Diagnostic Testing

- Laboratory findings
  - ↓ insulin-like-growth hormone factor or IGF-1
  - ↓ insulin-like-binding protein or IGFBP-3
  - Delayed bone age
  - Growth hormone level are not reliable
- Gold Standard Test
  - Growth hormone provocative stimulation test.
  - Agents used
    - Arginine
    - Clonidine
    - Insulin
    - Glucagon

Growth hormone deficiency

- Imagining
  - Brain MRI to rule out pituitary/brain neoplasm
- Treatment
  - Recombinant growth hormone shots at night time

Diabetes Insipidus (DI)

- Central DI:
  - Caused by complete or partial deficiency of antidiuretic hormone (ADH) from the posterior pituitary gland.
  - Caused by damage to the hypothalamus or pituitary stalk due hemorrhage, infarction, surgical or accidental trauma, infection or granulomas.
- Nephrogenic DI:
  - Defect in the kidney tubules that interferes with water absorption.
  - Medications: lithium, cisplatin, aminoglycosides, rifampin, vincristine, foscarnet

Clinical Presentation

- Intense thirst (polydipsia). Patient may drink from 2-20 liters of water/day
- Ice water craving
- Polyuria
- Hypernatremia:
  - Weakness
  - Altered mental status
  - Seizures
  - Coma

Diagnostic Criteria

- Low urine osmolality <300 mOsm/kg
- Elevated plasma osmolality >300 mOsm/kg
- Urine specific gravity <1.001 to 1.010
- Plasma sodium may be elevated or normal

Treatment of DI

- Central DI
  - Oral DDAVP (Desmopressin) 0.05 mg – 0.4 mg twice daily
  - Nasal DDAVP 0.05 - 0.1 every 12 hours
  - SC, IM or IV DDAVP 1- 4 mcg every 12-24 hours

Prolactinomas

- Prolactin-secreting tumors
- Account for 40% of pituitary tumors
- Is the most frequent pituitary tumor occurring in multiple endocrine neoplasia syndrome (MEN 1)

Clinical Presentation

Women

- Galactorrhea: most common in females
- Amenorrhea
- Oligomenorrhea
- Infertility

- **Prolactin inhibits LH, FSH and decreases production of estrogen**

Men

- Galactorrhea: less common in males
- Decreased libido
- Infertility
- Gynecomastia

- **Prolactin inhibits: LH, FSH and decreases production of Testosterone**

Diagnostic Criteria

- Elevated Prolactin level:
  - <100 ng/mL: possible prolactinoma
  - 100-200 ng/mL: likely prolactinoma
  - >200 ng/mL diagnostic of prolactinoma
- Brain MRI to define tumor size and location

Treatment

Pharmacological: First line of Treatment

Dopamine agonists:

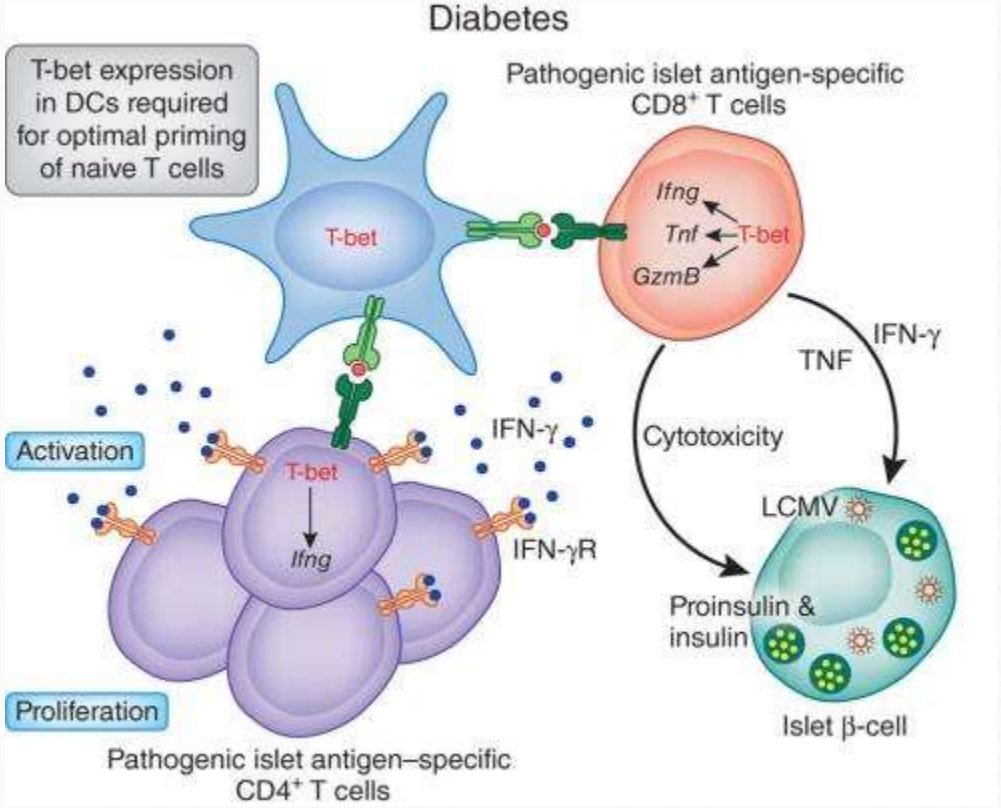
Bromocriptine 2.5 to 20 mg/day

Carbegoline 0.25-1.0 mg twice/wk

Surgery:

- Trans-sphenoidal
- Craniotomy (not preferred)

Type 1 Diabetes



- Autoimmune disorder leading to destruction of the beta cells of the pancreas leading to lack of insulin production.
- Genetics play a role in Type 1 DM

Antibodies to the Pancreas

Glutamic acid decarboxylase (GAD-65) : sensitivity 70-90% specificity 99%

Islet cell antibody (ICA-512): sensitivity 50-70% specificity 99%

Insulin antibodies (IAA): sensitivity 40-70% specificity 99%

Zinc Transporter 8 (ZnT8): sensitivity 50-70% specificity 99%

Symptoms of diabetes

- Increased thirst (polydipsia)
- Frequent urination (polyuria)
- Extreme hunger
- Weight loss
- Fatigue
- Blurred vision
- Vulvovaginitis or pruritus

Diagnosis of Diabetes

- Two fasting plasma glucose 126 mg/dL or greater
- Oral glucose tolerance test (OGTT):
  - 2 hour plasma glucose 200 mg/dL or greater
- Plasma glucose 200 mg/dL or greater with symptoms
- New onset diabetic ketoacidosis
- A1C 6.5% or greater

Treatment of Type 1 & 2 Diabetes

Long Acting Insulin (or Basal Insulin)

Glargine (Lantus)

Onset: 0.8-4 hours

Peak: minimal

Duration: 24 hours

Once daily or twice daily

Detemir (Levemir)

Onset: 0.8-4 hours

Peak: minimal

Duration: 18-20 hours

Once or twice daily

Long Acting Concentrated Insulin

Toujeo (Glargine U300)
Duration of action: >30 hours
Half life: 18-19 hours
Steady state: 5 days
Once daily

Degludec (Tresiba) (U100&U200)
Duration of action: 42 hours
Half life: 25 hours
Steady state: 2-3 days
Use once daily

Rapid Acting Insulin Analogs

Aspart (Novolog)

Onset: 10-20 minutes

Peak: 40-50 minutes

Duration: 3 to 5 hours

Rapid Acting Insulin Analogs

Lispro (Humalog)

Onset: 10-20 minutes

Peak: 40-50 minutes

Duration: 3 to 5 hours

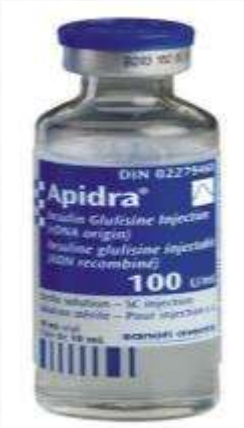
Rapid Acting Insulin Analog

Glulisine (Apidra)

Onset: 10-20 minutes

Peak: 40-50 minutes

Duration: 3 to 5 hours



Management of Diabetes

- Intense Insulin Treatment: Multiple daily injections

  Basal insulin (long acting) 50%

  Bolus insulin (rapid acting) 50%

- Continuous infusion: Insulin Pumps

  Rapid acting insulin

How to calculate Total Daily Dose (TDD) of Insulin in Adults

All persons ≥ 18 years:

TDD = Weight X 0.5 units/kg/day

e.g: a 25 year old male with weight 72 kg

70 kg X 0.5 = 36 units daily

50% of TDD will be Basal Insulin
Lantus (Glargine) or Levemir (Detemir):
18 units/day

50% of TDD will be Bolus Insulin:
18 units ÷ 3 equal doses

Novolog (Aspart) 6 units @ breakfast
Novolog (Aspart) 6 units @ lunch
Novolog (Aspart) 6 units @ dinner

Diabetic Ketoacidosis (DKA)

- Is a life threatening condition that is not sustainable without insulin
- The body begins to breakdown fatty tissue and protein
- Build up of acids called “ketones” in the blood and urine which are toxic to the body.

