ERRORS OF LIPID METABOLISM

Definition:

- Many childhood conditions are caused by gene mutations that encode specific proteins. These mutations can result in the alteration of primary protein structure or the amount of protein synthesized.

Definition:

- The functional ability of protein, whether it is an enzyme, receptors, transport vehicle, membrane, or structural element, may be relatively or seriously compromised.
- These hereditary biochemical disorders are collectively termed as **‘’Inborn errors of metabolism”**

Classifications:

1. Disorders of F.A-oxidation:-
   A. Defects in Beta-oxidation:-
      a) Sudden infant death syndrome(SIDS)
      b) Zellweger's Syndrome.
      c) Carnitine deficiency.
      d) Carnitine palmitoyl transferese deficiency.

Classifications:

1. Disorders of F.A-oxidation:-

   B. Defect in Alpha-oxidation:-

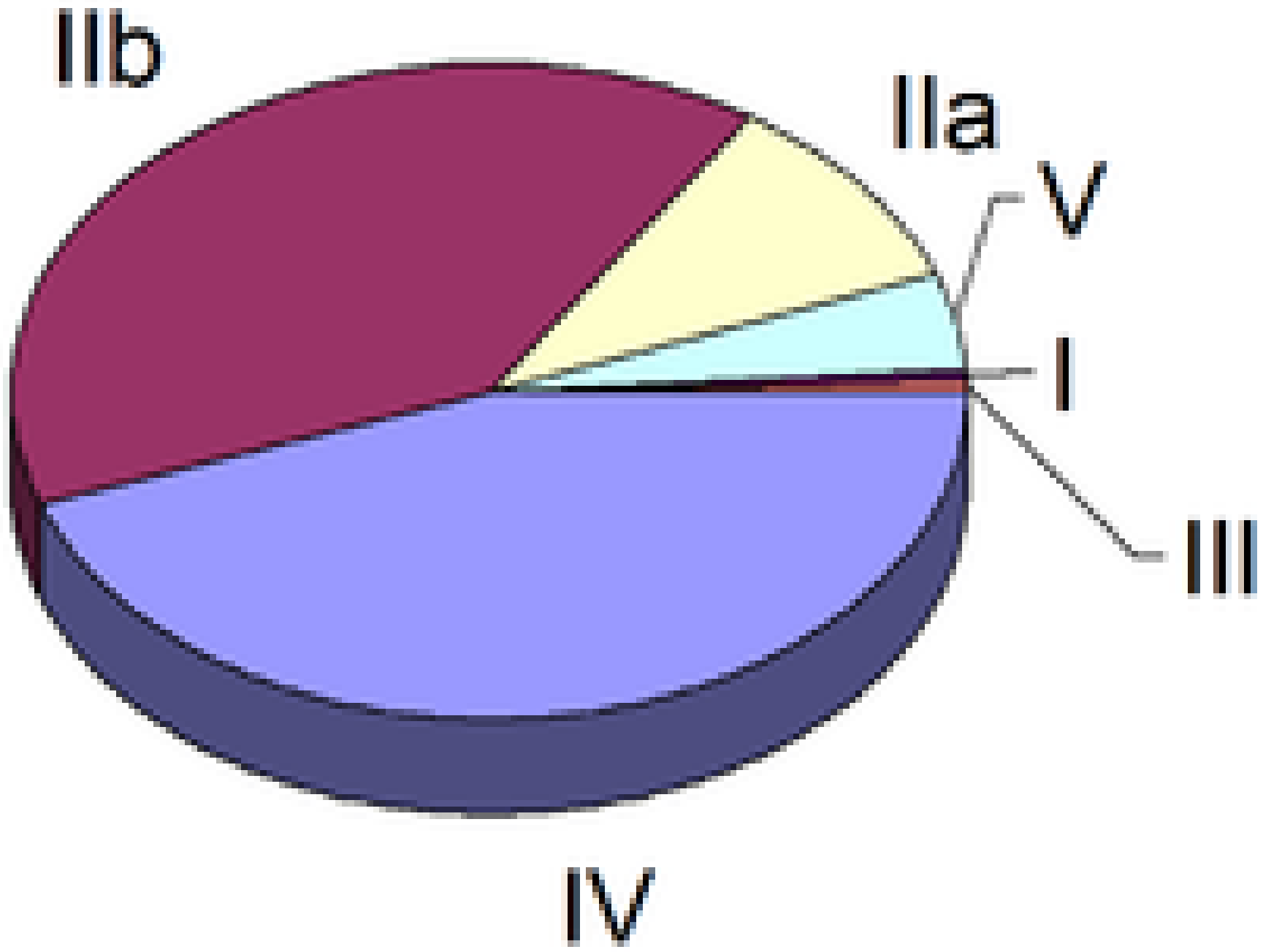
   Refsum’s disease.

