LIPID METABOLISM

BIOCHEMISTRY DEPARTMENT
FK UNISSULA
MEI 2016

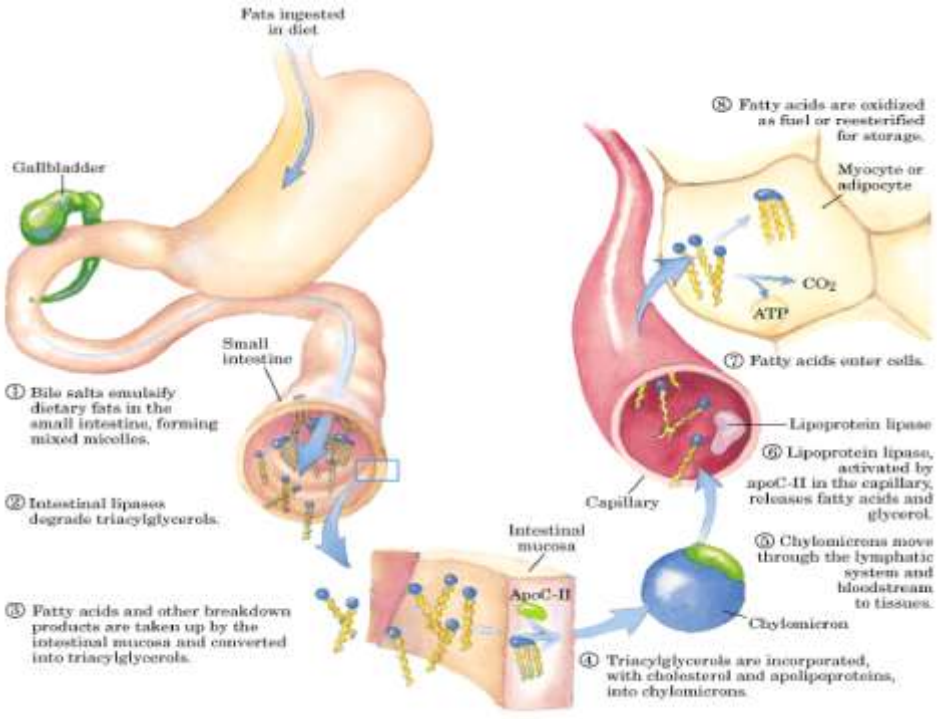
LEARNING OUTCOME

- HORMONAL INFLUENCE
- SYNTHESIS
- STORAGE
- OXIDATION
- KETOGENESIS
- LIPOPROTEIN

FATTY ACID (F.A.) OVERVIEW

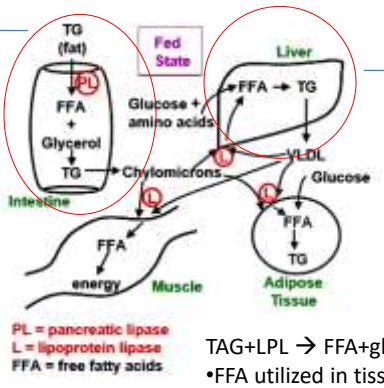
Transpor & storage F.A dipengaruhi oleh dietary status

FED STATE	FASTING STATE	PROLONGED FASTING
• Triacylglycerol (TAG) DISIMPAN → adipose tissue	• TAG di adipose tissue DIHIDROLISA → diedarkan ke seluruh tubuh untuk produksi energi	• >2DAYS • hepar konversi FA → badan keton, asetoasetat, dan β hidroksibutirat



FED STATE

TAG diet dicerna oleh gastric+pancreatic lipase → 2 MAG+FFA → epitel intestinal → dirangkai lagi mnjd TAG → dikemas sbg KILOMIKRON → limfe → blood stream



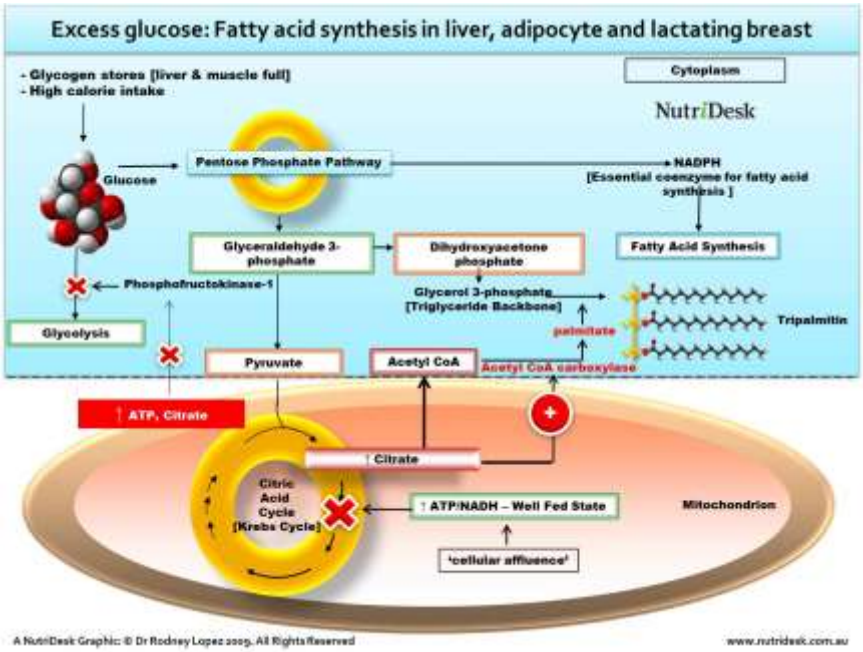
Liver is another source of TAG in fed state: FA berasal dari kelebihan KH+AA FA dari liver+gliserol dirangkai → TAG → dikemas dlm bntuk VLDL → blood stream

