DYSLIPIDEMIA

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Dyslipidemia

- Definition :

Dyslipidemias are disorders of lipoprotein metabolism, including lipoprotein overproduction or deficiency. These disorders may be manifested by elevation of the serum total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride concentrations, and a decrease in the high-density lipoprotein (HDL) cholesterol concentration.

Why we have a strong concern about dyslipidemias

- There is a strong relationship between elevated serum cholesterol levels and the genesis of coronary heart disease. Coronary artery disease yet remains one of the major killers in current society.

- There are variety of other diseases which have closer relation with dyslipidemias. dyslipidemia remains major etiological factor of those diseases.

Lipid profile

- Traditionally, most laboratories have required patients to fast for 9–12 hours before screening. However, recent studies have questioned the utility of fasting before lipid panels, and some diagnostic labs now routinely accept non-fasting samples.
- **The lipid profile typically includes:**
- Low-density lipoprotein (LDL)
- High-density lipoprotein (HDL)
- Triglycerides
- Total cholesterol
- **Using these values, a laboratory may also calculate**:
- Very low-density lipoprotein (VLDL)
- Cholesterol:HDL ratio

Total cholesterol levels in a lipid profile

- A total cholesterol level of less than 200 mg/dL (5.17 mmol/L) is **normal**.
- A total cholesterol level of 200 to 239 mg/dL (5.17 to 6.18 mmol/L) is **borderline high**.
- A total cholesterol level greater than or equal to 240 mg/dL (6.21 mmol/L) is **high**.

TG levels

- **Triglycerides** — High triglyceride levels are also associated with an increased risk of cardiovascular disease
- Normal - less than 150 mg/dL (1.69 mmol/L)
- Borderline high - 150 to 199 mg/dL (1.69 to 2.25 mmol/L)
- High - 200 to 499 mg/dL (2.25 to 5.63 mmol/L)
- Very high - greater than 500 mg/dL (5.65 mmol/L)

HDL levels

- A level greater than or equal to 60 mg/d is exelent level.
- while levels of HDL cholesterol less than 40 mg/dL lower than desired.

Cholesterol:HDL ratio

- Your cholesterol ratio is calculated by dividing your total cholesterol by your HDL number. For instance, if your total cholesterol is 180 and your HDL is 82, your cholesterol ratio is 2.2. According to the American Heart Association (AHA), you should aim to keep your ratio below 5, with the ideal cholesterol ratio at 3.5. this number represents the risk of a CV disease. Risk increase with the number.

LDL cholesterol

- Blood levels less than 130 mg/dl – desirable
- Between 130 and 159 mg/dl – borderline above 160 mg/dl – definite risk.

Classification

Etiological classification

1- Primary Hyperlipidemia.

2- Secondary Hyperlipidemia.

Familial Hypercholesterolemia

- Also known as primary Hypercholesterolemia(dyslipidaemias)
- They are classified in to few classes which is based on the pattern of lipoproteins on electrophoresis or ultracentrifugation

Familial hypecholesterolaemia

- **Familial hypercholesterolaemia**
- Suspect familial hypercholesterolaemia where:
- Adults have a raised TChol concentration (typically >7.5 mmol/L) and there is a personal or family history of premature CHD.
- Rule out secondary causes of hypercholesterolaemia.
- Do not rule out familial hypercholesterolaemia simply because physical signs such as tendon xanthomata are not present.
- Make a diagnosis using the Simon Broome criteria
- Check two fasting LDL-C measurements to confirm the diagnosis.

Diagnosis

- **Clinical features-**
- 1) Premature arcus senilis - a white or gray opaque ring in the corneal margin
- 2) Tendon xanthomata - these are hard, non-tender nodular enlargement of tendons. They are most commonly found on the knuckles and the Achilles tendons.
- 3) Xanthelasmas - fatty deposits in the eyelids.