2) Lipid Storage diseases:-

A. Niemann-pick disease
B. Farber’s disease
C. Gaucher’s disease
D. Krabbe’s disease
E. Tay- sachs disease
F. Fabry’s disease

Fredrickson Classification of Hyperlipidemia

Type	Lipoprotein Elevated	Cholesterol	Triglyceride	Risk of Atherosclerosis
I	Chylomicrons	+	+++	Not elevated
IIa	LDL	++	Normal	High
IIb	LDL + VLDL	++	++	High
III	IDL	++	++	Moderate
IV	VLDL	+	++	Moderate
V	Chylomicrons + VLDL	+	++	Not elevated


IIb
IIa
V
I
III
IV

Fredrickson Classification

= Common

Type	Elevated Particles	Associated Clinical Disorders	Serum Total Cholesterol	Serum Triglycerides
I	Chylomicrons	Lipoprotein Lipase deficiency, Apolipoprotein C-II deficiency	⟷	↑↑
IIa	LDL	Familial Hypercholesterolemia, polygenic hypercholesterolemia, Familial combined hyperlipidemia, Nephrosis, Hypothyroidism	↑↑	⟷
IIb	LDL, VLDL	Familial combined hyperlipidemia	↑↑	↑
III	IDL	Dysbetalipoproteinemia	↑	↑
IV	VLDL	Familial Hypertriglyceridemia, Familial combined hyperlipidemia, Diabetes	⟷↑	↑↑
V	Chylomicrons, VLDL	Diabetes	↑	↑↑

Clinical Disorders associated with Lipoprotein Metabolism:-

A. Hyper-lipoproteinaemia:-

Frederickson et al(1967) proposed 5 types based on changes in plasma lipoprotein.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Clinical Disorders associated with Lipoprotein Metabolism:-