Kilomikron & VLDL hydrolized by LPL in surface of endothelial capillary cells of muscle (skeletal&cardiac) & adipose tissue

TAG+LPL → FFA+gliserol
•FFA utilized in tissues
•Gliserol → bloodstream →LIVER → GLIKOLISIS & GLUKONEOGENESIS

HORMONE ON FED STATE

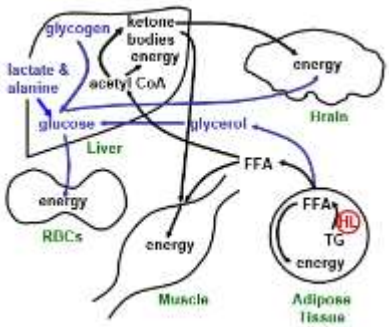
- INSULIN, mempunyai peran:
  1. Menstimulasi lipoprotein lipase
  2. Menstimulasi sintesis fatty acid and triglyceride di LIVER
  3. Menginhibisi hormone sensitive lipase di adipose tissue



FASTED STATE

Glukosa (dari pemecahan glikogen & alanin) → energy source sel darah merah+otak

Hampir seluruh jaringan, tmsk resting muscle, gunakan FA sbg energy source.
Exercising muscle will use both FA+glucose for energy.



prolonged starvation:
FA→ konversi jd ketone bodies di liver → energy source semua jar., (kec. yg tdk punya mitokondria: sel darah merah)
Brain adapts slowly to the use of ketone bodies during prolonged starvation.

PERILIPIN (melapisi permukaan fat droplet) terfosforilasi → hormone sensitive lipase (berada intra adiposit) translokasi ke permukaan fat droplets → hidrolisa TAG → gliserol+ FA
FA → fuel source all tissues (excl. brain)

HORMONE ON FASTED STATE

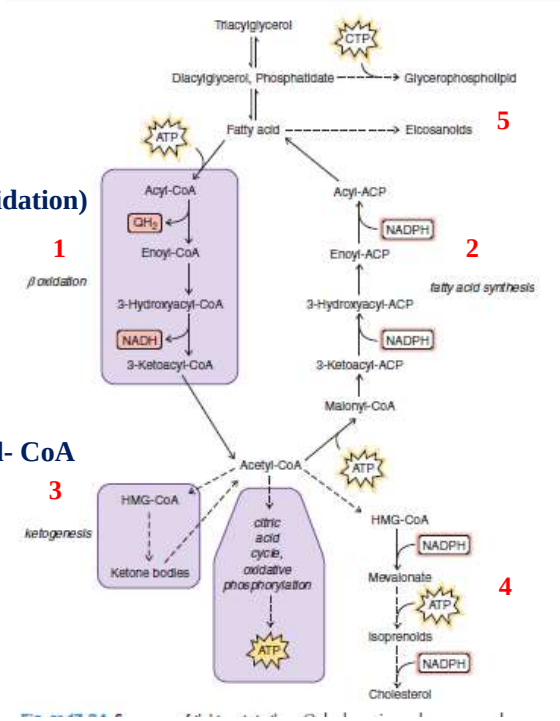
- Glucagon (fasted) & epinephrine (exercise) :
  1. Stimulate hormone-sensitive lipase
  2. Inhibit :
     a. Lipoprotein lipase
     b. Fatty acid synthesis
     c. Triglyceride synthesis

Lipid Metabolism

Major Pathways :

1. **Fatty acid catabolism (β-oxidation)**
2. **Fatty acid synthesis**
3. **Ketogenesis**
4. **Cholesterol synthesis**
5. **Synthesis of lipids**

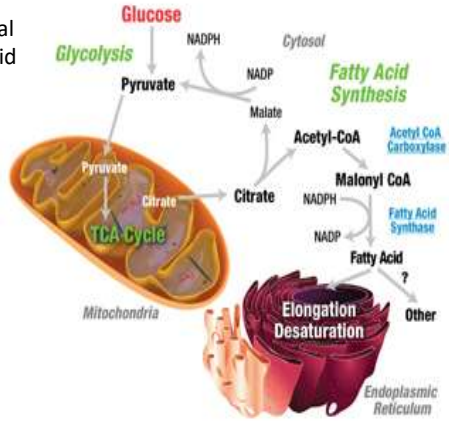
All pathways converge at acetyl- CoA



LIPOGENESIS (F.A. SYNTHESIS)