Hyperlipoprotenemias

Type I(Familial hyperchylomicronemia)

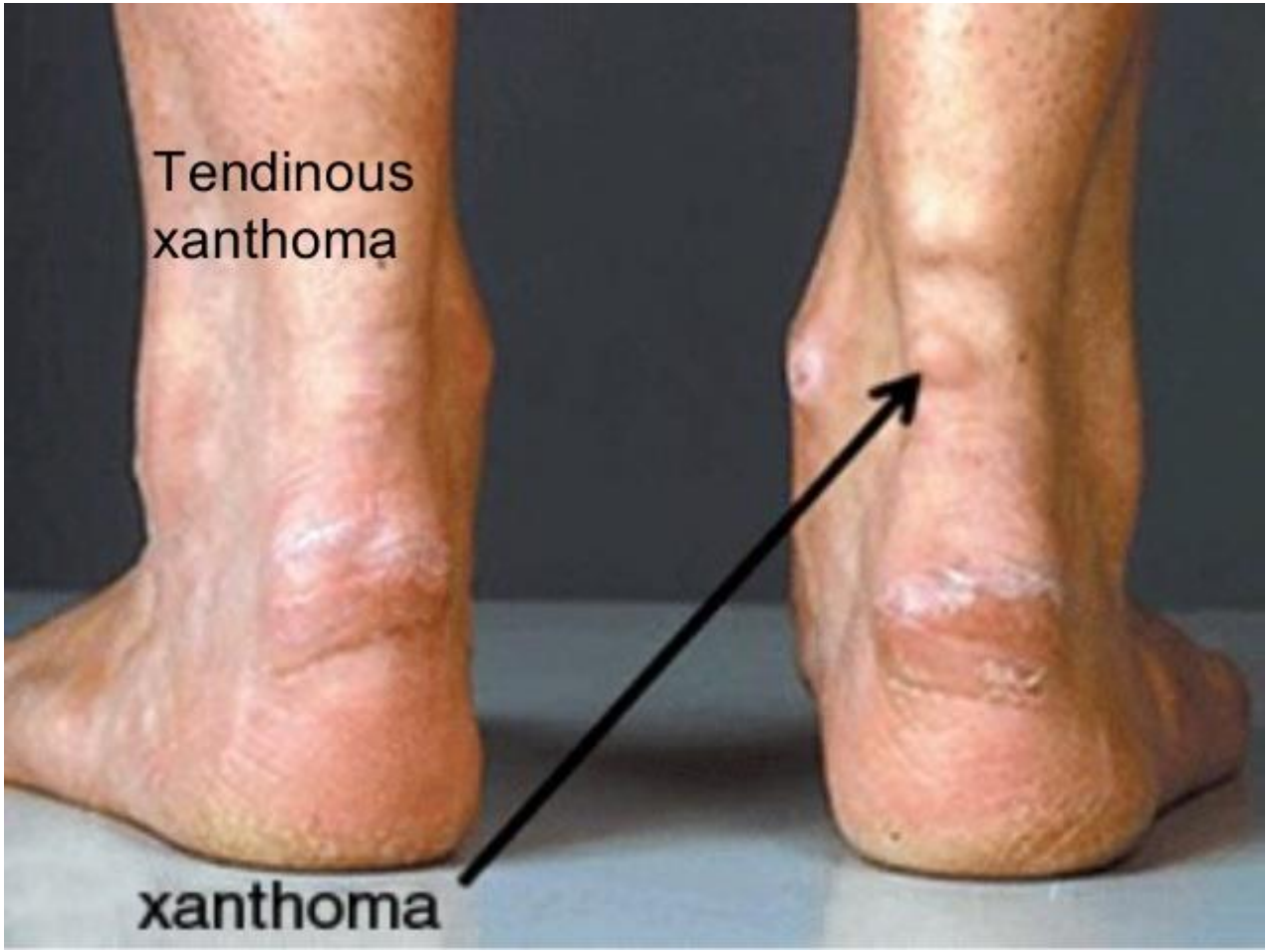
Defiency of lipoprotein lipase or its activator apo c-II.