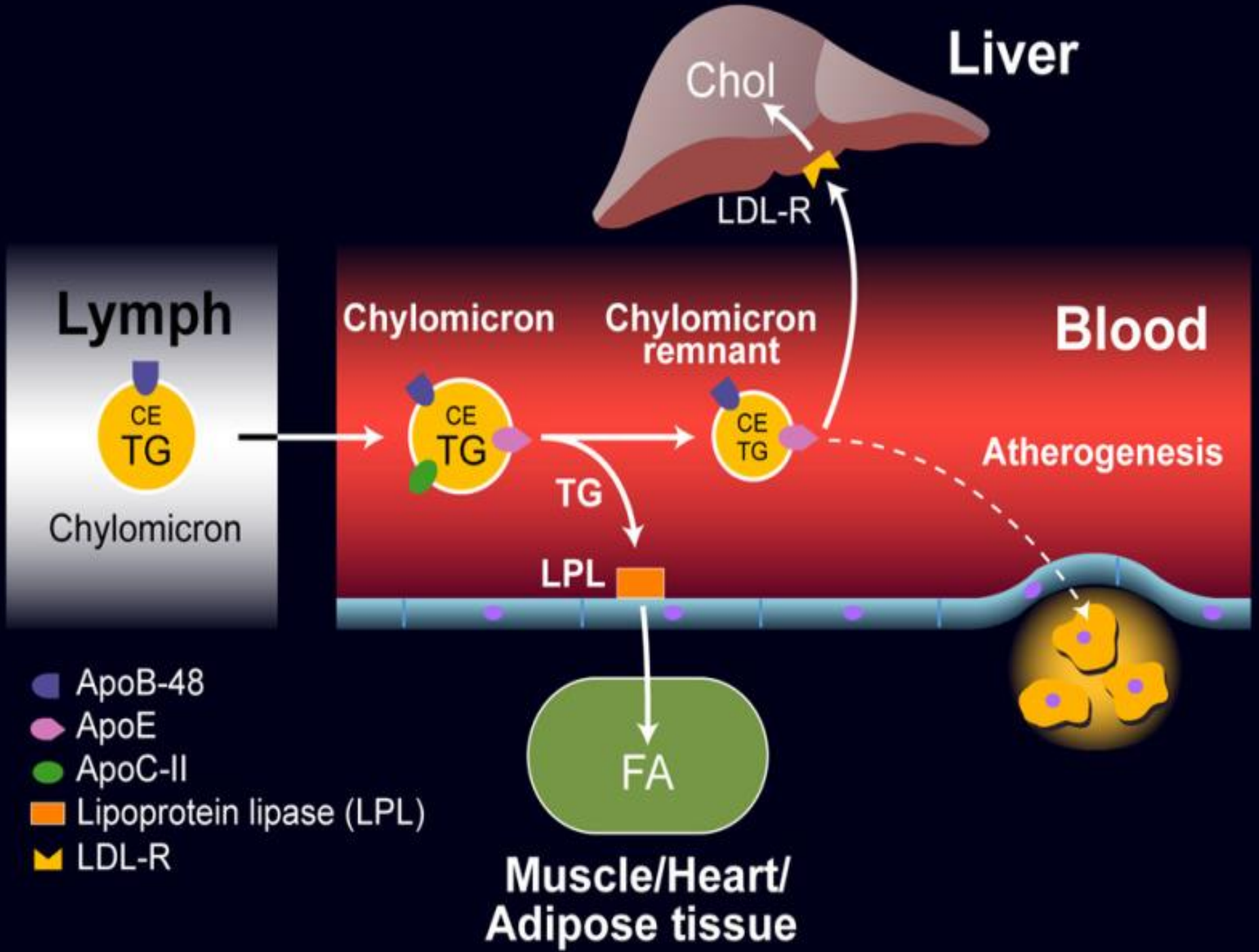
1. Type-I: familial lipoprotein lipase deficiency:-

- Rare disorder characterized by hypertriglyceridaemia & hyperchylomicronaemia.

- VLDL(Pre-beta Lipoproteins) also increased.
- Alpha Lipoprotein(HDL) & Beta-Lipoproteins(LDL) is decreased.

Inheritance:- Autosomal recessive.

Enzyme deficiency:- “Lipoprotein lipase”


Liver
Chol
LDL-R
Lymph
CE
TG
Chylomicron
Chylomicron
Chylomicron
remnant
Blood
CE
TG
CE
TG
TG
Atherogenesis
LPL
FA
Muscle/Heart/
Adipose tissue
ApoB-48
ApoE
ApoC-II
Lipoprotein lipase (LPL)
LDL-R

Clinical features:-

- Recurrent abdominal pain.
- Eruptive xanthomas.
- Hepatomegaly.

Lab.diagnosis:-

- **Refrigeration Test:-**

  If serum of suspected patients is taken in a narrow small tube & kept in refrigerator temp. for 24hrs undisturbed, a clean zone of chylomicrons is seen to float on the top and make a distinct separate layer.

Management:-

- Restriction of fat intake.
- Medium Chain Triglyceride.

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2) Type-II: familial hypercholesterolaemia(FHC):-

- Common disorder.

- Characterized by:-
  - Increased Total Cholesterol & HDL.
  - May be high TG & VLDL.

