CHS 2413
Pathology and Physiopathology

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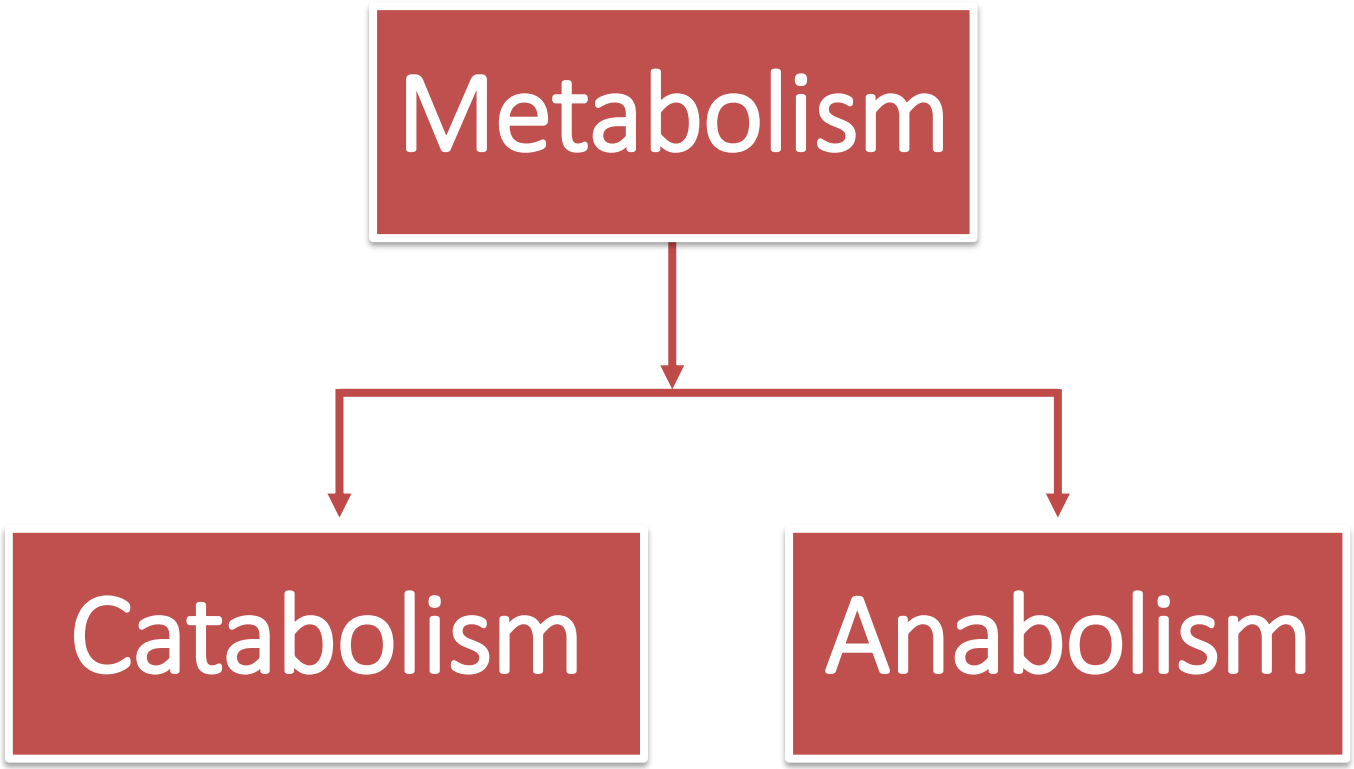
What is Metabolism?