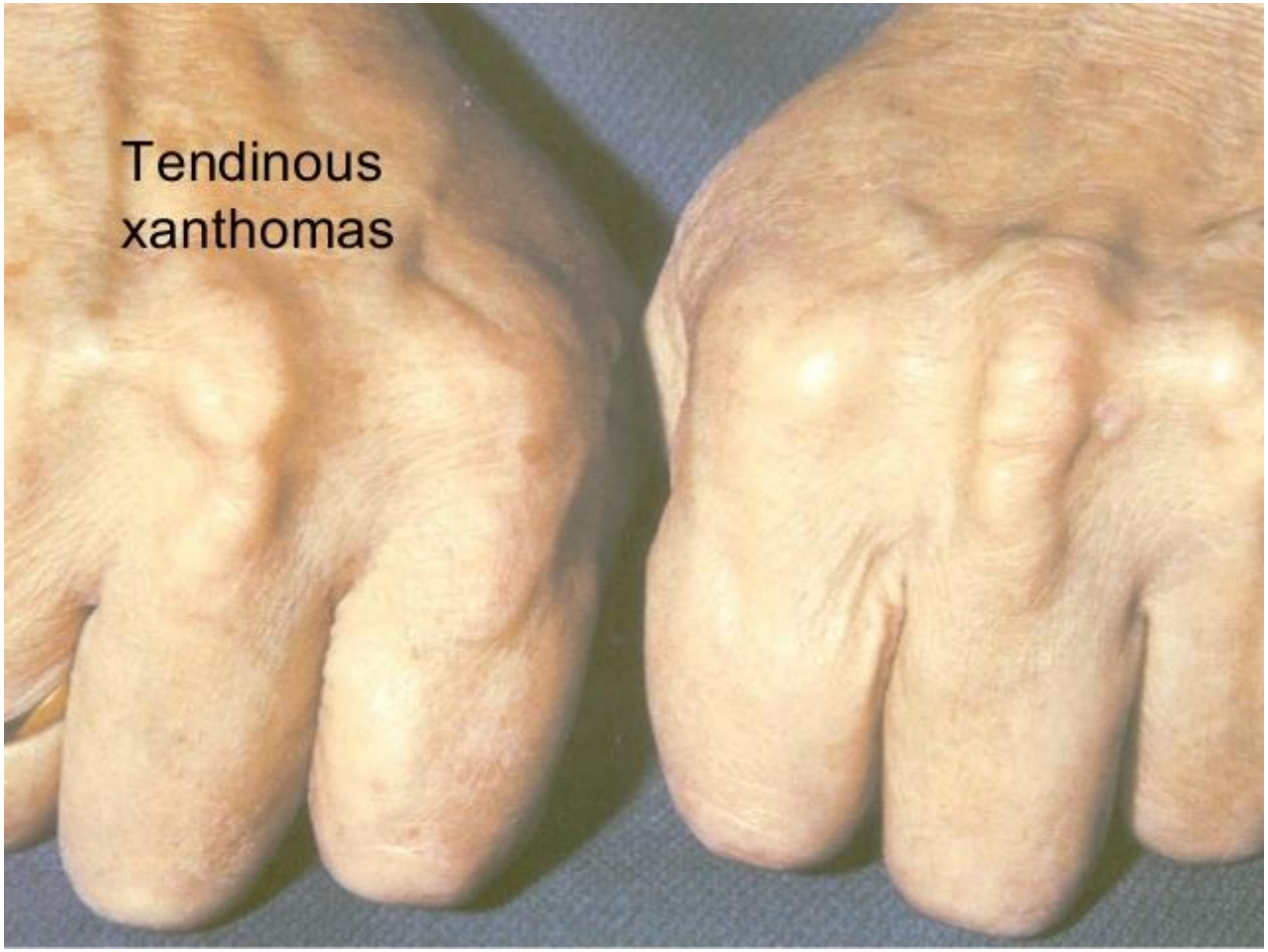
Impares breakdown of TGs ---- increase in TAG levels .

creamy layer over clear plasma.

Risk is minimal .Eruptive xanthoma ; hepatomegaly ; pain in abdomen.

Restriction of fat intake, supplementation with medium chain TGs.


Tendinous
xanthoma
xanthoma


Tendinous
xanthomas

Hyperlipoprotenemias

TYPE II A(primary familial Hypercholesterolemia)

The cause of primary type is LDL receptor defect .

Elevated levels of LDL and Hypercholesterolemia leading to atherosclerosis and ischemic heart disease. Tuberous xanthoma .

Plasma clear.

Low cholesterol diet , decreased intake of saturated fat , give PUFA and drugs like statins.