Electrolytes Imbalance

- High glucose
- Low sodium
- Potasium is high, normal and then low
- Low phosphate

When to Suspect DKA

- Decreased alertness
- Rapid "Kussmaul" breathing
- Flushed face
- Dry skin and mouth
- Fruity smell breath (ketones)
- Stomach pain
- Nausea and vomiting
- Altered mental status
- Coma

Criteria for DKA

- Blood glucose >200
- Ketonemia
- Metabolic acidosis:
    - ph <7.25
    - Serum bicarbonate <15 mmol/L
    - Increased anion gap >10

Treatment

- Careful replacement of fluid deficits to correct the dehydration.
- Correction of acidosis and hyperglycemia via insulin drip (0.1 units/kg/hr)
- Correction of electrolytes imbalance
- Treatment of underlying cause: infection

Complications

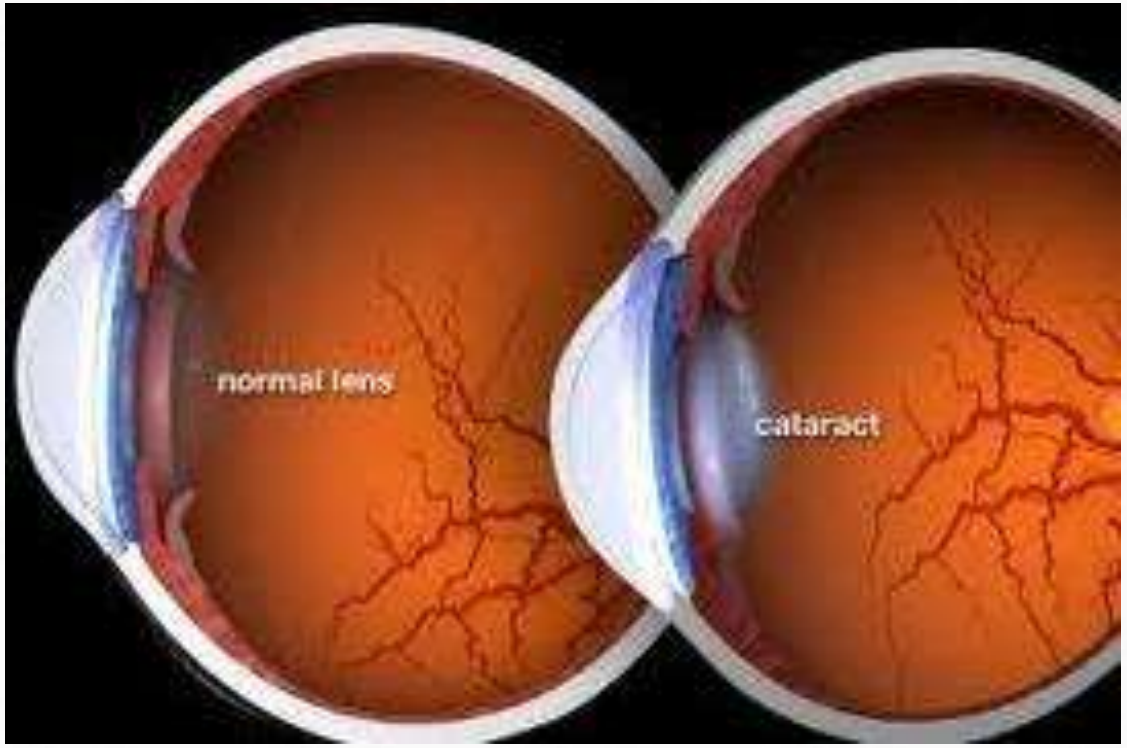
- Cerebral Edema
- Intracranial thrombosis or infarction
- Acute tubular necrosis
- Peripheral edema

Complications of Diabetes

Diabetic Cataracts:

60% of diabetics will experience cataracts (cloudiness of the lens).

Correlates with the duration of the disease and severity of the hyperglycemia.

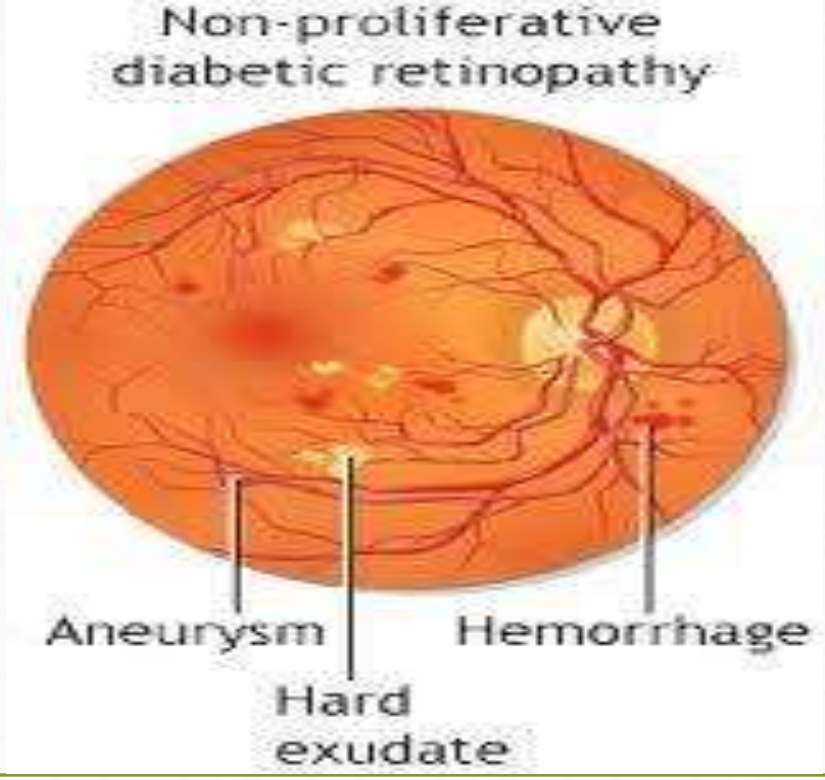


Diabetic Retinopathy

After 10-15 years: 25-50%

-After 15 years: 75-95%

-After 30 years: 100%

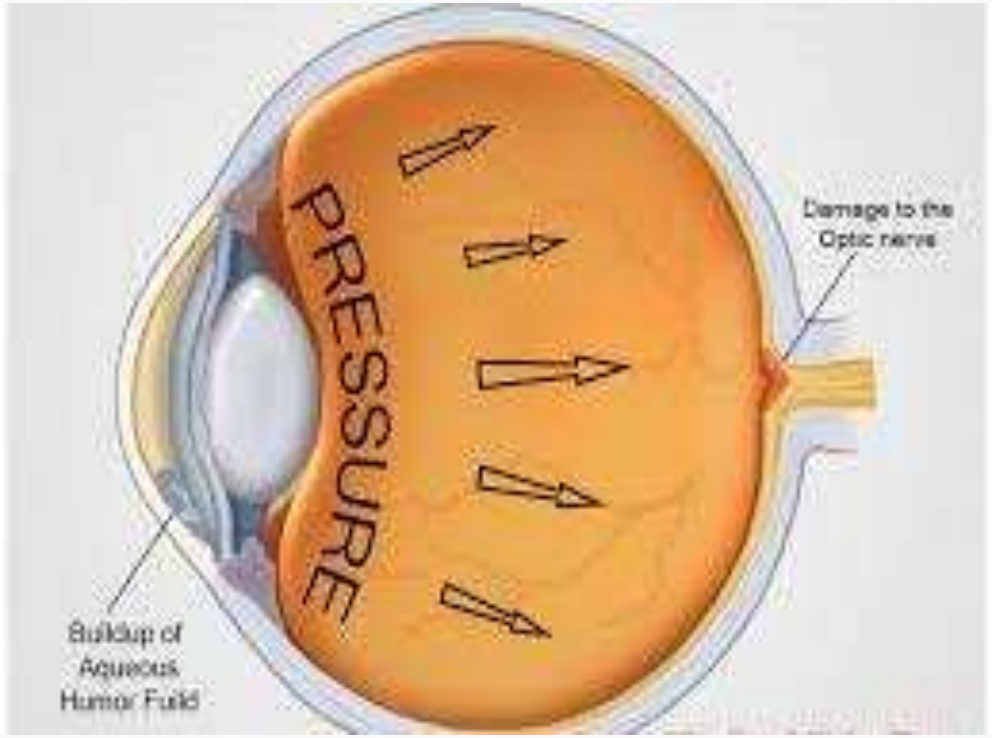


Glaucoma

--Increased intraocular pressure due to fluid collection.

--Can lead to blindness due to damage to the optic nerve.

--Occurs ins 6% of patients with diabetes.



Diabetic Nephropathy

- Type 1 DM have 30-40 risk of having nephropathy after 20 years of diagnosis.
- Type 2 diabetics have 15-20% risk
- Manifestation: Proteinuria

Labs to order:

Morning Microalbumin/creatinine ratio:

<30 mcg/mg is normal

30-300 mcg/mg abnormal

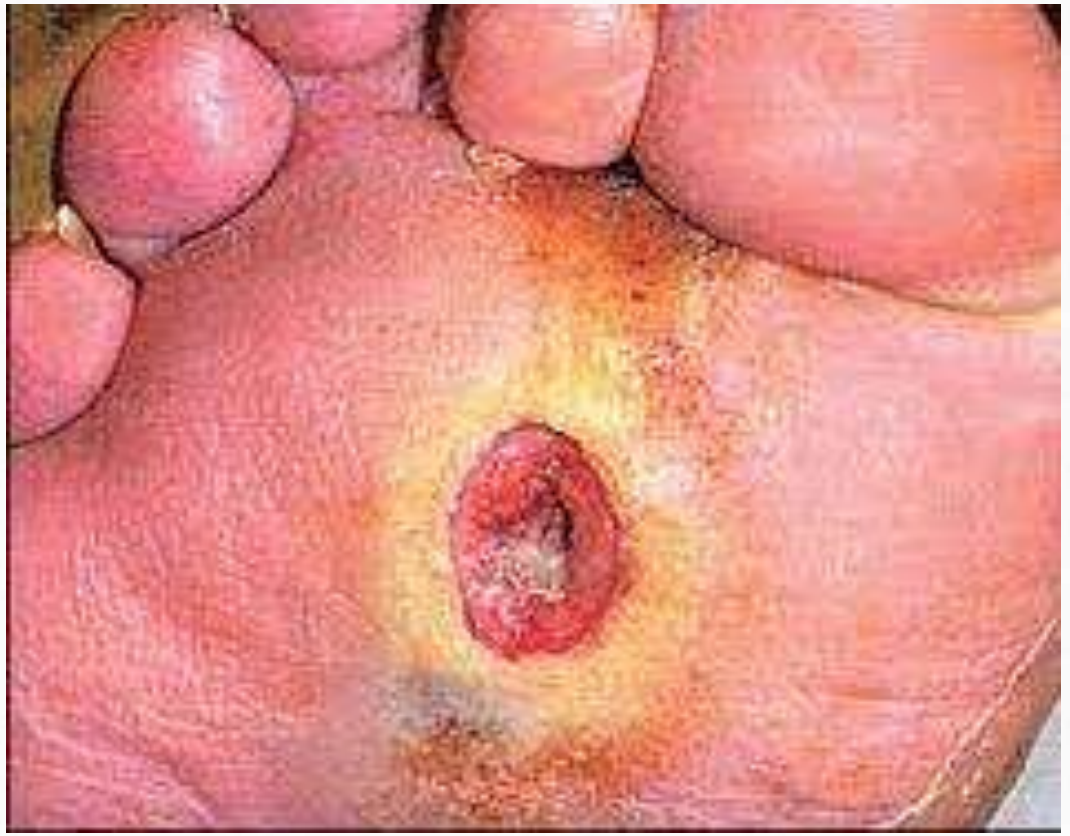
24 hour urine microalbumin (normal <30 mcg/mg)

