics are synthetic incretin analogs that mimic the actions of incretin hormones.
- Therefore incretin mimetics cause an increase in insulin release and a decrease in glucagon release.
- Incretin mimetics are administered by subcutaneous injection and are used as adjunctive therapy with biguanides or sulfonylureas.
- Adverse effects include:

    - Hypoglycemia
    - Pancreatitis