Hyperlipoprotenemias

- **TYPE II B**
- **TYPE II B also accurs as both primary or secondary.**
- Overproduction of apo B occurs resulting in the elevation of both LDL and VLDL.
- Elevation of plasma cholesterol and TGs observed
- Plasma is slightly cloudy.

Hyperlipoprotenemias

- **TYPE II B**
- Clinical features Corneal arcus.
- Restriction of fat intake, supplementation with medium chain TGs.


Arcus corneae

Hyperlipoprotenemias

TYPE III

Abnormal apo E affects the clearance of chylomicron and VLDL remnants by remnant receptors in liver.

The condition is characterised by hypercholesterolemia atherosclerosis and xanthomas.(deposition of lipid in subcutaneous tissues.

Plasma slightly cloudy.

Reduction of weight , restriction of fat and chol, give PUFA and drugs.

Hyperlipoprotenemias

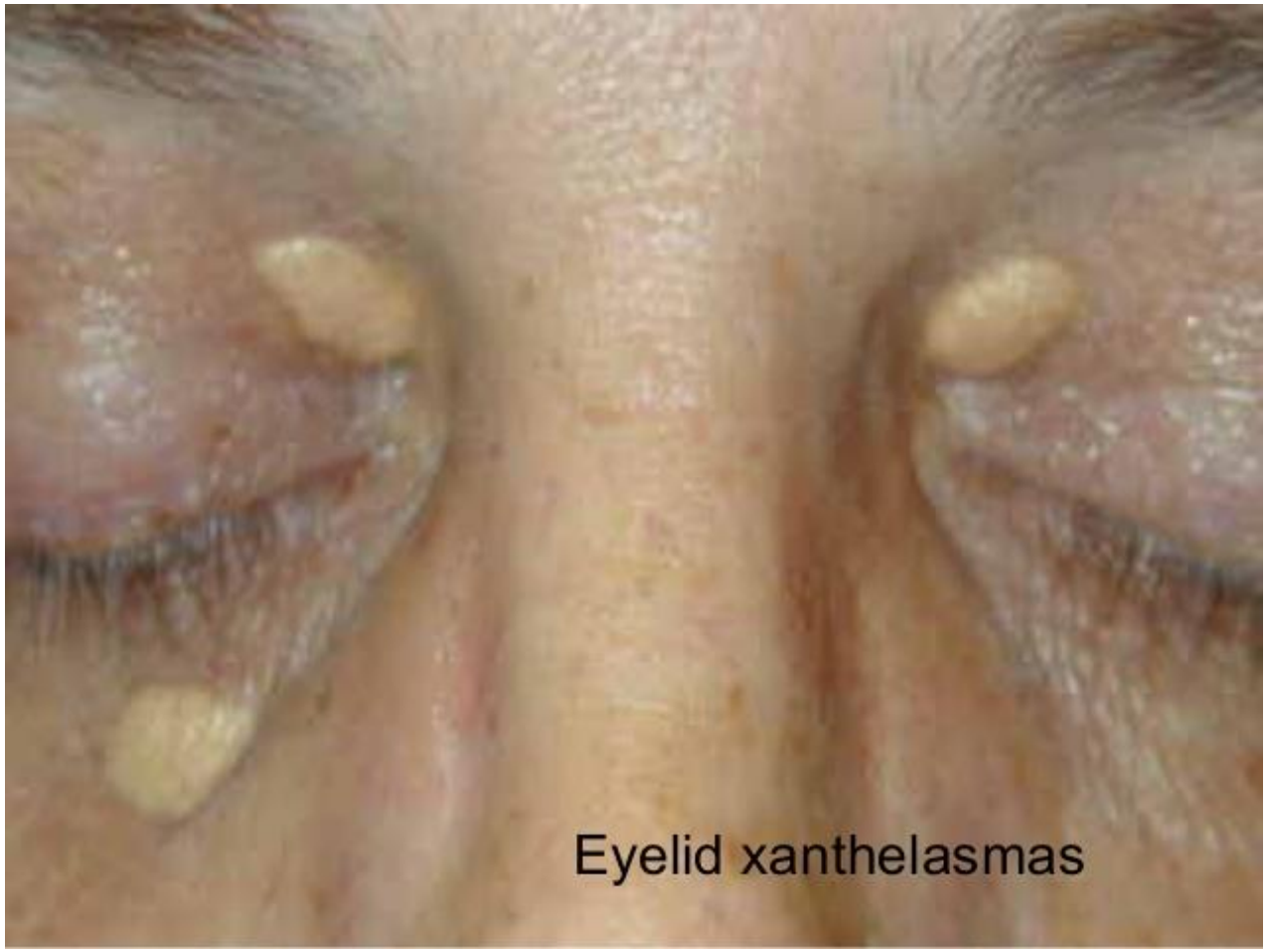
TYPE IV

Overproduction of TAG in liver results in elevated VLDL levels in blood.

plasma is cloudy or milky.