Sintesis FA yang berasal dari substrat selain lipid

Terjadi di SITOSOL, gunakan Acetyl Co-A



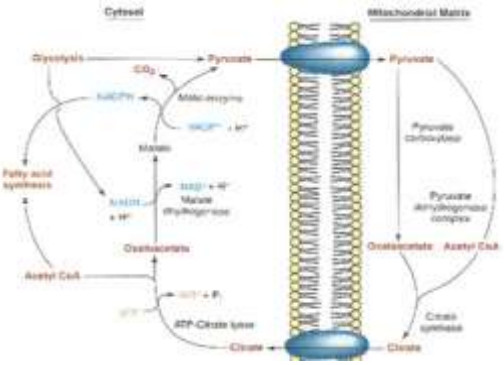
Intake KH >> (prod energi & sintesis glikogen sdh tercukupi) → dikonversi → FA di liver selama fed state

AA juga dapat berperan dlm lipogenesis

FA disintesis melalui sequential addition of 2 C unit of acetyl co-A oleh fatty acid synthase hingga menjadi rantai panjang → terbentuk asam palmitat & modifikasinya

LIPOGENESIS de Novo

Acetyl co-A tidak bisa melewati inner membrane mitokondria → sitosol → CITRATE CLEAVAGE PATHWAY
Citrate pada TCA → melalui TCA transporter membran mitokondria → sitosol → oleh citrate lyase (CITRATE CLEAVAGE ENZYME)→ asetil ko-A +oxaloasetat



NADPH yg digunakan dlm sintesis palmitat berasal dari glycolytic pathway & pentose phospate pathway

STORAGE OF F.A

Storage : adipose tissue, liver, skeletal & cardiac muscle

ADIPOSE tissue is a specialized organ designed for synthesis, storage, & hydrolysis for TAG
Adipose tissue → long term energy storage

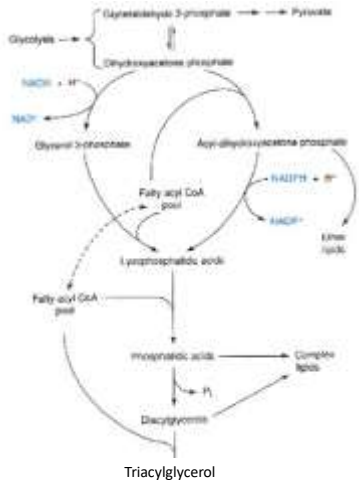
TAG terletak di sitosol sbg liquid droplet yg dikelilingi membran monolayer lipid+protein (PERILIPIN)

Sintesis TAG di LIVER → produksi lipoprotein plasma berasal dari :

1. Diet
2. Jar. Adipose
3. Sintesis (dari katabolisme glukosa)

Storage di CARDIAC & SKELETAL MUSCLE → local use

Pathway of TAG synthesis



TAG disintesis dari Fatty Acyl Co-A+ prekursor gliserol (gliserol 3-fosfat)
Gliserol 3 fosfat berasal dari:

1. Glukosa dari proses GLIKOLISIS (fed state)
2. Piruvat dari proses GLISERONEOGENESIS (fasting state)

PENGGUNAAN FA UTK PEMBENTUKAN ENERGI

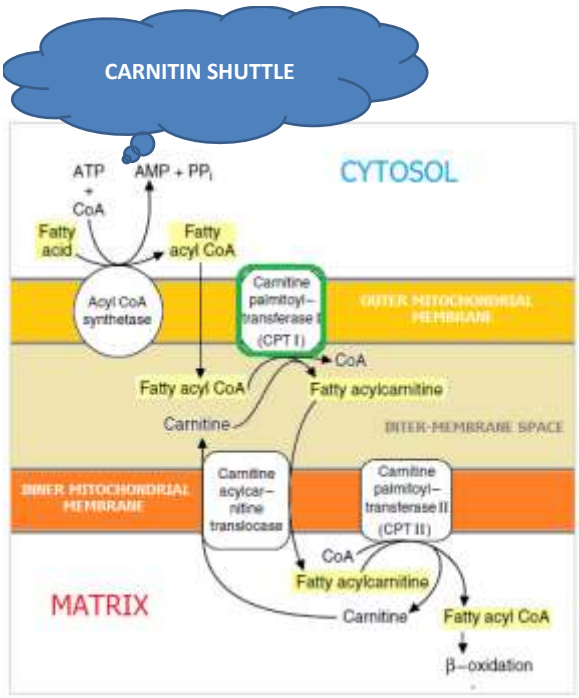
Penggunaan FA tergantung dietary status (fed, fasted, starvation, exercising, rest)