Treatment:

- Ace-Inhibitor: Zestril (Lisinopril) 10 mg daily
- Angiotensin Receptor blocker: Cozaar (Losartan)25 mg daily

Foot Ulcers

Repetitive stress and high foot pressure lead to calluses and ulcerations



Peripheral Neuropathy

-Involvement of only one or several nerves.

-Characterized by sudden onset of loss of sensory with subsequent recovery of all or most of the function.

Painful Diabetic Neuropathy:

-Hypersensitivity to light touch

-Burning pain at night

Treatment:

-Gabapentin (Neurontin) 900 mg/day

-Amitriptyline (Elavil) 25-75 mg daily

Cardiovascular Complications

Heart Disease:

- Microangiopathy leading to congestive heart failure in diabetics
- Coronary atherosclerosis
- Myocardial infarction is 3-5 times more common in diabetics
- Hypertension
- Hyperlipidemia

Labs: Fasting lipid profile yearly

Treatment: Statins (HMG-coA inhibitors)

- Simvastatin (Zocor)
- Atorvastatin (Lipitor)
- Rosuvastatin (Crestor)

Aspirin 81-321 mg daily

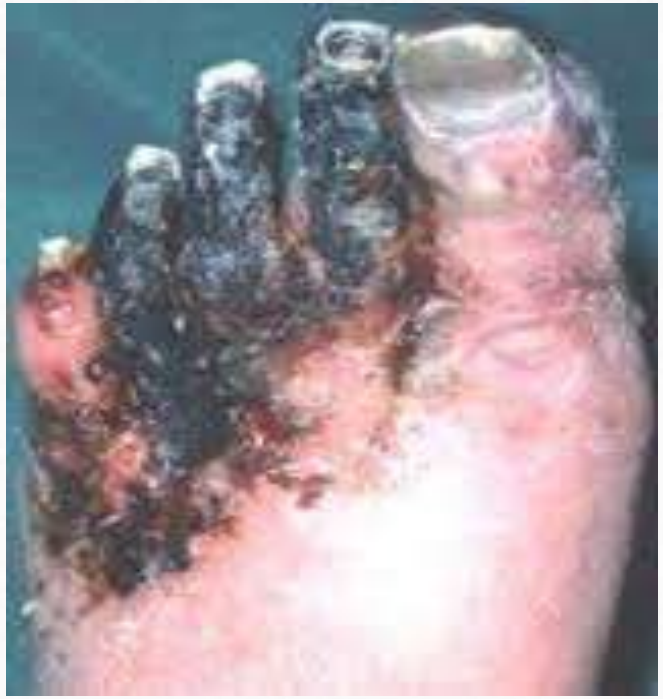
Peripheral Vascular Disease

-Atherosclerosis is markedly accelerated in the larger arteries.

-Ischemia of the lower extremities is common

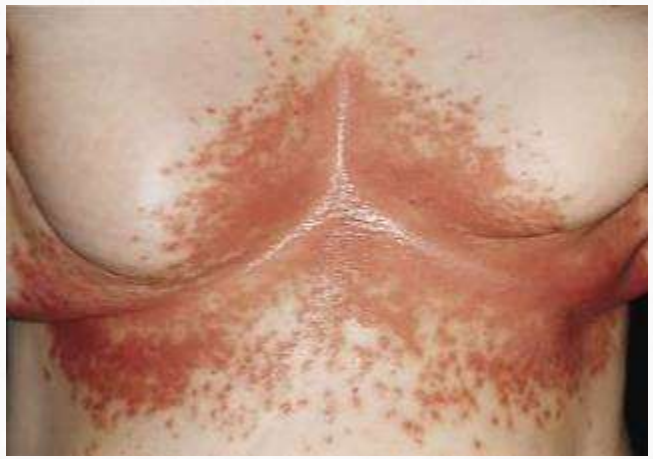
-Erectile dysfunction

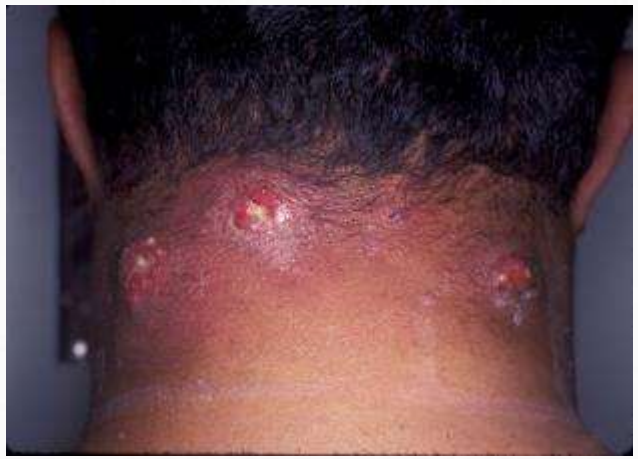
-Intestinal angina



Gangrene of the Feet: toes and leg amputations

Skin complications





Candida Infections:

-erythema and edema below the breasts, axilla and between fingers.

-Chronic pyogenic infections of the skin

-Vulvovaginitis

Treatment:

Antifungal creams

Miconazole (Monistat)

Clotrimazole (Lotrimin)

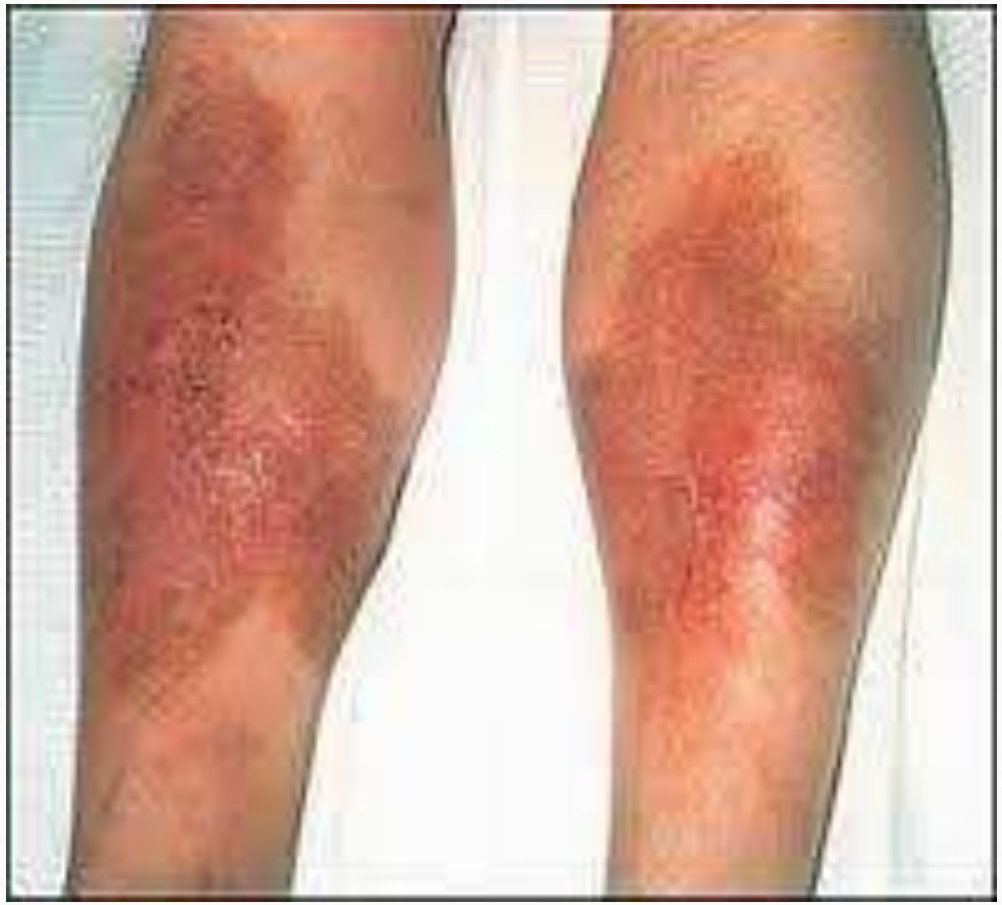
Fluconazole (Diflucan)150 mg x1

Necrobiosis Lipoidica Diabeticorum

-Degeneration of collagen, inflammation of the tissues and blood vessels, capillary membrane.

-Oval or irregularly shaped plaques with demarcated borders located mainly in the anterior surfaces of the legs.