The disease is commomnly associated with coronary artery disease, obesity, chronic alcohol abuse , Diabetes mellitus II.

Reduction of weight , restriction of fat and chol.


Eyelid xanthelasmas

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Hyperlipoprotenemias

TYPE V

Mostly secondary to other disease obesity, chronic alcohol abuse ,diabetes melitus.

Elevated levels of chylomicrons and VLDL couse increased levels of TAG and cholesterol in plasma .Risk of coronary artery disease is increased.

Plasma – creamy layer over milky plasma .

High PUFA intake , hypocholololipidemic drug.

Type	Synonym	Defect	Serum abnormality	Clinical Features	Treatment	Serum appearance
Type 1	Familial Hyperchylomicronemia	Low LDL Altered ApoC2	Chylomicron ↑	Pancreatitis, Lipemia retinalis, skin eruptions, Xanthoma, Hepatosplenomegaly	Diet	Creamy top layer
Type IIa	Familial Hypercholestrolemia	↓LDL receptor	LDL↑	Xanthelasma, Arcus senilis, Tendon xanthomas	Cholestyramine or Cholestipol, Statins, Niacin	Clear
Type IIb	Familial Combined Hypercholestrolemia	↓LDL receptor & ↑Apo B	LDL & VLDL↑		Statins, Niacin, Fibrate	Clear
Type III	Familial dysbetalipoproteinemia	Apo E2 synthesis defect	IDL↑	Tubo-eruptive xanthomas, palmar xanthoma	Fibrate, Statins	Turbid
Type IV	Familial Hyperlipemia	↑VLDL production, ↓elimination	VLDL↑		Statins, Niacin, Fibrate	
Type V	Endogenous hypertriglyceridemia	↑VLDL production, ↓LPL	VLDL & Chylomicron↑		Niacin, Fibrate	Creamy top layer & Turbid bottom

TABLE 356-3 Fredrickson Classification of Hyperlipoproteinemias

Phenotype	I	IIa	IIb	III	IV	V
Lipoprotein, elevated	Chylomicrons	LDL	LDL and VLDL	Chylomicron and VLDL remnants	VLDL	Chylomicrons and VLDL
Triglycerides	↑↑↑	N	↑	↑↑	↑↑	↑↑↑
Cholesterol (total)	↑	↑↑↑	↑↑	↑↑	N/↑	↑↑
LDL-cholesterol	↓	↑↑↑	↑↑	↓	↓	↓
HDL-cholesterol	↓↓↓	N/↓	↓	N	↓↓	↓↓↓
Plasma appearance	Lactescent	Clear	Clear	Turbid	Turbid	Lactescent
Xanthomas	Eruptive	Tendon, tuberous	None	Palmar, tuberoeruptive	None	Eruptive
Pancreatitis	+++	0	0	0	0	+++
Coronary atherosclerosis	0	+++	+++	+++	+/−	+/−
Peripheral atherosclerosis	0	+	+	++	+/−	+/−
Molecular defects	LPL and ApoC-II	LDL receptor, ApoB-100, PCSK9, LDLRAP, ABCG5 and ABCG8		ApoE	ApoA-V	ApoA-V and GPIHBP1
Genetic nomenclature	FCS	FH, FDB, ADH, ARH, sitosterolemia	FCHL	FDBL	FHTG	FHTG

Secondary causes of hyperlipidemia (dyslipidemias)

- Medical conditions - eg, hypothyroidism, obstructive jaundice, Cushing's syndrome, anorexia nervosa, nephrotic syndrome, diabetes mellitus, and chronic kidney disease.
- Drugs - eg, thiazide diuretics, glucocorticoids, ciclosporin, antiretroviral therapy, beta-blockers, combined oral contraceptive pill, atypical antipsychotics, and retinoic acid derivatives.
- Pregnancy.
- Pregnancy.
- Alcohol abuse.

