Metabolism: Define as set of chemical reactions that happen in living organisms **to**

1. maintain life 2. allow grow 3. allow reproduce

4. maintain their structure 4. respond to their environments**.**

Metabolism divided in to two categories:

1.Catabolism : Breaking down of large molecules into small particles producing energy as ATP.

Ex: Breaking down and oxidizing food molecules.

2. Anabolism : Constructive of large molecules from small molecules using energy produce from catabolism.

Ex: Synthesis of fats , glucose and DNA.

Lipolysis :

Define as break down of TG to the fatty acid and glycerol as an energy source in adipose tissue by the effect of

lipase enzyme and hormone sensitive TG .

hormones sensitive TG are epinephrine, nor epinephrine and glucagon.

These hormones are increase hydrolysis of fat (TG).

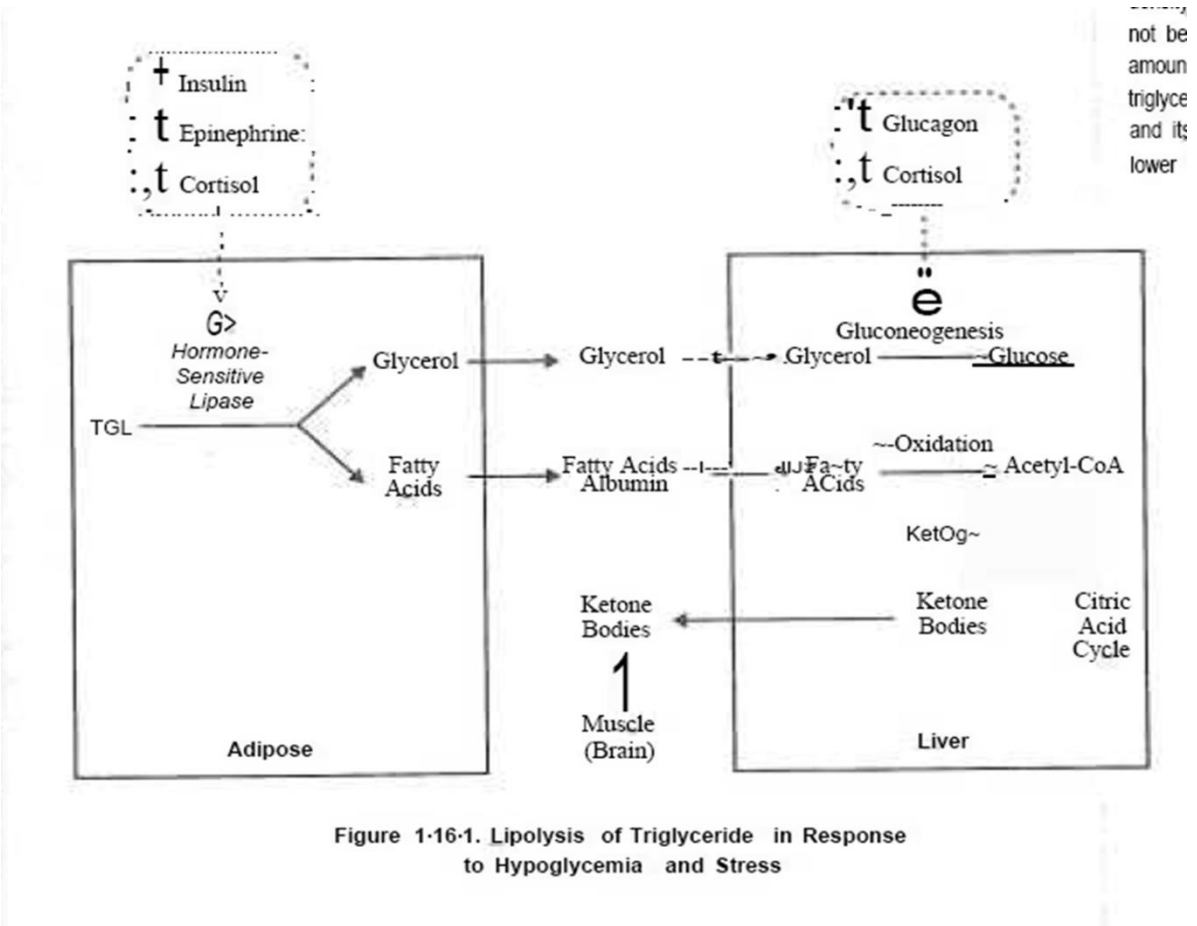


Figure 1·16·1. Lipolysis of Triglyceride in Response to Hypoglycemia and Stress

Lipogenesis :

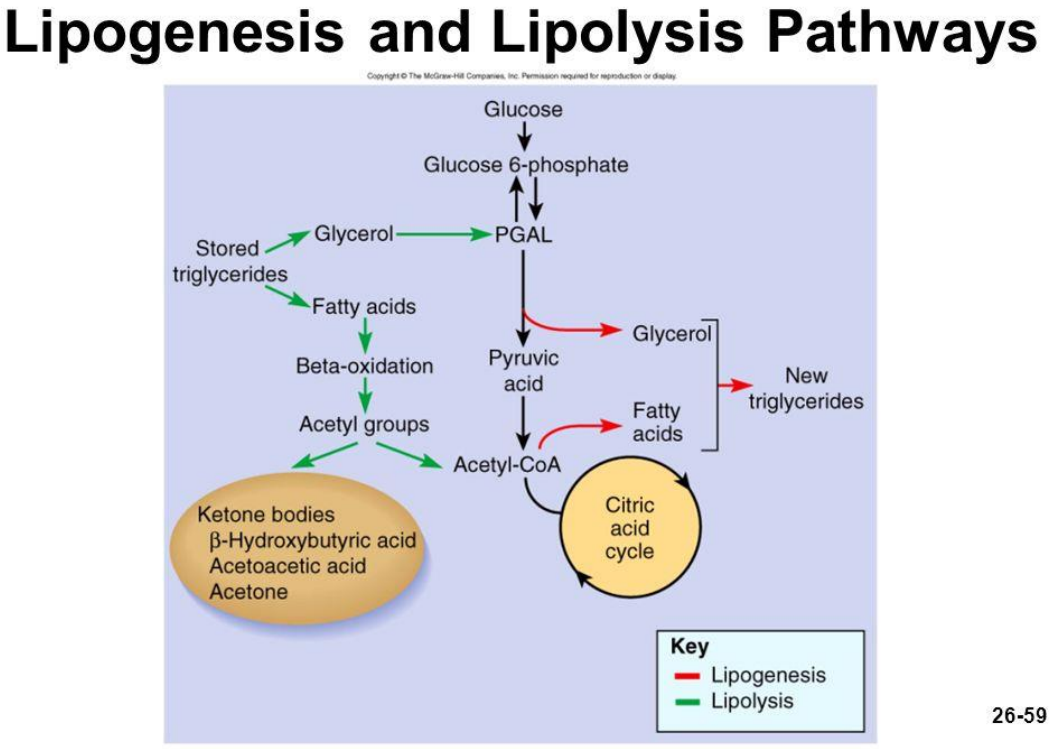
Define as synthesis of TG from primary substances fatty acids and glycerol (esterification).

Hormones increase the rate of esterification (lipogenesis) in adipose tissues.

1. insuline 2. prolactin

Benefits of insulin:

1. enhanced the uptake of glucose into adipose tissues.
2. inhibit the release of FFA from adipose tissues



B - Oxidation of fatty acids :

Oxidation is occurs in mitochonderia (power houses).

1. Long chain fatty acids first activated to acyl COA in the cytosol by the enzyme acyl-COA synthetase , ATP, COA and Mg ion.