-Most common in women than men

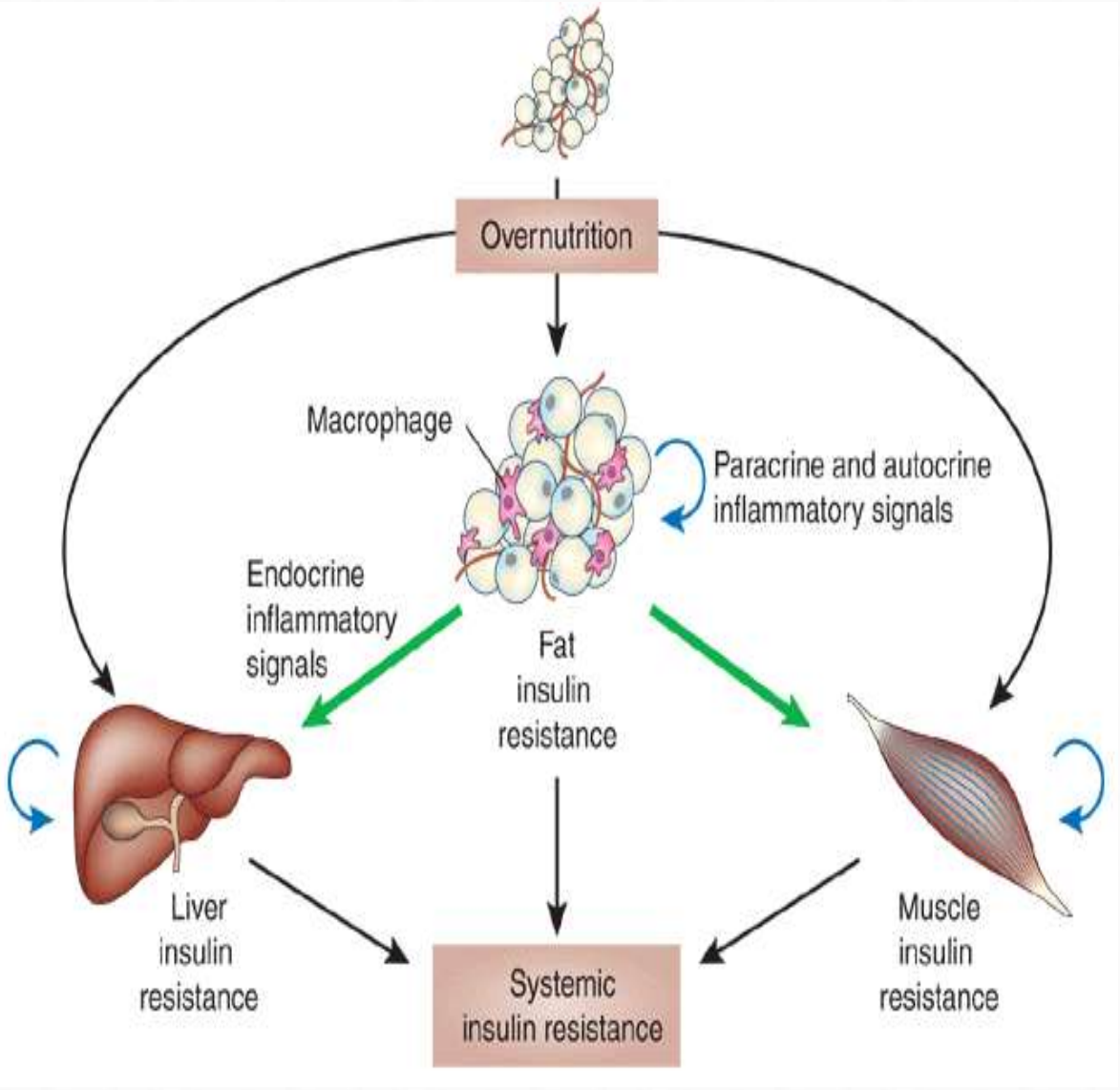


Type 2 Diabetes

- Multifactorial: Genetics and Environmental factors
  - Family history of T2DM
  - Genes predisposition
  - Sex, age, ethnicity
  - Excessive caloric intake
  - Lack of daily exercise

Pathophysiology

- Insulin resistance
  - Inability cells to respond to stimulation of insulin
  - Precedes the onset of T2DM



Clinical Presentation: T2DM

Asymptomatic or mild hyperglycemia:

--glucose 120-140 mg/dL.

Elevated blood sugars: >200 mg/dL

- Polyuria
- Polydipsia
- Blurred vision
- Sexual dysfunction
- Diabetic ketoacidosis (not as common as Type 1 DM)

Metabolic Syndrome

Men

- Waist circumference >40” (102 cm)
- Triglycerides ≥ 150 mg/dL
- High-density lipoprotein (HDL) <40 mg/dL
- Blood pressure≥130/85 mm Hg
- Fasting glucose ≥100 mg/dL

Women

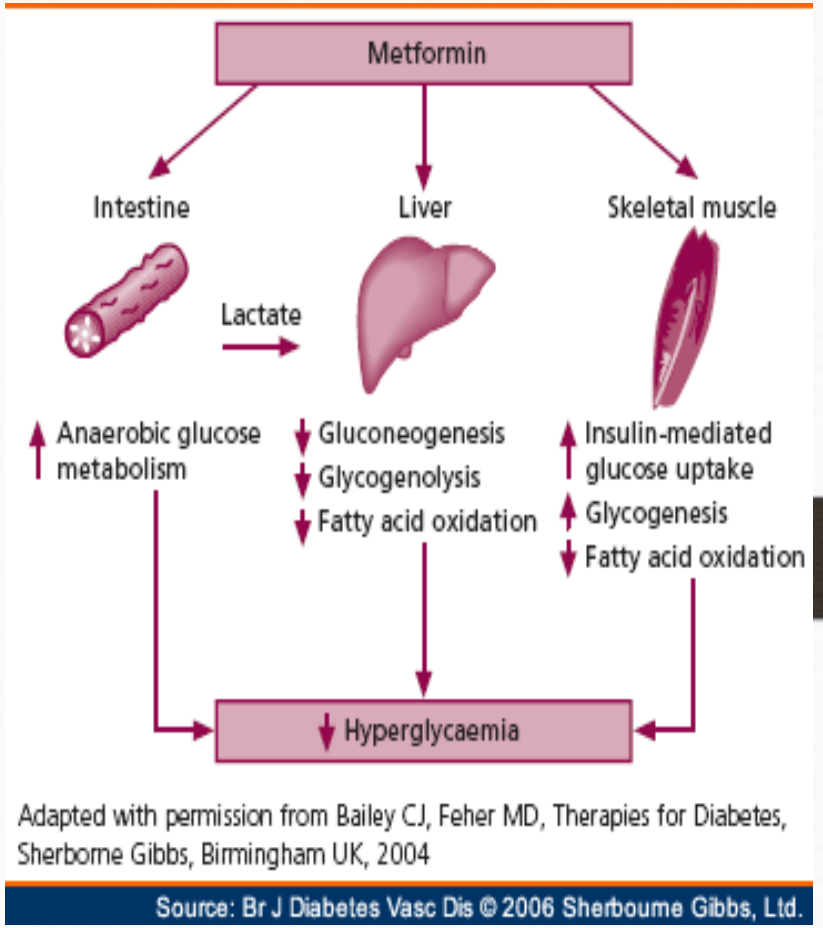
- Waist circumference >35” (88 cm)
- Triglycerides ≥150 mg/dL
- High-density lipoprotein (HDL) <50 mg/dL
- Blood pressure ≥ 130/85 mm HG
- Fasting glucose ≥ 100 mg/dL

Treatment of T2DM

- Lifestyle modification: first line of treatment
  - Healthy eating
  - Physical activity
- Weight loss reduces insulin resistance
- Weight loss is recommended for all overweight and obese individuals at risk for diabetes

Medications for Type 2 DM

- Biguanides: Target organs: Liver and Skeletal Muscles
- Mechanism of action:
  - Reduces hepatic glucose output
  - Reduces intestinal absorption of glucose
  - Improves insulin sensitivity by increasing peripheral glucose uptake and utilization
- **Metformin (Glucophage)**
  - 500-1000 mg twice daily
- Benefits:
    - Low risk for hypoglycemia
    - Decreases cardiovascular disease
    - Low cost (very inexpensive)
- Disadvantage: Nausea, diarrhea, abdominal cramping, risk for lactic acidosis
- Contraindications: Creatinine >1.4, Liver or heart failure, Age >80 years



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Source: Br J Diabetes Vasc Dis © 2006 Sherbourne Gibbs, Ltd.