Secondary hyperlipidemia

Causes:

- Type 2 diabetes mellitus
- Cholestatic liver diseases
- Nephrotic syndrome
- Chronic renal failure
- Hypothyroidism
- Cigarette smoking
- Obesity & Anorexia nervosa
- Drugs : such as thiazides, β-blockers, retinoids, highly active antiretroviral agents, estrogen and progestins, and glucocorticoids.

Increased triglyceride level

- Alcoholism
- Diabetes mellitus
- Hypothyroidism
- Obesity
- Renal insufficiency
- Drugs: Beta-adrenergic blockers ,Bile acid–binding resins, Estrogens ,Ticlopidine
- Acute hepatitis
- Systemic lupus
- Ileal bypass surgery
- Monoclonal gammopathy :myeloma
- Sepsis
- Pregnancy

Decreased HDL cholesterol level

- Cigarette smoking
- Diabetes mellitus
- Hypertriglyceridemia
- Menopause
- Obesity
- Puberty (in males)
- Uremia
- Drugs: Anabolic steroids,Beta-adrenergic blockers ,Progestins

Increased LDL cholesterol level

- Diabetes mellitus
- Hypothyroidism
- Nephrotic syndrome
- Obstructive liver disease
- Drugs: Anabolic steroids, Progestins ,Beta-adrenergic blockers ,Thiazides
- Anorexia nervosa
- Acute intermittent porphyria

Diabetes mellitus

Diabetes is an especially significant secondary cause because patients tend to have an atherogenic combination of **high TGs; high small, dense LDL fractions; and low HDL (diabetic dyslipidemia)**

The combination may be a consequence of **obesity, poor control of diabetes, or both**, which may increase circulating free fatty acids (FFAs), leading to increased hepatic very-low-density lipoprotein (VLDL) production.

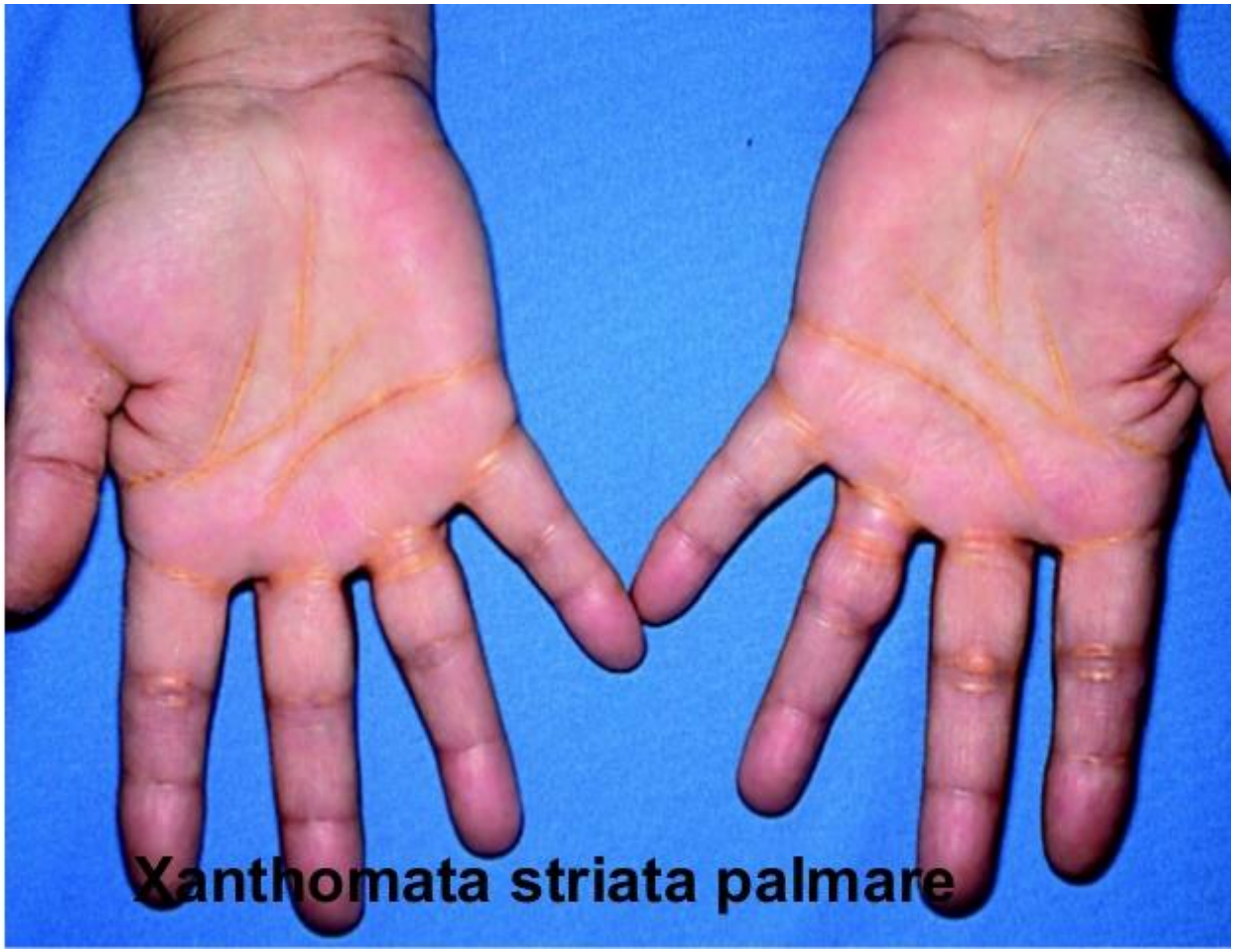
TG-rich VLDL then transfers TG and cholesterol to LDL and HDL, promoting formation of TG-rich, small, dense LDL and clearance of TG-rich HDL.