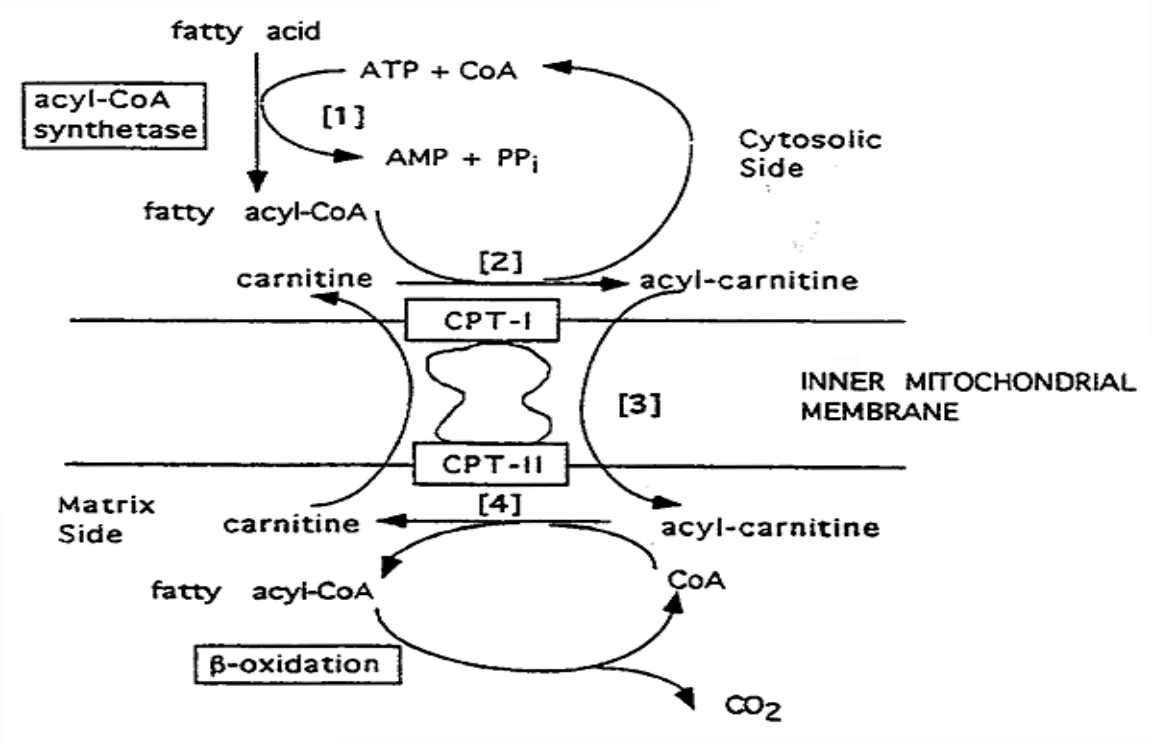
2. Carnitine is a carrier transport acyl-COA from cytoplasm to mitochondria.

3. acyl-COA convert to B- keto acyl need FAD and NAD as coenzyme and multiple enzyme.

4. B-ketoacyl COA splits to acetyl-COA and acyl-COA. The latest compound undergoes further oxidation until completely oxidized. Each acetyl-COA liberate, is oxidized by Krebs cycle to CO2, H2O and ATP within mitochondria.

Q: Why it is named B-oxidation.

Transport of fatty acid from cytoplasm to the mitochondria



Energetices:

1. How many Acetyl CoA units will be formed?
2. How many cycles are necessary for converting all fatty acid to acetyl CoA?
3. in each cycle, an Acetyl CoA, NADH.H+ and FADH2 are produced.

Number of Acetyl coA = number of carbon atom (n) / 2

The number of necessary cycles = (n / 2) -1

Ex: calculate number of acetyl COA and number of cycles of palmitic acid (16C).

number of acetyl COA = 16 /2 = 8

each acetyl COA give ----------12 ATP 12 × 8 = 96 ATP

number of cycles = 16/ 2 – 1 = 7

each NADH2 give 3 ATP

each FADH2 give 2 ATP

---

5 ATP produce from each cycle

5 × 7 = 35 ATP

96 + 35 = 131 ATP -2 = 129 the net ATP produce from the oxidation of palmitic acid

2 ATP consume in transport of fatty acid to the fatty acyl in cytoplasm

Energy production = 129 × 7.6 = 980 kcal/ mol of palmitic acid

The remaining energy is used as heat by the body.