FA yang beredar di aliran darah, diambil sel & digunakan utk pembentukan energi → dipecah → Acyl co-A dan terbentuklah NADH & FADH2 → MITOKONDRIA matriks → TCA cycle & oxidative phosphorylation

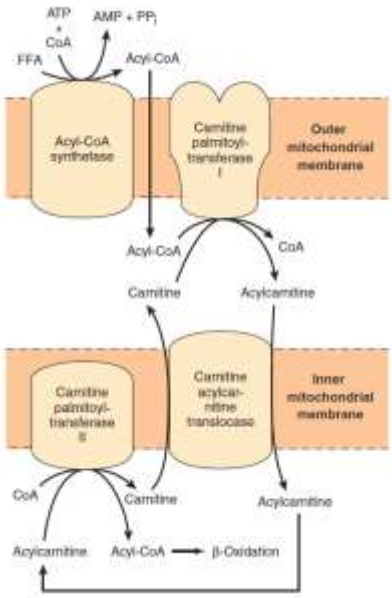
Sel darah merah tdk punya mitokondria → tdk bisa gunakan FA sbg sumber energi

Otak gunakan FA scr terbatas → harus melintasi BBB

Prolonged fasting: LIVER mengkonversi asetil ko-A dari oksidasi FA & memecah asam amino → BADAN KETON → major fuel



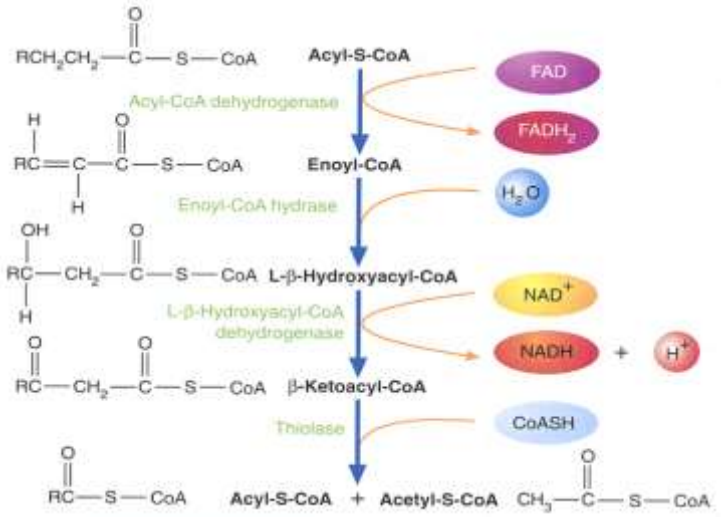
FA yang digunakan sbg fuel source tdk bisa lewati membran mitokondria
FA → FA co-A → CARNITINE SHUTTLE → membran mitokondria → β OKSIDASI



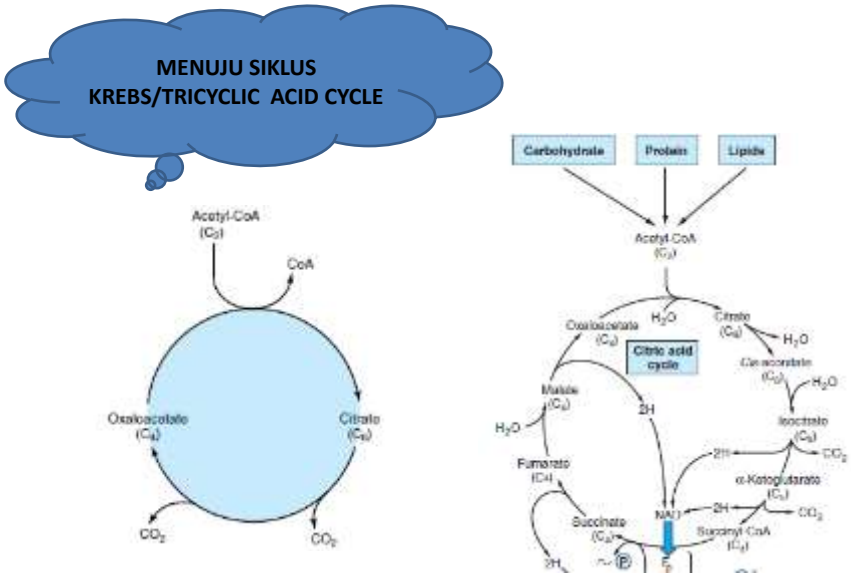
2. Translokasi Acyl-CoA : Peran Carnitine

- ❑ Setiap acyl - CoA dikonversi → acylcarnitine; proses ini dikatalisis oleh carnitine acyltransferase I
- ❑ Carrier protein yg tdpt di membran dalam mitokondria mentransfer acylcarnitine ke matriks mitokondria
- ❑ Acyl - CoA is regenerated by carnitine acyltransferase II
- ❑ Carnitine ditranspor kembali ke membran dalam mitokondria oleh carrier protein dan siklus berulang

β-Oksidasi Acyl-CoA



- Karena tiap jenis asam lemak memiliki atom C yang bervariasi maka jumlah asetil-KoA yang dihasilkan berbeda
- Setiap asam lemak akan dipecah setiap 2 atom C
- Asam palmitat (16 atom C) → 8 asetil-KoA (masing-masing 2atom C).
- Asetil-KoA kemudian dapat masuk ke dalam siklus krebs untuk menghasilkan ATP.