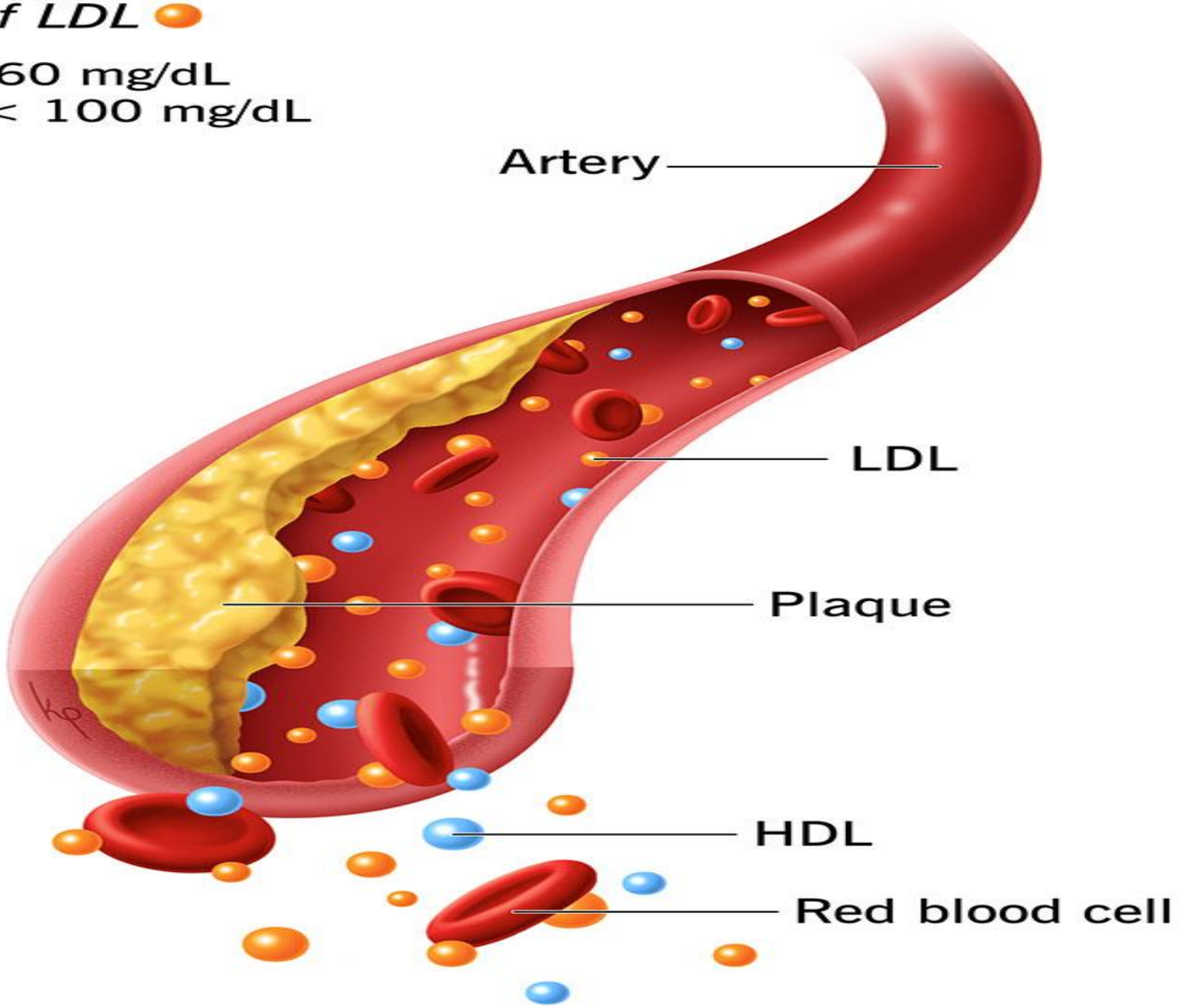
2) Type-II: familial hypercholesterolaemia(FHC):-

- Inheritance:- Autosomal dominant
- Frequency:- 1:500(0.2%)
- Metabolic defect:- No enzyme deficiency but defect of LDL receptors.