Fatty Liver

Fatty liver: Define as deposition of excess triglycerides in the liver cells in excess of 5% of the liver weight.

The reasons of fat accumulation in liver mainly due to:

1. The liver take up fatty acids from blood stream and esterify into triacylglycerol (TAG) (from diet).

2. These triglycerides with endogenously synthesized in liver Incorporated into VLDL secreted from liver (limited).

3. The liver has only limited capacity for oxidation of fatty acids, balance between storage of TAG in adipose tissue and liver is delicate and can revert to a net transfer of f.a to liver resulting in accumulation of TAG in liver.

Factors increase liver fat

1- dietary lipids

2- synthesis of F.a from CHO and proteins

3- mobilization of FA from depots to liver.

LIVER

Factors decrease liver fat

1- mobilization of fats from liver as VLDL.

2. degradation of FA in the liver

(**3/4 as phospholipids** , **1/4 as TG**)

Causes of Fatty Liver

1. physiological : increase mobilization of fat from depots to liver, occurs in

a. diabetes mellitus.

b. starvation

c. carbohydrate deprivation (stress, exercise).

2. pathological: there is metabolic blockage in the synthesis of VLDL due to.

a. deficiency of fatty acids.

b. choline deficiency

c. deficiency in coenzyme such as, Vit E, pantothenic, pyridoxine and inositol.

d. alcoholism.

e. poisoning CCl4.

Lipotropic factor: substances prevent accumulation of fat in liver such as choline and methionine.

Ketone bodies: Ketone bodies are three water-soluble molecules that are produced by the liver from fatty acids during **periods of**:

1. low food intake 2. carbohydrate restrictive diet 3.starvation
4.prolonged intense exercise 5. untreated type 1 diabetes mellitus.

Ex : acetoacetic acid, B- hydroxy butyric acid and acetone

Ketonemia: the concentration of ketone bodies in the blood increase more than normal value.

- At this stage ketone bodies appear in urine.

Ketoneuria: detectable amount of ketone bodies appear in urine.

Ketosis: ketonemia, ketoneurea and smell of acetone in breath appear.

Acidosis: severe ketosis accompained by excretion of large amount of water carry ketone bodies.

Clinical Significance of Ketogenesis

- Carbohydrate shortages cause the liver to increase

Fatty acid oxidation ⟶ Acetyl-coA ⟶ Ketone bodies

- Ketone bodies serve as a energy source for **Heart Renal cortex and Skeletal muscles**, thereby preserving the limited glucose for use by the brain.
- ↑Mainly in Starvation & untreated insulin-dependent diabetes mellitus [**diabetic ketoacidosis** (DKA)].
- Ketone bodies increase **lowers the pH of the blood**.
- Acidification of the blood is **dangerous** chiefly because it **impairs the ability of hemoglobin to bind oxygen** ---- results in coma & even death.

Metabolism of ketone body formation

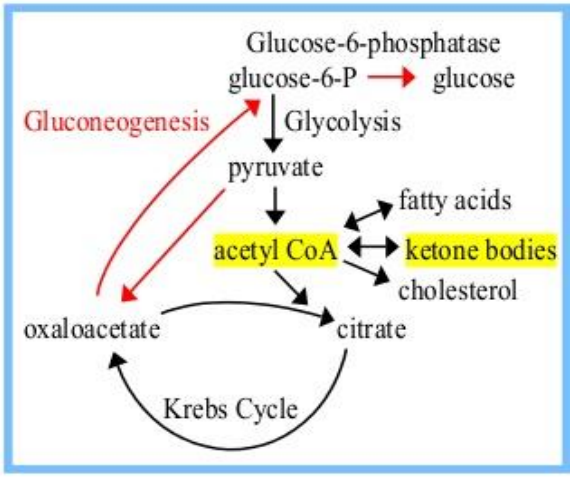
1-- Reduce amount of oxaloacetate lead to acetyl COA cannot be metabolized for Krebs Cycle.
2-- Therefore acetyl COA tend to form ketone bodies.
3-- oxaloacetate utilize to produce glucose for brain and muscle by gluconeogenesis.