Ketone Bodies

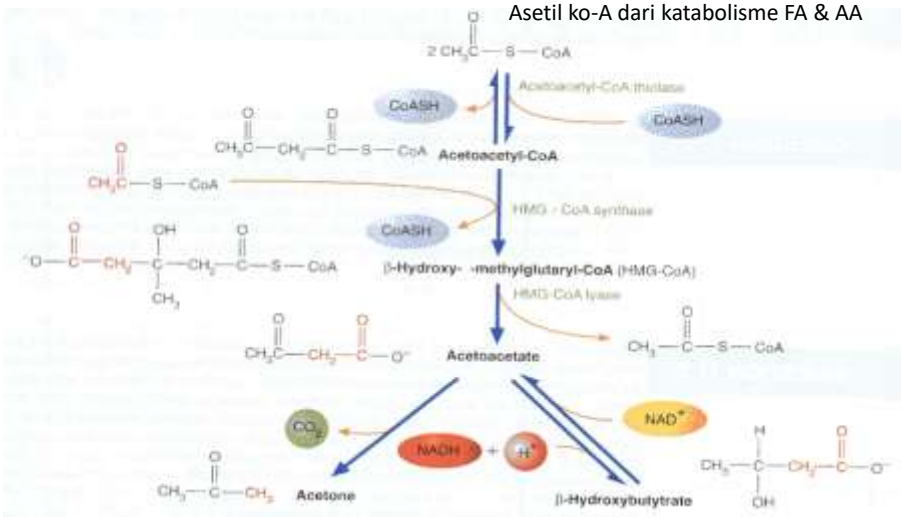
Most of the acetyl-CoA product during fatty acid oxidation is utilized by the citric acid cycle or in isoprenoid synthesis. In a process called ketogenesis, acetyl–CoA molecules are used to synthesize acetoacetate, β-hydroxy butyrate and acetone, a group of molecules called the ketone bodies

Badan keton bersifat water soluble, diproduksi di LIVER & KIDNEY

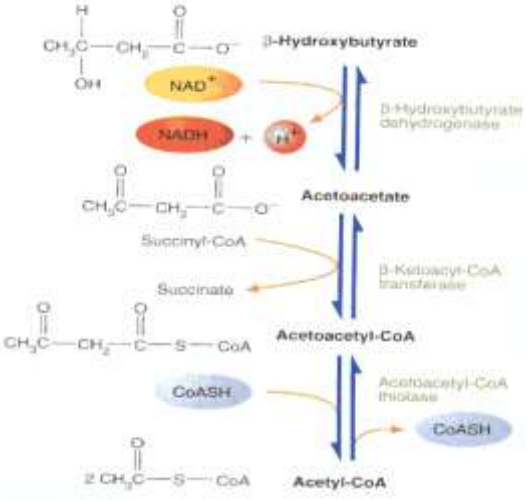
Ketone body formation occurs within mitochondria

Ketone bodies are used to generate energy by several Tissues, e.g., cardiac and skeletal muscle and brain