Sulfonylureas

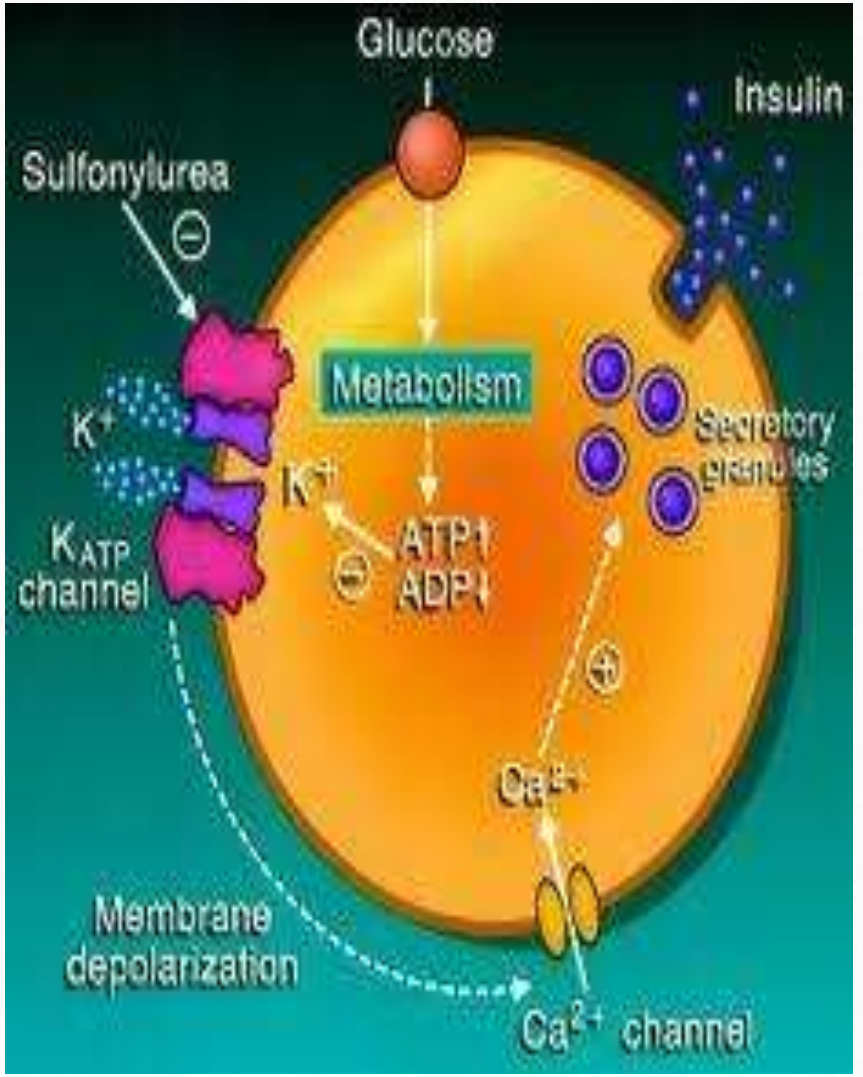
- Sulfonylureas (2nd generation)
- Target organ: Pancreas
- Mechanism of action:
  - Increase insulin secretion via ß cell
- Glyburide (DiaBeta) 2.5 -20 mg/d
- **Glipizide(Glucotrol) 2.5-20 mg/d**
- Glimepiride (Amaryl) 2-8 mg/d

Benefits:

- Well tolerated
- Inexpensive

Disadvantage:

- Hypoglycemia
- Weight gain



Dipeptidyl Peptidase IV Inhibitor (DPP-4 inhibitor)

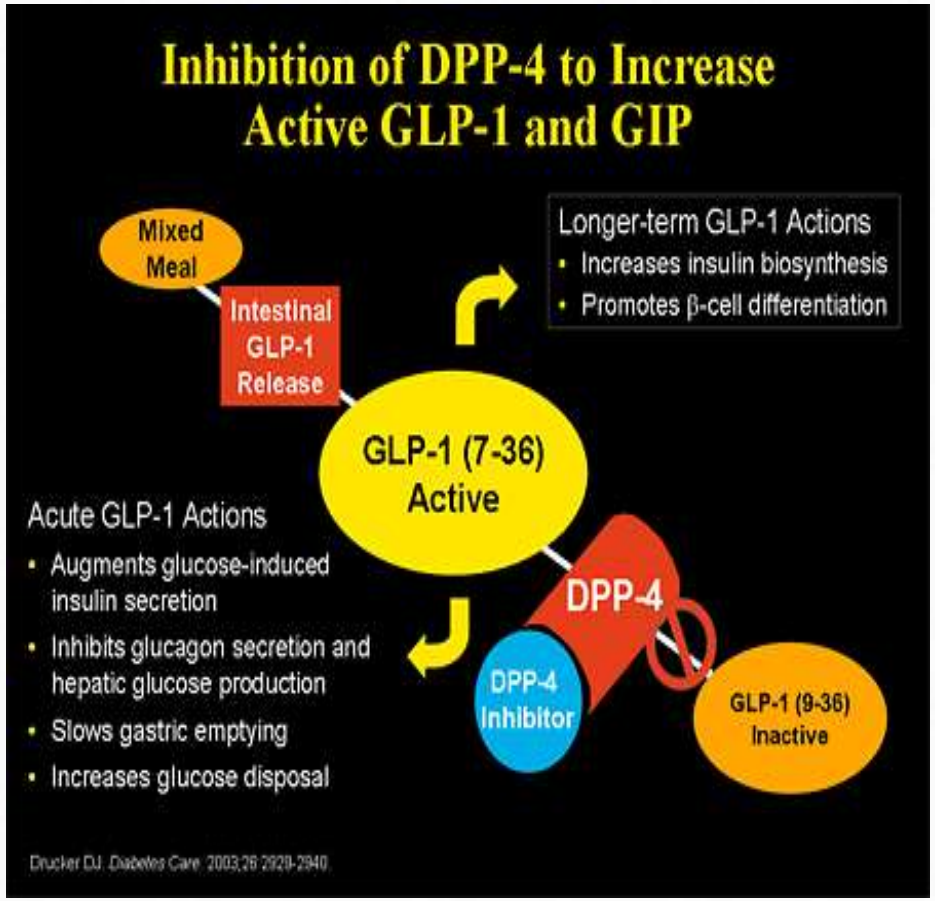
DPP-4 Inhibitors:

Target Organs:

Liver, pancreas (ß cell), Adipose tissue, GI

Mechanism of action:

Increases endogenous glucacon-like-peptide 1)(GLP-1) by inhibiting dipeptidyl peptidase 4 (DPP-4) that breaks down gastric inhibitory polypeptide (GIP) and GLP-1



DPP-4 Inhibitors

Sitaliptin (Januvia)

-100 mg daily

-50 mg in stage 3 renal disease

-25 mg in stage 4 renal disease

Saxagliptin (Onglyza)

-5 mg daiy

-2.5 mg in stage 3,4,5, renal disease (CKD)

Linagliptin (Tradjenta)

-5 mg daily

-No adjustment in CKD

Benefits:

-No weight gain

-Well tolerated

-Low risk for hypoglycemia

Disadvantage:

-Dose adjustment in CKD

-Risk of interfering with the immune system

Glucagon-Like-Peptide-1 Mimetics (GLP-1)

Target Organ:
Liver, Pancreas (ß cell), Adipose tissue and GI

Mechanism of action:
-↑insulin secretion
-↓glucagon secretion
-slow gastric emptying
-decreases appetite

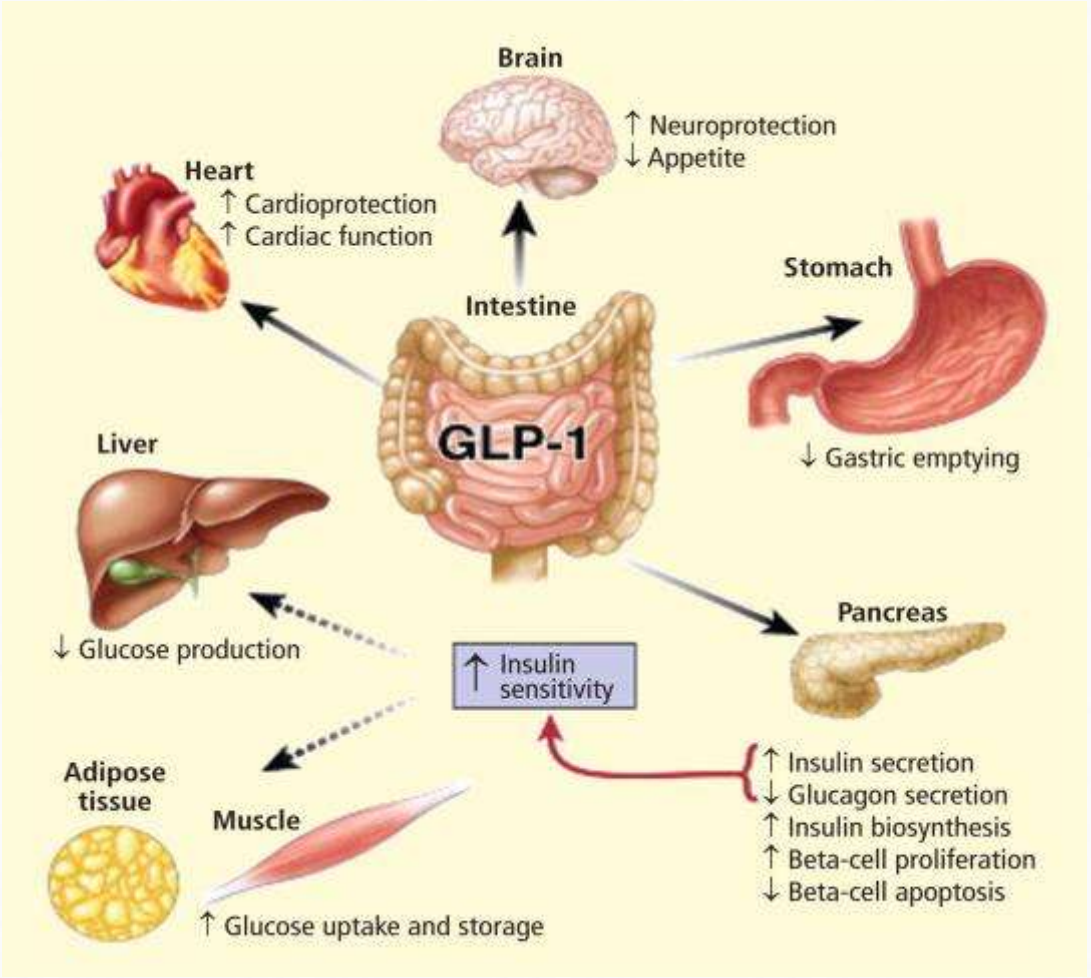
Exenatide (Byetta, Bydureon)