Diabetic dyslipidemia is often exacerbated by the increased caloric intake and physical inactivity that characterize the lifestyles of some patients with type 2 diabetes.

Cholestatic Liver Disease

Primary biliary cirrhosis and similar disorders may be accompanied by marked **hypercholesterolemia** that results from an accumulation of lipoprotein-X.

Clinical stigmata include xanthomata striata palmare that may appear when the serum cholesterol concentration is 1400 mg/dL or higher.


Xanthomata striata palmare

Xanthomata appear on the extremities as well.

Marked elevations in lipoprotein X has been associated with the hyperviscosity syndrome, but no clear association with coronary heart disease (CHD) has been established.

Nephrotic Syndrome

Marked hyperlipidemia can occur in the nephrotic syndrome due primarily to **high serum total and low-density lipoprotein (LDL)** cholesterol concentrations.

Increased hepatic production of lipoproteins, induced by part by the fall in plasma oncotic pressure is the major abnormality, but diminished lipid catabolism may play a contributory role.

Hypothyroidism

Hypothyroidism is frequently associated with and is a common cause of hyperlipidemia.

This relationship was illustrated in a study of patients with primary hypothyroidism. **Hypercholesterolemia** was present in 56 percent, **hypercholesterolemia and hypertriglyceridemia** in 34 percent, and **hypertriglyceridemia** in 1.5 percent; only 8.5 percent had a normal lipid profile.

Reversal of the hypothyroidism with thyroid hormone replacement leads to correction of hyperlipidemia.

Serum TSH should be measured in all patients with dyslipidemia.

Chronic renal failure

Dyslipidemia is less prominent in chronic renal failure, but **hypertriglyceridemia** occurs in 30 to 50 percent of cases.

Smoking

Smoking modestly **lowers the serum HDL** cholesterol concentrations and may induce insulin resistance.

These effects are reversible within one to two months after smoking cessation.

Nicotin increases lipolysis

Obesity

- People with apple type of obesity or truncal obesity are more prone to get myocardial infarction.
- BMI exceeds 27.8 kg /m^2 in men and 27.3 kg /m^2 in women .

Obesity

Obesity is associated with a number of deleterious changes in lipid metabolism, including **high serum concentrations of total cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides, and a reduction in serum HDL** cholesterol concentration of about 5 percent. Loss of body fat can reverse the hypercholesterolemia and hypertriglyceridemia.