Familial Hypercholesterolemia

Levels of LDL

High > 160 mg/dL
Normal < 100 mg/dL



2) Type-II: familial hypercholesterolaemia(FHC):-

Clinical features:-Atherosclerosis, CAD, Corneal arcus & Tuberous xanthoma.

Management:-

- Low cholesterol diet decreased intake of saturated fat.
- Give PUFA & drug like statins.

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3) Type-III: familial dys-beta Lipoproteinaemia:-

Synonyms:- ***Broad beta disease & Remnant removal disease.***

Characterised by:-

- Increased LDL & VLDL.
- Rise in IDL
- Hypercholesterolemia & hypertriglyceridaemia

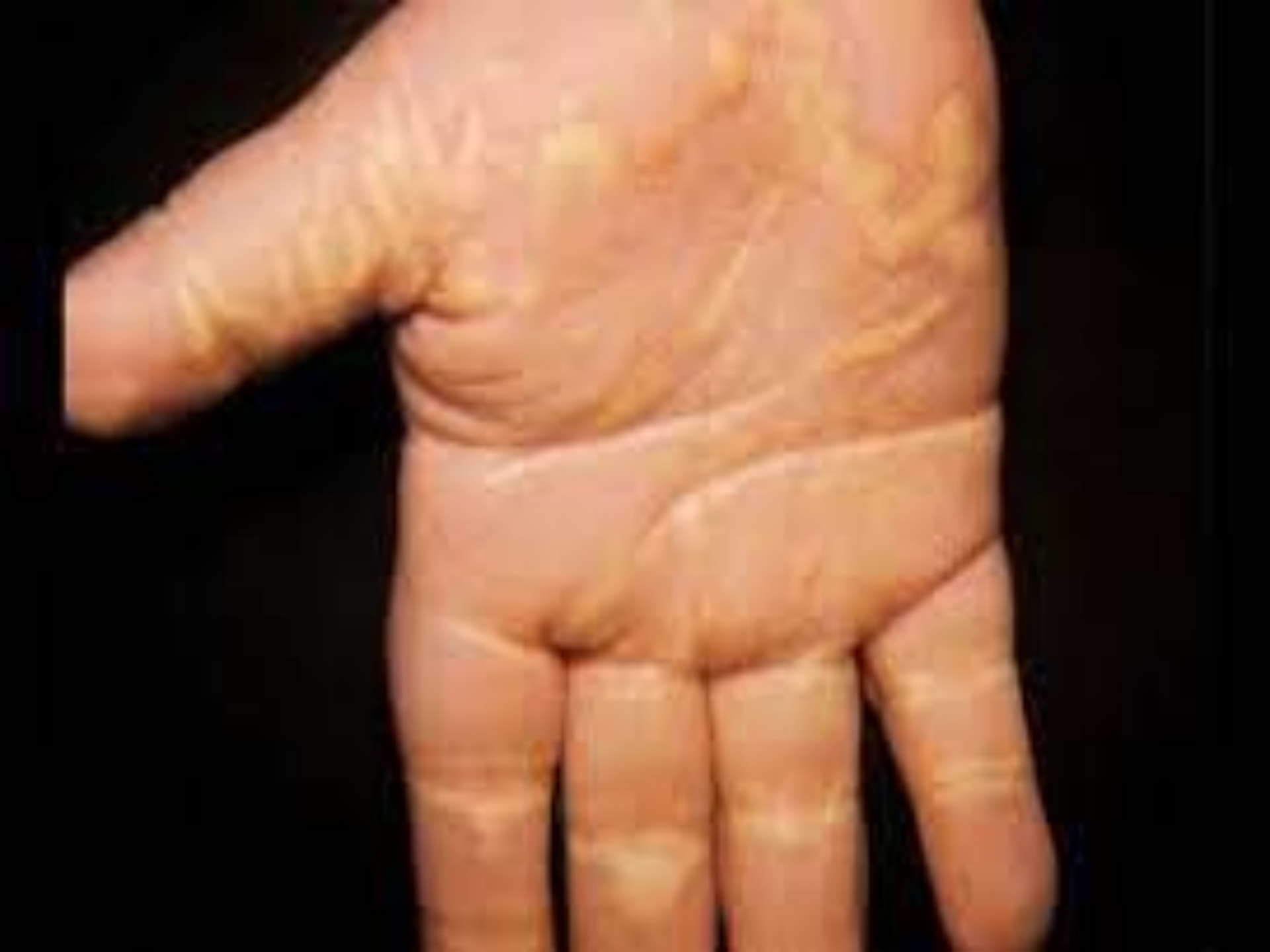
3) Type-III: familial dys-beta Lipoproteinaemia:-