5-10 mcg twice daily via injection
2 mg once/wk via injection

Liraglutide (Victoza)
0.6-3 mg daily via injection

Albiglutide (Tanzeum)
30-50 mg once a week via injection

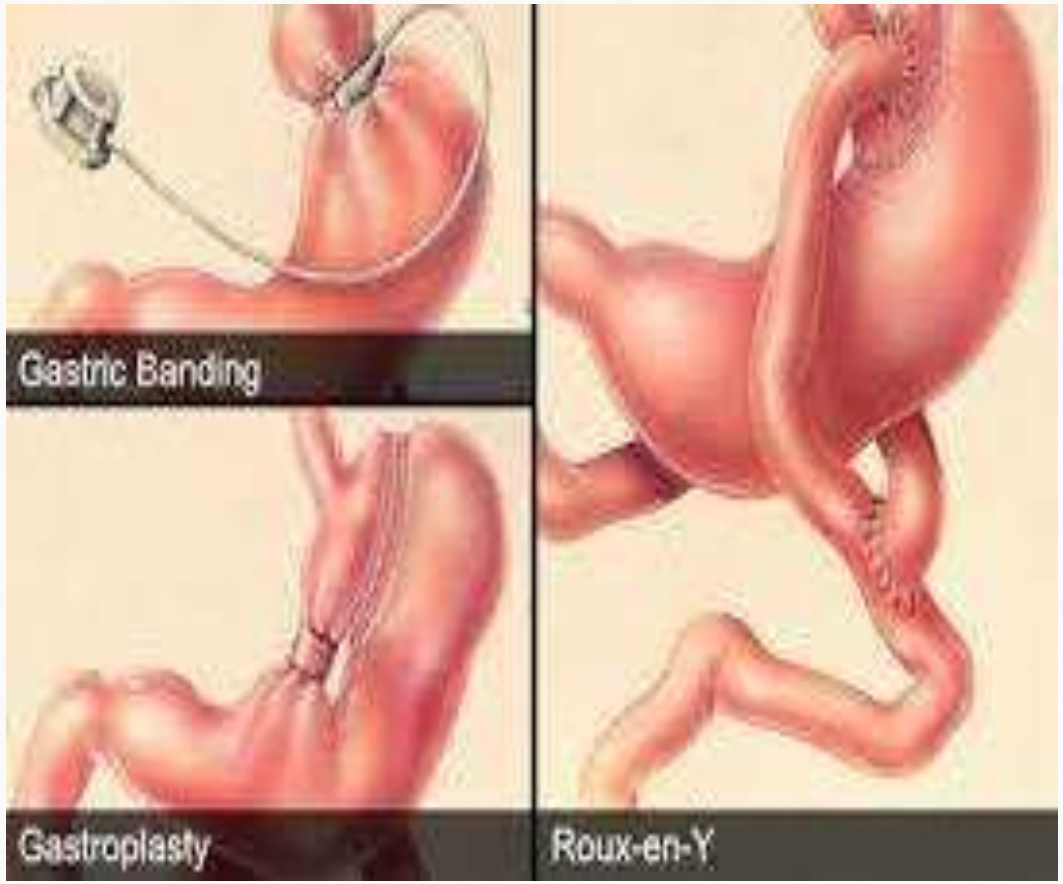
Dulaglutide (Trulicity)
0.75- 1.5 mg once a week via injection



Bariatric Surgery

-Leads to near or complete normalization of glycemia in 50 to 90% of T2DM

-Patients with multiple co-morbidities and BMI≥ 35 are candidates for bariatric surgery



Complications of T2DM

Nonketotic Hyperglycemia Hyperosmolar Coma:

Is a form of hyperglycemic coma characterized by:

-Severe hyperglycemia

-Hyper osmolality

-Dehydration

-Absence of ketosis

It tends to occur in patients:

- with mild or occult diabetes

-middle aged or elderly

Nonketotic Hyperglycemia Hyperosmolar Coma

Signs and Symptoms

- -weakness & lethargy
- -polyuria
- -polydipsia
- -profound dehydration
- -absence of Kussmaul respirations
- -confusion
- -coma

Labs

- Glucose >600 - 2400 mg/dL
- Serum Osmolality >310 – 440 mOsm/kg
- No acidosis: pH >7.3
- Serum Bicarbonate >15 mEq/L
- Normal anion gap <14 mEq/L

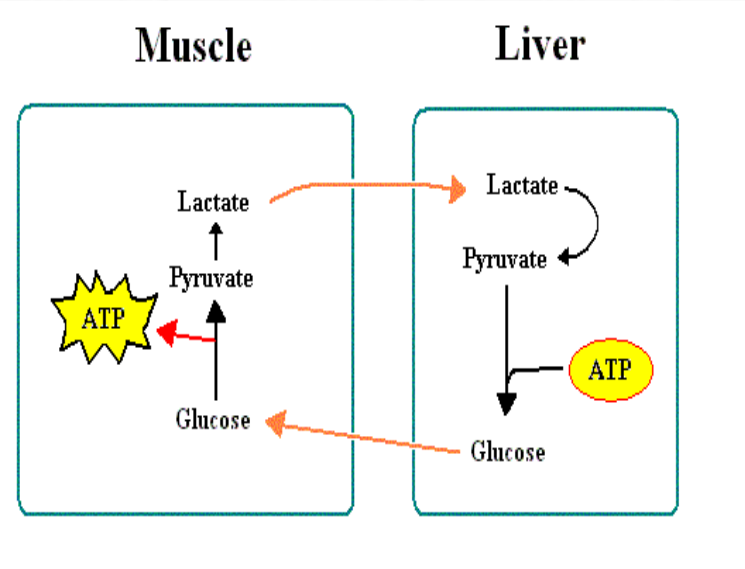
Lactic Acidosis

Pathogenesis:

-Diabetic patients presenting with profound acidosis and increased anion gap greater than 15 mEq/L in the absence of ketoacidosis.

-Lactate >5 mmol/L (normal 0.5-2.2 mmol/L)

The Cori Cycle



Causes of Lactic acidosis

Clinical conditions

Tissue hypoxia

hepatic failure

circulatory collapse

Medications

Metformin (Glucophage): high dose or overdose

Treatment of Lactic Acidosis

-ABC: airway, breathing and circulation

-Correct the offending cause

-Cultures of blood if sepsis is suspected and start antibiotics immediately

-Alkalinization with intravenous sodium bicarbonate to keep pH >7.2 (there is no evidence that mortality rate is decreased). The use of sodium bicarbonate remains controversial.

Diabetes and Hypertension

- Most people with diabetes develop high blood pressure during their life.
- Diabetes causes damage to the arteries and makes them targets for atherosclerosis.
- Atherosclerosis leads to high blood pressure, which if not treated, can lead to blood vessel damage, stroke, heart failure, heart attack, or kidney failure.

- Treatment: Angiotensin-Converting-Enzyme Inhibitor (ACE inhibitor)

  Lisinopril (Zestril) 10-40 mg daily

Diabetes and Dyslipidemia

All patient with diabetes must have a fasting lipid profile checked yearly.

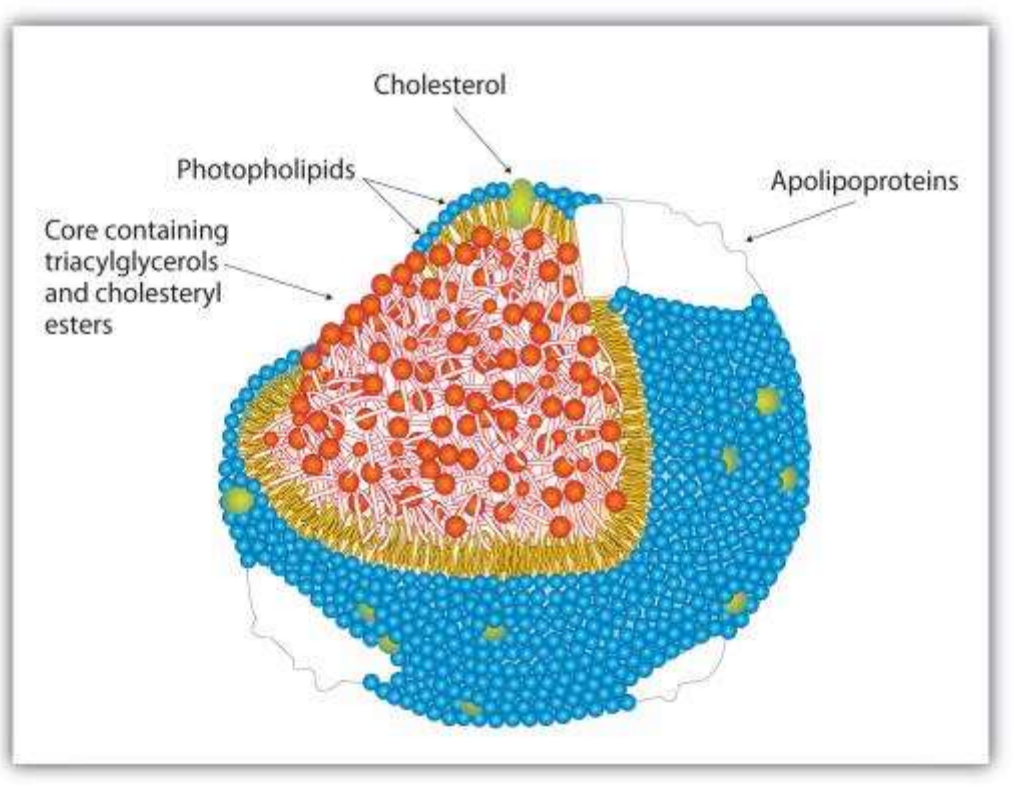
Lipid targets:

- LDL <100 mg/dL
- HDL >40 mg/dL in men; >50 mg/dL in women
- Triglycerides: <150 mg/dL

Treatment: HMG-CoA Reductase Inhibitors (Statins)