Anorexia nervosa

- Hypercholesterolemia has long been known to be associated with anorexia nervosa. Typically total cholesterol and LDL are elevated; HDL may be high also. With refeeding, cholesterol levels return to baseline. Other forms of malnutrition are not usually associated with high cholesterol. However, until recently the underlying mechanism has not been clearly delineated

Clinical Presentation

- Dyslipidemia itself usually causes no symptoms but can lead to symptomatic vascular disease, including coronary artery disease (CAD) and peripheral arterial disease.
- High levels of TGs (> 1000 mg/dL) can cause acute pancreatitis.
- High levels of LDL can cause eyelid xanthelasmas; arcus corneae; and tendinous xanthomas at the Achilles, elbow, and knee tendons and over metacarpophalangeal joints.

- Patients with severe elevations of TGs can have eruptive xanthomas over the trunk, back, elbows, buttocks, knees, hands, and feet.
- Extremely high lipid levels also give a lactescent (milky) appearance to blood plasma.

Diagnosis

- Serum lipid profile (measured total cholesterol, TG, and HDL cholesterol and calculated LDL cholesterol and VLDL)
- Tests for secondary causes of dyslipidemia—including measurements of fasting glucose, liver enzymes, creatinine, thyroid-stimulating hormone (TSH), and urinary protein—should be done in most patients with newly diagnosed dyslipidemia.

Treatment

- Treatment of the cause.
- Lifestyle changes (eg, exercise, dietary modification)
- For high LDL cholesterol, statins, sometimes bile acid sequestrants.
- For high TG or low HDL cholesterol, niacin , fibrates, and sometimes other measures.

Treatment

- Reduce Dietary cholesterol- keep less than 200 mg per day. Avoid eggs and meat which contains high cholesterol.
- Vegetable oils and PUFA
- Sunflower oil and fish oil – high PUFA
- PUFA are required for the esterification and final excretion of cholesterol.

Treatment

- Green leafy vegetables : due to high fibre content leafy vegetables will increase the motility of bowels and reduce the reabsorption of bile salts.
- High carbohydrate diet , especially sucrose should be avoided by patients with hypercholesterolemia.

Hypolipidemic drugs

- HMG –CoA reductaseinhibitors **STATIN**
- Bile acid binding resins – decreases the reabsorption of bile acids
- Probucol – increases LDL catabolism and prevents accumulation of LDL in arterial walls. So more cholesterol will be converted bile acids.

Hypolipidemic drugs

- Aspirin – prevent thrombus formation.
- Vitamin E – minimize oxidation of LDL and so atherosclerosis may be reduced.

Hypolipoprotenemias

- **Lowered lipoprotein levels reduce the risk of cardiovascular disease but the resultant deficiency of fats and fat soluble vitamins is otherwise dangerous leadnig to retinal lesions and peripheral neuropathy.**

Hypolipoprotenemias

- **Abetalipoprotenemia**
- There is a defect in synthesis of apo B
- Microsomal triglyceride transfer protein is defective.TG is not incarporated in VLDL and chylomicrons.
- chylomicrons and VLDL and LDL are not formed .

Hypolipoprotenemias

- Fat soluble vitamins are not absorbed causing mental and physical retardation.

- TAG and cholesterol in plasma are extremely low .it can be effectively treated by giving **large doses of fat soluble vitamins , vitamin E**

Hypolipoprotenemias

- **Hypobetalipoprotenemia**
- There is only a **partial deficiency of apo B**
- Chylomicrons, VLDL, LDL are present but in low concentration.
- It is harmless and person affected are healthy and long lived.

Hypolipoprotenemias

- **Hypobetalipoprotenemia**
- There is only a **partial deficiency of apo B**
- CM, VLDL, LDL are present but in low concentration.
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Hypolipoprotenemias

- **Hypoalphalipoprotenemia (Tangier disease)**
- It was first detected in persons living in Tangier island .
- The biochemical diffect is the absence of ATP-binding cassete transporter 1 (ABC-1) which is involved transferring cellular cholesterol to HDL .
- Low plasma HDL, alpha band is not seen in electrophresis.

Hypolipoprotenemias

- Cholesterol esters are accumulated in tissues .
- Manifestations are large orange yellow tonsils , muscle atrophy, recurrent peripheral neuropathies, and atherosclerosis.

- THANK YOU