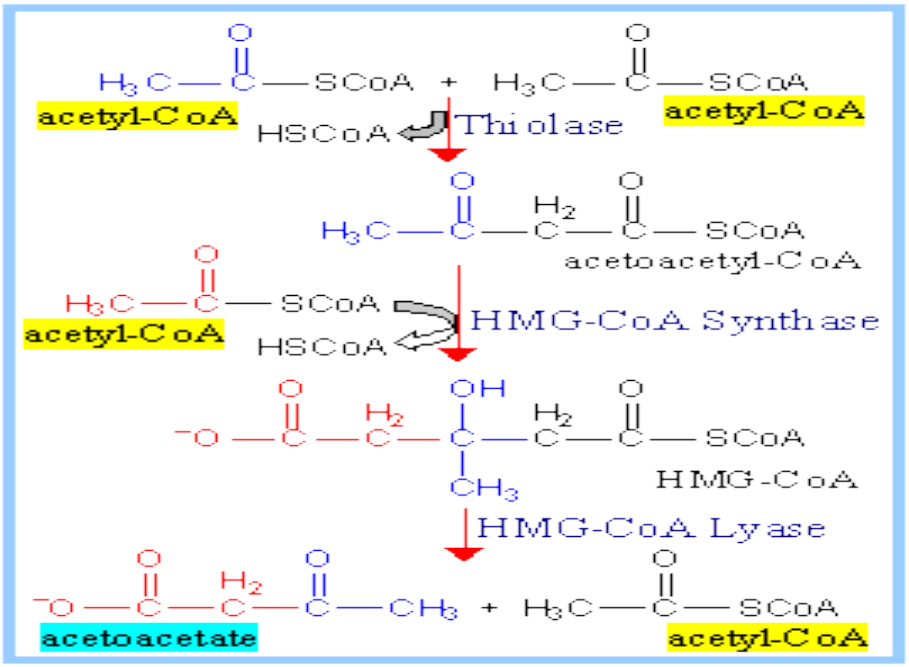
-- Normal level of ketone body in blood, below 1 mg per 100 ml.
-- Normal level in urine, less than 125 micro gm In 24 hrs.

Risk: ketonbodies increase lowers the PH of blood, make it acidic.
Acidification of the blood dangerous because **it impairs the ability of hemoglobin to bind with oxygen**. Result in **coma even death.**

Ketone Bodies Metabolism

- Ketone synthesis occurs in the Liver - Mitochondria
- During prolonged starvation, fasting (and in diabetes) oxaloacetate is depleted in liver due to gluconeogenesis
- This impedes entry of acetyl-CoA into Krebs cycle.
- Acetyl-CoA in liver mitochondria is converted then to ketone bodies - Acetone, Acetoacetate & β-hydroxybutyrate.





Normal concentration of plasma lipids

fractions	range (mg/dl)	mean

Total lipids	**360- 820**	**560**
Triglyceride	**80- 180**	**150**
Total phospholipids	**125- 390**	**210**
Lecithin	**50- 200**	
Cephalin	**50- 130**	
Sphingomyelin	**15- 35**	
Total cholesterol	**100- 200**	**150**
Serum HDL- cholesterol :		
Male :	**35- 60**	
Female :	**40- 70**	
Serum LDL- cholesterol	**< 120**	

Abnormalities in blood lipids

Hypertriglyceridemia:

Increase the level of triglyceride in the blood more than normal value in

1. hypothyroidism **2. uncontrolled diabetic** **3. kidney disease**

4. pancreatitis **5. alcoholic consumption**

Hypercholesterolemia:

Increase the level of cholesterol in the blood more than normal value in

1. atherosclerosis **2. diabetes mellitus** **3. hypothyroidism**

4. Pancreatitis **5. obstructive jaundice**

Familial hypercholesterolemia:

Excessive synthesis of cholesterol by the liver

Leading to increase in level of cholesterol and LDL in plasma.