- Simvastatin (Zocor) 10-40 mg/d
- Atorvastatin (Lipitor) 10-40 mg/d
- Rosuvastatin (Crestor) 10-40 mg/d

Lipid Disorders



Atherosclerosis

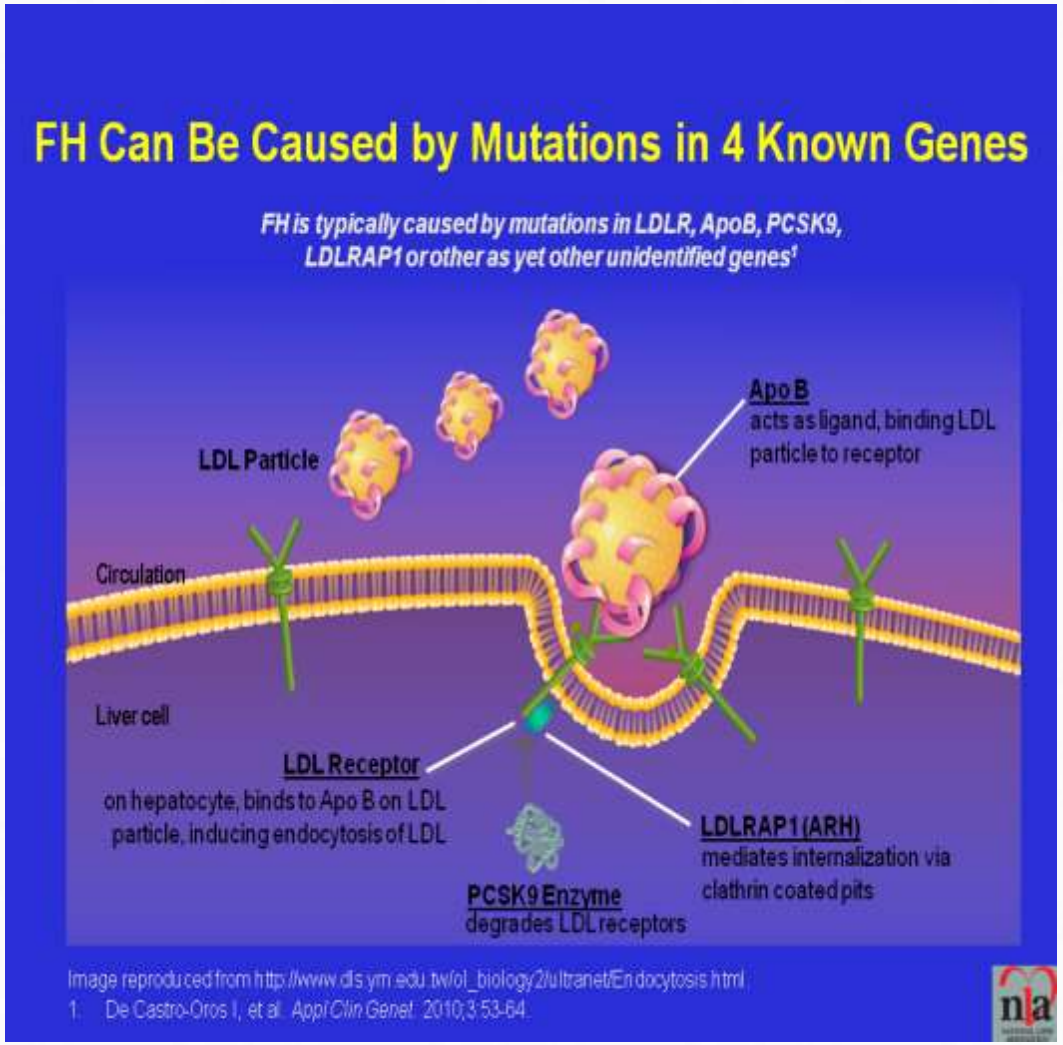
- Genetics and environmental factors play a role in the development of dyslipidemia.
- In the Western society, dyslipidemia affects 90% of the population due to high fat diet.
- Less than 10% of the cases are related to genetics.

Risk factors for Atherosclerosis

- Hyperlipidemia
- Hypertension
- Smoking
- Diabetes
- Physical inactivity
- Low high density lipoprotein (HDL)

Familial Hypercholesterolemia (FH)

- Mutation of the LDL receptor leads to defective uptake and degradation of the LDL
- Autosomal dominant pattern



Familial Hypercholesterolemia Presentation

--Premature coronary artery disease that can present during childhood.

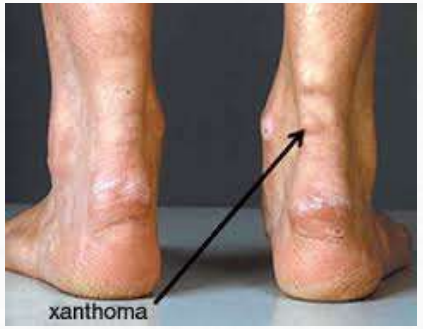
--Myocardial infarction as early as 40 years of age

--Tendon xanthomas

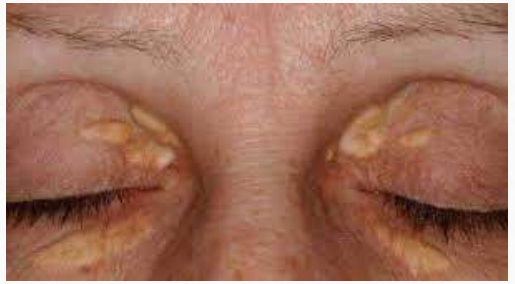
--Xanthelesmata

--Premature arcus cornealis

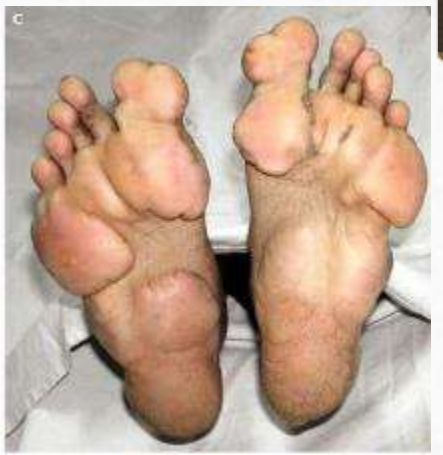
Tendon Xanthomas



Xanthalesmata



Arcus Cornealis



Familial Hypercholesterolemia

Labs

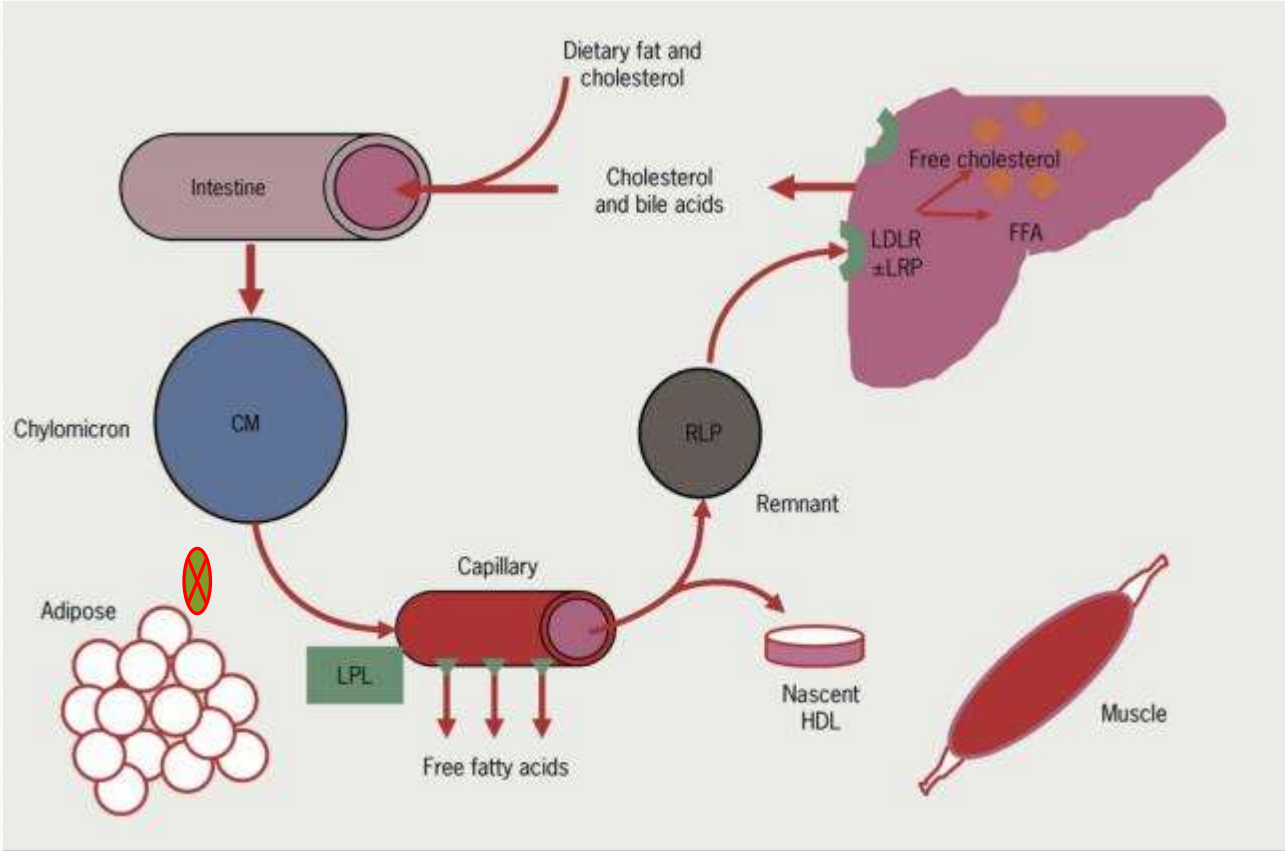
- Heterozygous mutation:
  - LDL >220 mg/dL (desirable <100)
- Homozygous mutation
  - LDL >550 mg/dL