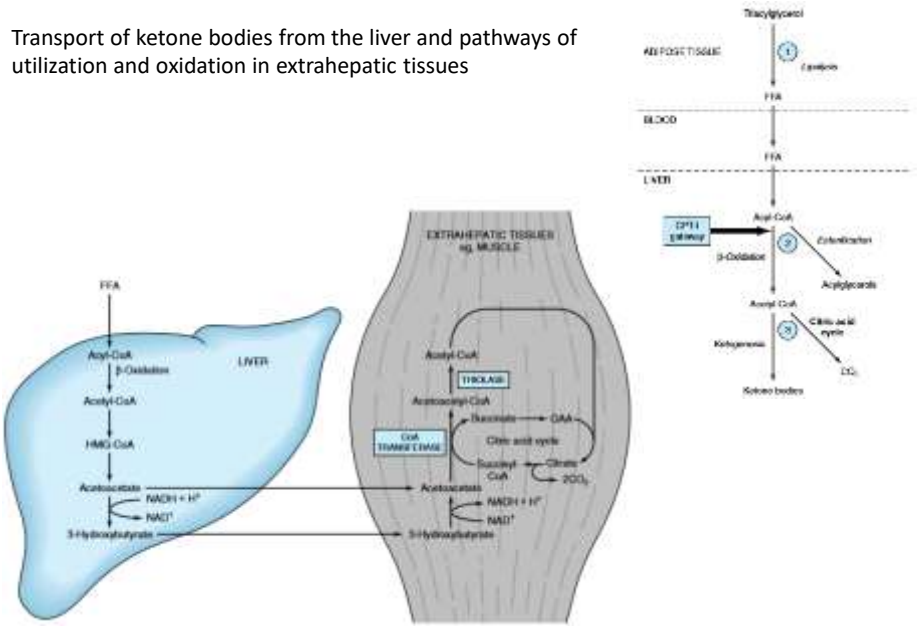
Ketone Body Formation



Conversion of Ketone Bodies to Acetyl-CoA

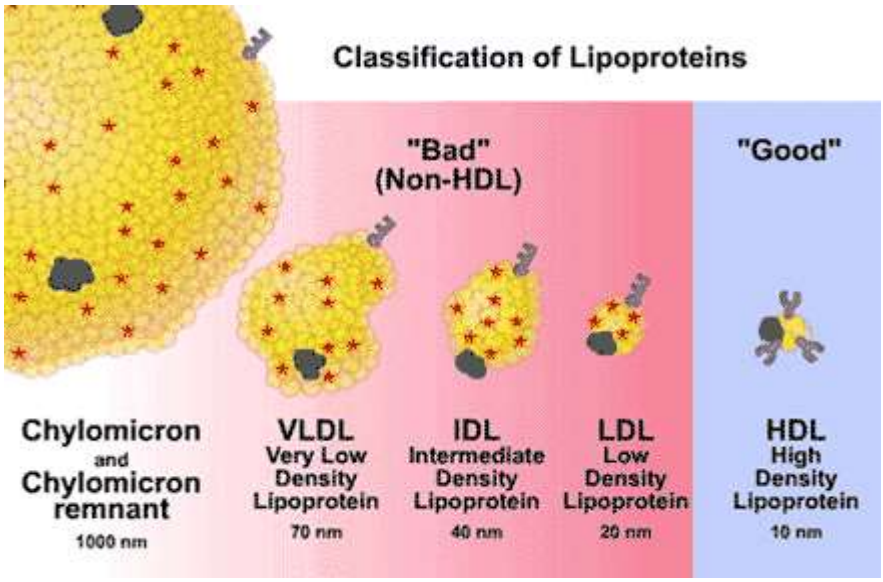


Transport of ketone bodies from the liver and pathways of utilization and oxidation in extrahepatic tissues



PLASMA LIPOPROTEIN

- TAG, kolesterol, dan ester kolesteril beredar dalam darah melalui vehicle yg disebut LIPOPROTEIN
- Lipoprotein memfasilitasi metabolisme lipid & transfer lipid ke jaringan
- 5 kelas lipoprotein:
  - ❖ Kilomikron
  - ❖ High-density lipoprotein (HDL)
  - ❖ Low -density lipoprotein (LDL)
  - ❖ Intermediate-density lipoprotein (IDL)
  - ❖ Very Low -density lipoprotein (VLDL)

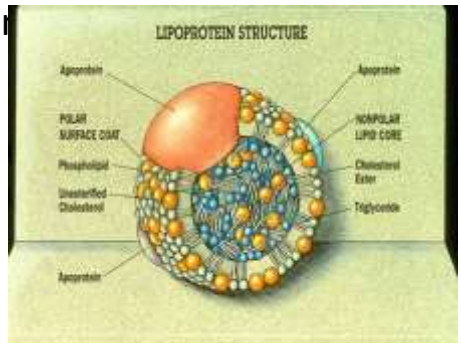


- Lipoprotein lipase (LPL) berikatan dg heparin sulfate proteoglikan menempel pada permukaan endotel pembuluh darah → hidrolisa TAG dari VLDL dan kilomikron
- LPL diaktifkan oleh apolipoprotein C-II (apoC) dan heparin (dilepaskan oleh sel mast RES)
- FA yg dilepaskan dipakai sel → β oksidasi → bergabung dg fosfolipid → penyusun membran sel
- Pd adiposit: disimpan sbg TAG

LIPOPROTEIN PATHWAYS

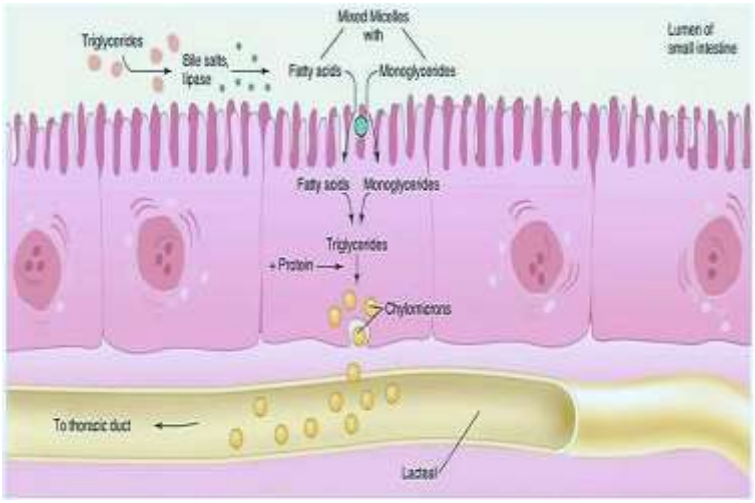
Terdapat 3 jalur pengangkutan lipoprotein:

- Exogenous pathway (kilomikron)
- Endogenous pathway (VLDL-IDL-LDL)
- Reverse cholesterol tra



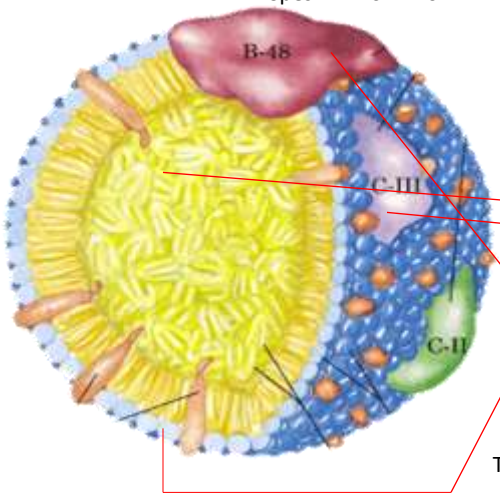
EXOGENOUS PATHWAY

Formation and Transportation of Chylomicrons



Structure of Chylomicron

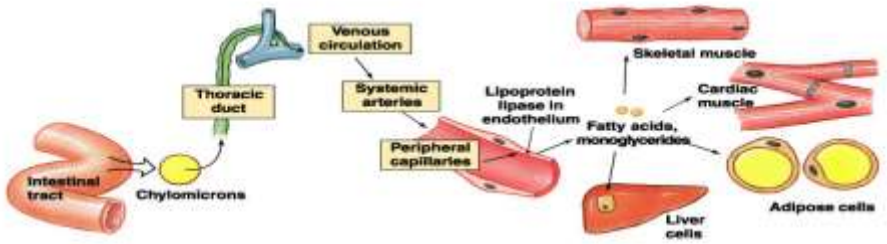
Spesifik kilomikron



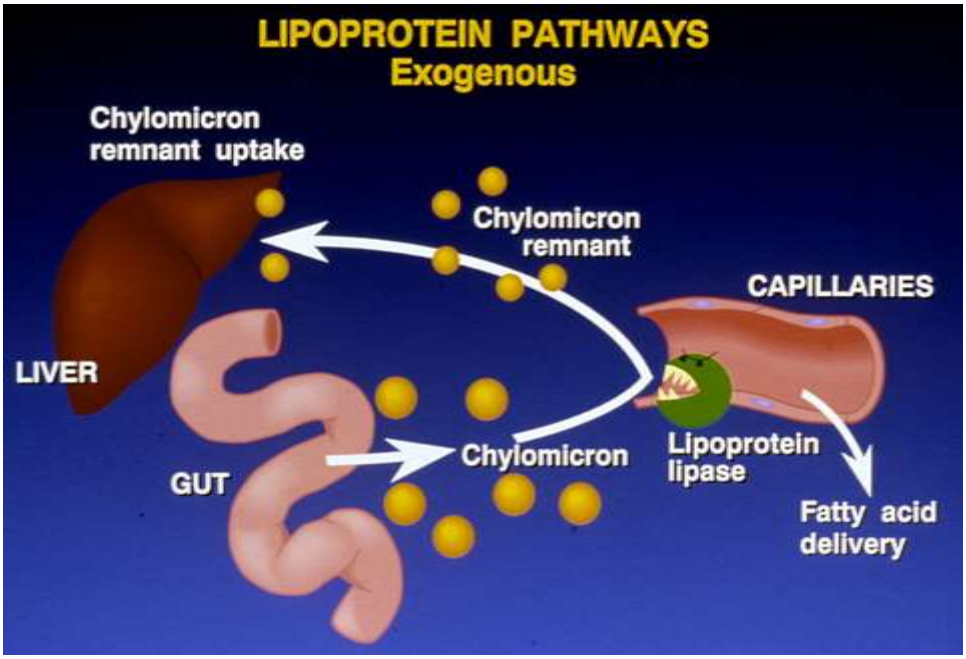
- *Size:* 0.1–1 µm
- *Average composition*
  - TAG (89%)
  - Cholesterol(2%) → sintesis de novo
  - Phospholipid (8%) → sintesis de novo
  - Apo lipoproteins (1%) → disintesis di enterosit