Hyperlipoproteinemia:

Increase the level of lipoproteins in plasma more than normal value as in:

1. increase in Chylomicrons due to absence of lipase enzyme.

2. Increase in VLDL and LDL , allow to increase in Cholesterol and TG which give strong point to atherosclerosis.

Hypolipoproteinemia:

Decrease the level of lipoproteins from their normal value due to Genetic disorder**.**

Ex : B- lipoproteinemia :

it is rare inherited disease , chol is low due to absence of LDL , TG, no chylomicron and VLDL is formed, allow to accumulate of TG in liver and intestine.

Abnormalities in blood lipids

Hypertriglyceridemia:

A condition in which triglyceride levels are elevated in the blood.
It is a common disorder in the United States. It is often caused or worsened by factors
Such as
1. uncontrolled diabetes mellitus. 2. obesity 3. sedentary habits
all of which are more prevalent in industrialized societies than in developing nations.
The level of triglycerides in our blood usually increases with age, but risk factors that increase the likelihood of the triglyceride level becoming too high include the following:
Lifestyle*:*

- Overweight or obesity
- Excess alcohol intake
- Lack of physical activity
- Inherited disorders
- Pregnancy
- Type 2 diabetes
- Metabolic syndrome

A triglyceride level is considered **normal if it is below 150 mg /dL**
while **borderline ranges from 150 to 199 mg /dL**
high from 200 to 499 mg/ dL
very high is 500 mg/dL or above.
When level reaches 1000 to 2000 mg/dL, at which point the signs and symptoms may appear.

Signs and symptoms
Hypertriglyceridemia does not usually present with symptoms until the level reaches 1000 to 2000 mg/dL, at which point the signs and symptoms may include:

- Gastrointestinal pain
- Difficulty breathing
- Memory loss
- Dementia
- Xanthelasmas - yellowish deposits of fat on or around the eyelids
- Corneal arcus - a thin, whitish or grey arc around the outer part of the cornea
- Xanthomas - yellowish deposits of fat under the skin found on the back, chest, elbow, knee.

hypertriglyceridemia have risk factors associated with
heart disease and stroke
obesity
metabolic syndrome(high blood pressure, high blood sugar, excess fat around the waist and abnormal cholesterol levels).
increase the risk of pancreatitis or **inflammation of the pancreas.**
Pancreatitis can cause problems with digestion, stomach pain, pancreatic damage and eventually, diabetes.

2. Hypercholesterolemia.

Increase the level of cholesterol in the blood more than normal value.
High levels of LDL cholesterol are linked to atherosclerosis.

atherosclerosis : accumulation of cholesterol-rich fatty deposits in arteries cause arteries to narrow or become blocked, slowing or stopping the flow of blood to vital organs, especially the heart and brain.

Atherosclerosis affecting the heart is called coronary artery disease, or heart attack.

When atherosclerosis blocks arteries that supply blood to the brain, it can cause a stroke.

There are two main types of cholesterol:

low-density lipoprotein (LDL) cholesterol (the "bad" cholesterol) and high-density lipoprotein (HDL) cholesterol (the "good" cholesterol).

High levels of **HDL cholesterol** actually protect against heart attacks and strokes by removing cholesterol from the arteries and bringing it back to the liver.

risk factors for coronary artery disease include:

high LDL cholesterol level and diabetes.