Treatment

- Low fat diet and daily exercise
- ***HMG CoA reductatse inhibitors (Statins)***
- Nicotinic Acid
- Bile Acid sequestrants

Lipoprotein Lipase Deficiency (LPL)

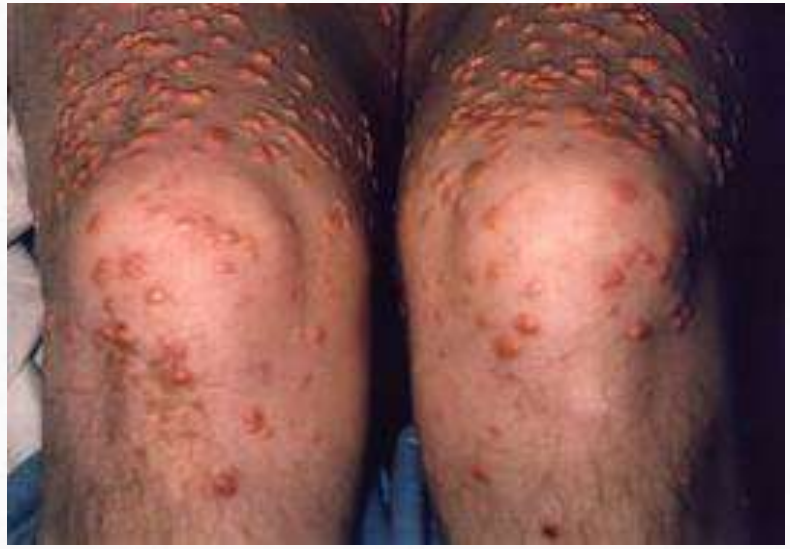
- Deficiency in LPL or its cofactor Apo C-II impairs uptake of triglycerides into the peripheral tissues
- Autosomal recessive



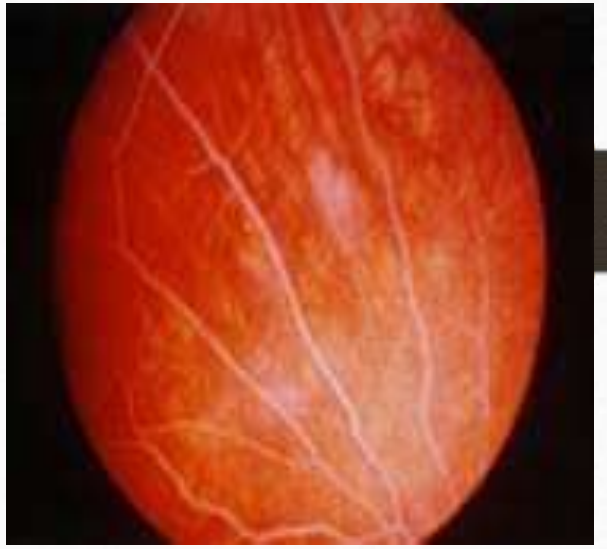
LPL Deficiency Presentation

--Diagnosed always in childhood
--Eruptive xanthomas
--Lipemia retinalis
--Pancreatitis
--Hepatospleenomegaly
--Triglycerides >1500 mg/dL (desirable <150)

Eruptive xanthomas



Lipemia Retinalis



LPL deficiency

Fasting Labs

- Triglycerides >1500

Treatment

- Omega -3 fatty acid
  - Lovaza (Omega-3-Acid Ethyl Esters) 3-4 grams daily
  - Over the counter fish oil 1-4 grams daily

Familial Hypertriglyceridemia

- Caused by overproduction of triglycerides
- Genetic defect has not been established
- Autosomal dominant
- Diagnosed in adulthood
- Xanthomas
- Pancreatitis

Familial Hypertriglyceridemia

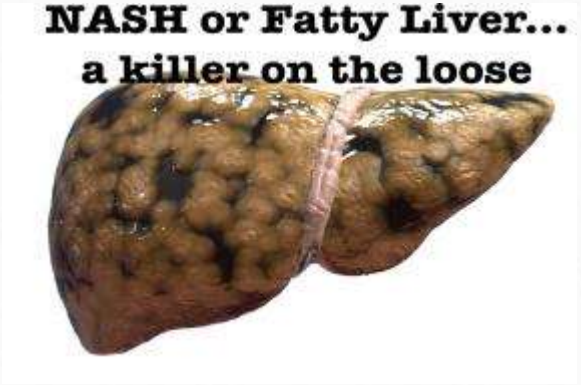
Labs

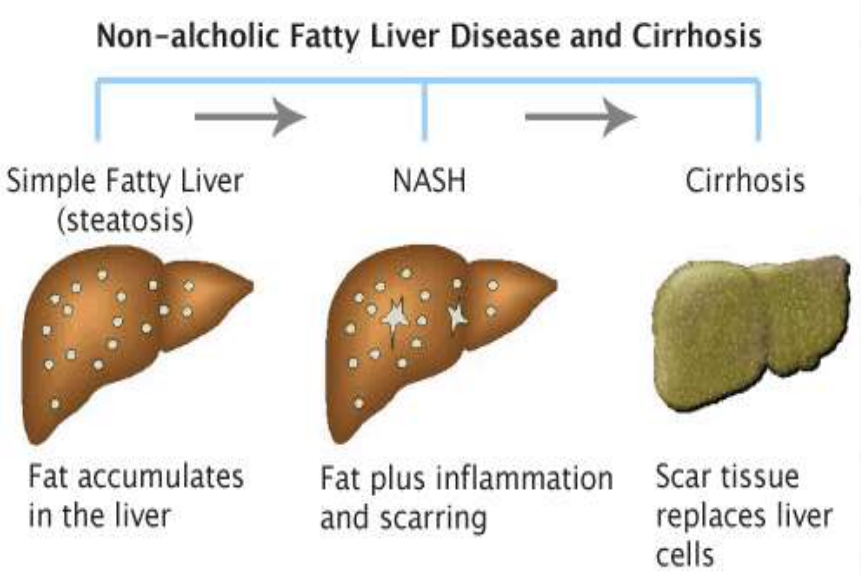
- Fasting triglycerides >150-500 mg/dl or greater if person is obese, consumes alcohol or has diabetes

Treatment

- Fibric acids
  - Gemfibrozil (Lopid) 600 mg twice daily
  - Fenofibrate (Tricor) 135-200 mg daily

- Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH)
  - Fatty liver disease in the absence of alcohol ingestion
  - Characterized by inflammation of the liver with concurrent fat accumulation resulting in liver cirrhosis
  - The pathophysiology is not well understood but there is elevated triglycerides and liver enzymes
  - Risk factors for NASH
    - Diabetes
    - Obesity
    - Metabolic Syndrome

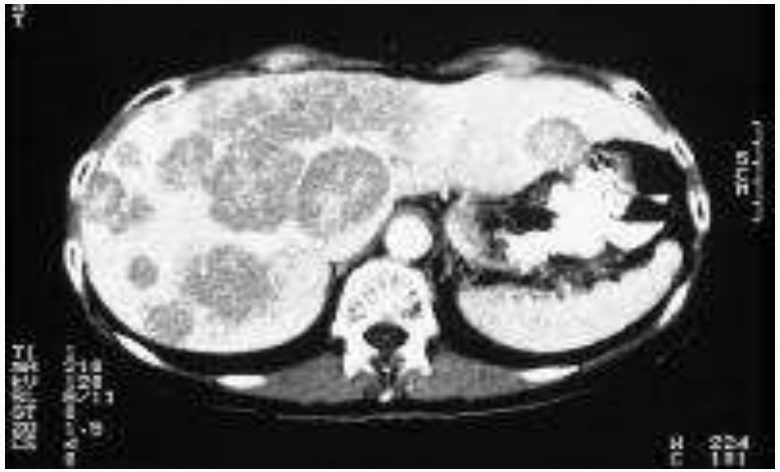




Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH)

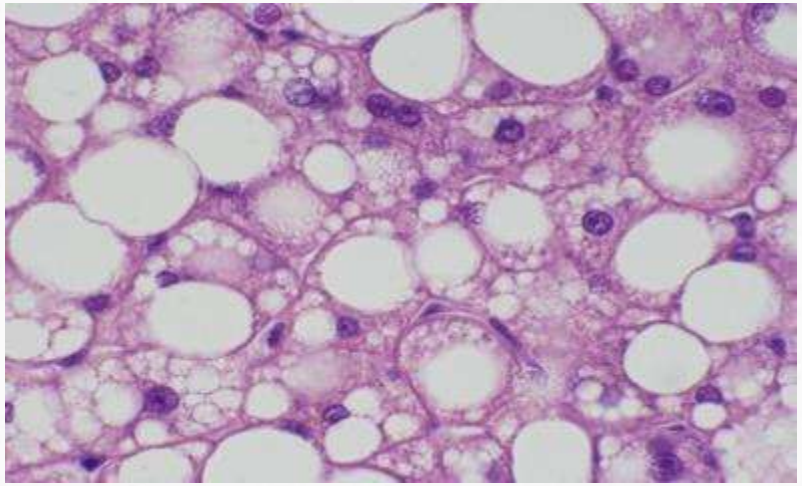
Laboratory Findings:

--Elevated triglycerides >200 mg/dL (<175)
--Elevated alanine aminotransferase (ALT) >40 U/L (10-40)
--Elevated aspartate aminotransferase (AST) >56 U/L (7-56)



Imaging: liver ultrasound or CT scan

Liver biopsy: definite diagnosis



Treatment : Weight loss, healthy diet, avoid alcohol

Metformin (Glucophage) 500 mg twice daily or
Pioglitazone (Actos) 15 mg daily (max 45 mg daily)
Vitamin E 1000 mg/daily