Inheritance:- Autosomal dominant

Frequency:- 1:5000(0.02%)

Metabolic defect:-

- Increased apo-E & apo-B
- Conversion of normal VLDL to IDL & its degradation without conversion of LDL.
- Defect is in “Remnant” metabolism



Clinical Features:-

- Palmar xanthoma.
- High incidence of vascular disease.

Management-

- Reduction of weight.
- Restriction of fat & chol.
- Give PUFA & drugs.

4) Type-IV: familial hypertriglyceridaemia:-

Characterised by:-

- Increased TG & VLDL.
- Chol. May be normal or increased.
- Decreased HDL & LDL.

4) Type-IV: familial hypertriglyceridaemia:-

Inheritance:- Autosomal dominant

Metabolic defects:-over production of VLDL & Apo-CII

Clinical features:- Associated with diabetes mellitus, IHD & Obesity.

Management:-

- Reduction of weight.
- Restriction of Carbohydrate & chol.
- Hypolipidaemic drugs.

5) Type-V: Combined hyperlipidaemias:-

- Hypercholesterolemia & hypertriglyceridaemia.
- Decreased HDL & LDL.

- Inheritance:- Autosomal dominant

5) Type-V: Combined hyperlipidaemias:-

Metabolic defects:-Secondary to other causes

Clinical features:-

- Manifested only in adulthood.
- Xanthomas.
- Abnormal glucose tolerance.
- Frequency Associated with diabetes mellitus & Obesity.

- Management:-
- Reduction of weight.
- High PUFA intake & Hypocholipidemic drugs.

Wolman's Disease:-

- Also called *cholesteryl ester storage disease*.
- Hyper-cholesterolaemia.

Enzyme deficiency:-

"Cholesteryl ester hydrolase" in lysosomes; such deficiency in cells of fibroblasts have been demonstrated.

B)Hypolipo-proteinaemias:-

1) A-Beta Lipoproteinaemia:-

- Rare inherited disorder.

Characterized by:-

- Decreased plasma cholesterol due to absence of LDL.
- Low TG.
- No Chylomicrons & VLDL formed.\

B)Hypolipo-proteinaemias:-

Clinical features:-

- Malabsorption.
- Mental & physical retardation.
- Acanthocytosis.

Metabolic defect:- Defect in *"Synthesis of apo-B"* leading to gross deficiency of apo-B resulting to deficiency of lipoproteins containing apo-B i.e mainly Chylomicrons, VLDL & LDL.

2) Familial Alpha-Lipoprotein deficiency:-

- Also called Tangier's disease

Characterized by:-

- Deficiency of HDL.
- In homozygous patients plasma HDL may be nearly completed absent.