TAG core berasal dari dietary fat

Transport and Utilization of chylomicrons



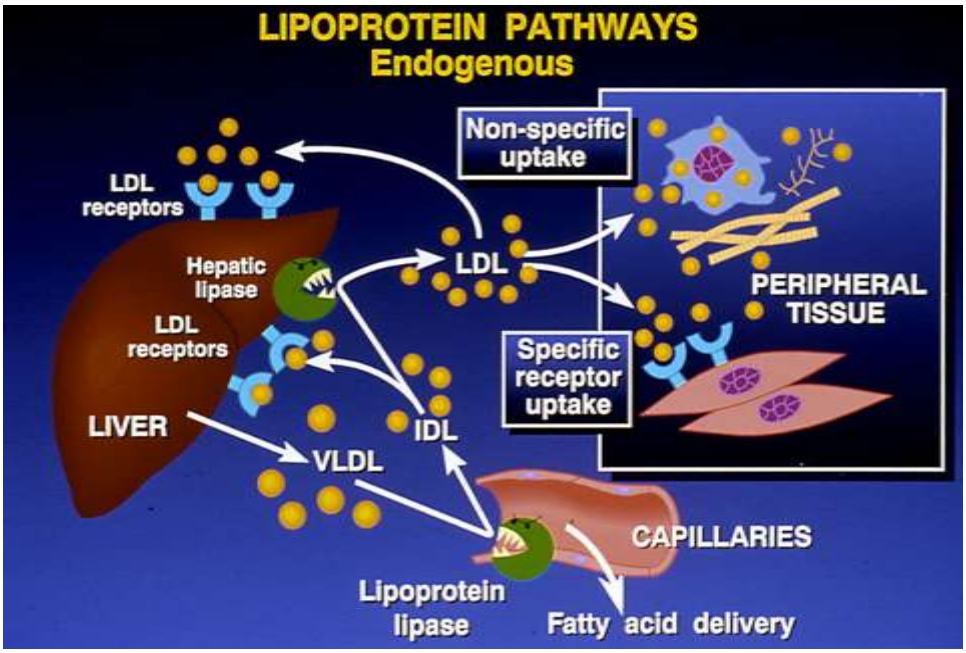
KILOMIKRON REMNAN: tanpa inti TAG, mengandung vitamin larut lemak & kolesterol → berikatan dg reseptor di membran hepar → endositosis → katabolisme



ENDOGENOUS PATHWAY

- VLDL dibuat di parenkim liver , inti TAG berasal dari:
  - FA yang dilepaskan dari cadangan lemak adiposa
  - Konversi FA dari glukosa di liver
  - Hidrolisis lipoprotein trigliserida kapiler endotel&liver
- Diet tinggi karbo →↑ VLDL

- Nascent VLDL (apoB-100) menerima apo C&E dari HDL→VLDL→endotelial LPL→ TAG dihidrolisa jd FA+gliserol →VLDL remnant/IDL (apoB-100&apoE)→hepatic lipase → LDL (apoB-100)
- LDL yg kaya kolesterol beredar di plasma hingga 2,5 hari
- LDL menjadi sumber kolesterol jaringan tubuh
- Kolesterol yg dilepaskan di dalam sel→ sintesis membran sel dan utk reaksi yg memerlukan inti sterol (pembentukan hormon

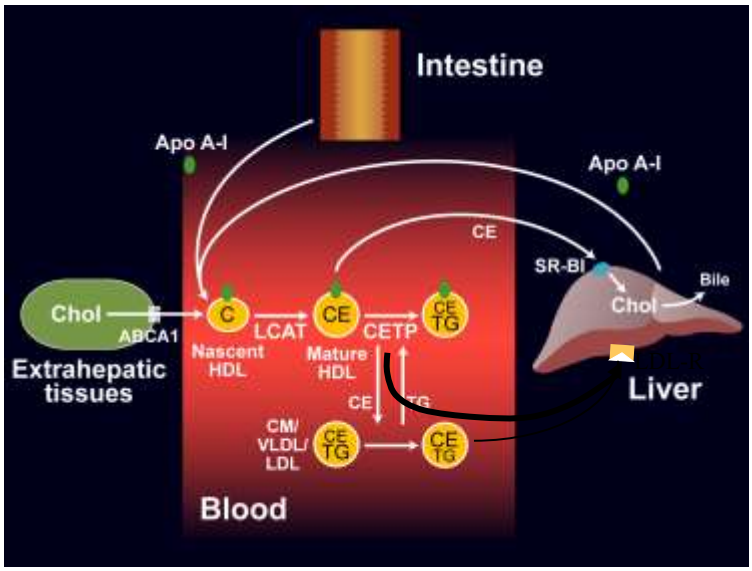


REVERSE CHOLESTEROL TRANSPORT

- Kolesterol sel >> → diambil & ditranspor ke liver oleh HDL → dieliminasi → kolesterol (non esterifikasi) & garam empedu

Free chol (FC) membran plasma+ HDL"nascent" yg miskin lipid (dimediasi o/ ATP-binding cassette transporter/ ABCA-1)→ transfer fosfolipid+FC → HDL3 → +FC yg teresterifikasi oleh (Lecitin:Cholesterol Acyl Transferase/LCAT) → HDL 2(matur) → degradasi TAG di liver (mell Scavenger Receptor-BI/SR-BI) oleh lipase permukaan hepatik

HDL and Reverse Cholesterol Transport



Ester kolesterol pd LCAT ditransfer ke VLDL/LDL mell CETP (Chol Ester Transfer Protein)

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