- Being a male older than 45
- Being a female older than 55
- Being a female with premature menopause
- Having a family history of premature coronary artery disease (a father or brother younger than 55 with coronary artery disease or a mother or sister younger than 65 with coronary artery disease)
- Smoking cigarettes
- Having high blood pressure
- Not having enough good cholesterol (high density lipoprotein or HDL).

LDL cholesterol level 100 is best, but less than 130 may be acceptable for people with few or no risk factors.

HDL cholesterol level People **below 40 mg/ dl** are more likely to develop atherosclerosis, heart disease and stroke.

Levels of HDL cholesterol **above 60 mg/dl** are associated with less atherosclerosis and are thought to help protect against heart disease and stroke.

Symptoms

Most people with high cholesterol don't have any symptoms until cholesterol-related atherosclerosis causes significant narrowing of the arteries leading to their hearts or

brains. result can be heart-related **chest pain (angina)** or other symptoms of **coronary artery disease,** as well as symptoms of **decreased blood supply to the brain** (transient ischemic attacks or stroke).

Familial hypercholesterolemia :

About 1 out of every 500 people has an inherited disorder called familial hypercholesterolemia,

which can cause extremely high cholesterol levels (above 300 milligrams per deciliter).

People (xanthomas) over various tendons, especially the Achilles tendons of the lower leg.
Cholesterol deposits also can occur on the eyelids, where they are called xanthelasmas.

Diagnosis

1. Your doctor will ask if anyone in your family has had coronary artery disease,
2. high cholesterol or diabetes.
3. The doctor will ask about your diet and if you have ever smoked.
4. check blood pressure.
5. look for xanthomas and xanthelasmas.
6. Your doctor can confirm a diagnosis of high cholesterol with a simple blood test.

Treatment

1. The initial treatment of high cholesterol should always be lifestyle changes
2. altering your diet and avoid processed foods, especially those that contain saturated fats.
3. eat more fresh fruits and vegetables, whole-grain breads and cereals, and low-fat dairy products.
4. getting more exercise.

Hyperlipoproteinemia

It results from an inability to break down lipids or fats in body, specifically cholesterol and triglycerides.

There are several types of hyperlipoproteinemia. **The type depends on the concentration of lipids and which are affected.**

High levels of cholesterol or triglycerides are associated with **heart problems.**

Causes of hyperlipoproteinemia

Hyperlipoproteinemia can be a **primary or secondary** condition.

1. Primary hyperlipoproteinemia is often **genetic**. It's a result of a **defect or mutation in lipoproteins.** cause accumulation of lipids in body.

2. Secondary hyperlipoproteinemia is the result of other health conditions that lead to high levels of lipids in your body. These include:

- diabetes
- hypothyroidism
- pancreatitis
- use of certain drugs, such as contraceptives and steroids
- certain lifestyle choices

Symptoms of hyperlipoproteinemia

- pancreatitis
- abdominal pain
- enlarged liver or spleen
- lipid deposits or xanthomas
- family history of heart disease
- family history of diabetes heart attack
- stroke

How hyperlipoproteinemia is diagnosed

A doctor can diagnose hyperlipoproteinemia with a blood test. Sometimes, family history is useful. If you have lipid deposits on your body, your doctor will also examine those.

Other diagnostic tests might measure thyroid function, glucose, protein in the urine, liver function, and uric acid.

How hyperlipoproteinemia is treated

Treatment for hyperlipoproteinemia will depend on which type you have. When the condition is the result of hypothyroidism, diabetes, or pancreatitis, treatment will take the underlying disorder into account.

Your doctor may prescribe medications like the following to help lower lipid levels:

- atorvastatin (Lipitor)
- Fluvastatin (Lescol XL)
- pravastatin (Pravachol)
- ezetimibe (Zetia)

Certain lifestyle changes can also help with hyperlipoproteinemia. These include:

- a low-fat diet
- increased exercise
- weight loss
- stress relief
- a decrease in alcohol consumption

Consult your doctor to find out which lifestyle changes are right for your condition.

Article resources