Inheritance:- Autosomal recessive

Metabolic defect:-

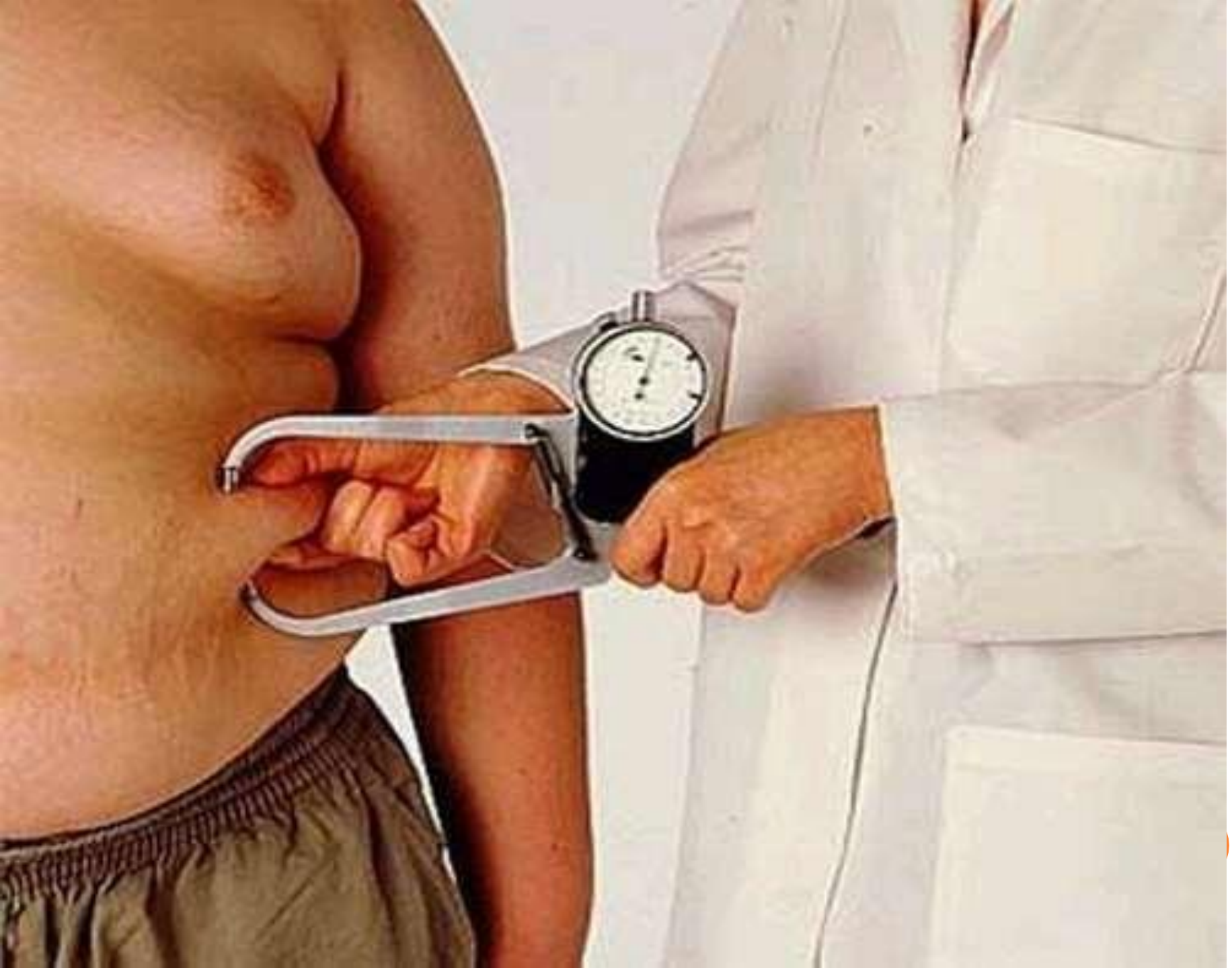
- Reduction in apo-AI & apo-AII
- Leading to accumulation of cholesteryl esters in diff. tissues.

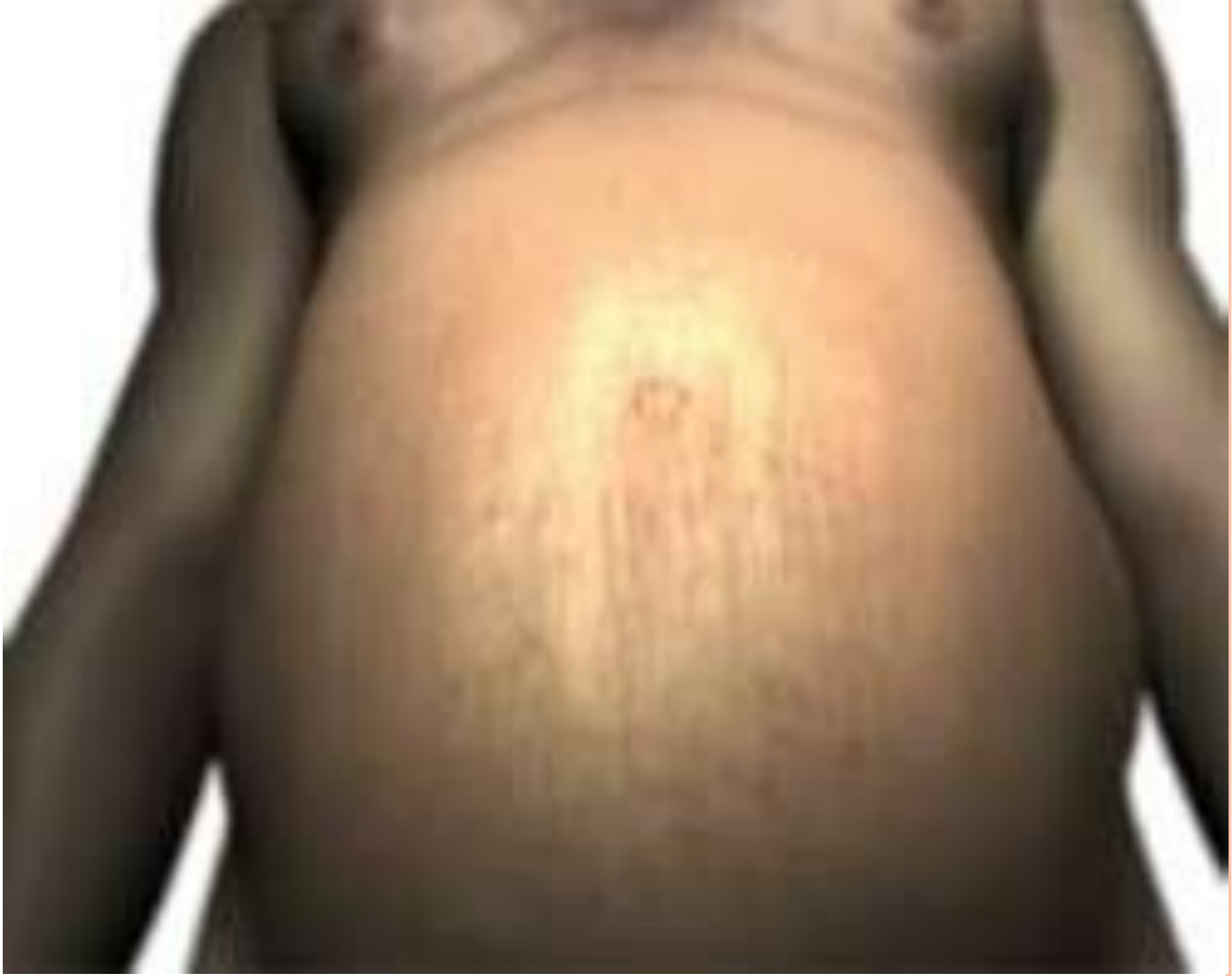
Clinical features-

- Increased risk of CAD.
- Adenoids.

All these Disease can be diagnosed Prenatally by:-

- Amniocentesis
- Chorionic Villi Sampling
- Ultrasonography
- Fetal blood Sampling
- Maternal blood Sampling



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