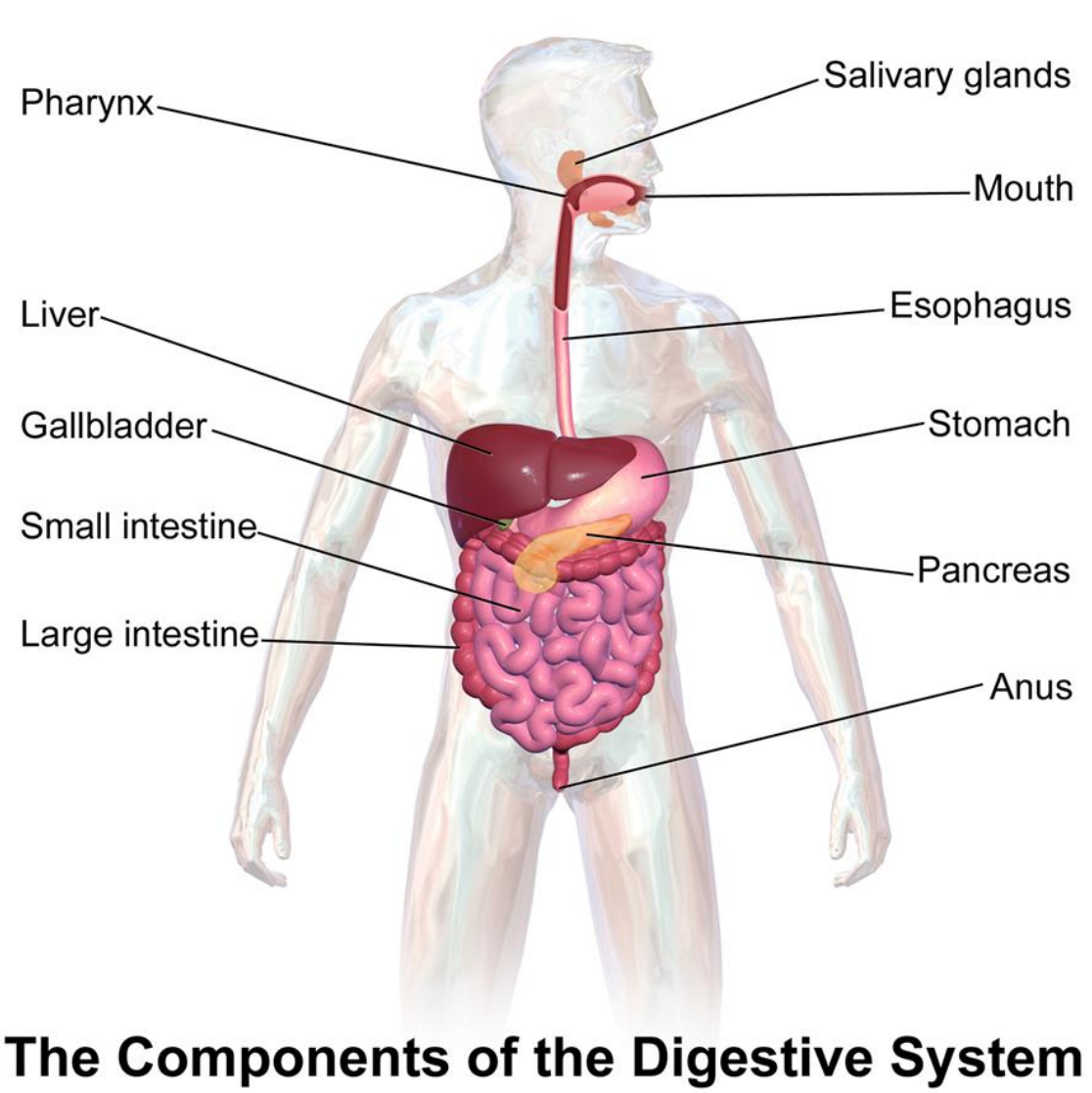
- การเผาผลาญเป็นกระบวนการที่ร่างกายใช้ในการรับหรือสร้างพลังงานจากอาหารที่กิน
- อาหารประกอบด้วยโปรตีนคาร์โบไฮเดรตและไขมัน (โมเลกุลใหญ่)
- สารเคมีในระบบย่อยอาหารของคุณแบ่งส่วนอาหารออกเป็นโมเลกุลซึ่งเป็นเชื้อเพลิงของร่างกาย
- ร่างกายสามารถใช้เชื้อเพลิงนี้ได้ทันทีหรือสามารถเก็บพลังงานไว้ในเนื้อเยื่อร่างกาย เช่น ตับ กล้ามเนื้อ และไขมัน

What is Metabolism?



What is Metabolic Disorder?

- ความผิดปกติของการเผาผลาญเกิดขึ้นเมื่อปฏิกิริยาทางเคมีที่ผิดปกติในร่างกายของคุณขัดขวาง
- กระบวนการนี้ เมื่อสิ่งนี้เกิดขึ้นจากการมีสารบางชนิดมากเกินไปหรือสารอื่น ๆ น้อยเกินไปที่ต้องมีสุขภาพดี
- กลุ่มที่มีการสลายตัวผิดปกติของกรดอะมิโนคาร์โบไฮเดรตหรือไขมัน
- อีกกลุ่มหนึ่งคือ Mitochondrial disease ที่มีผลต่อส่วนของเซลล์ที่ผลิตพลังงาน


Pharynx
Salivary glands
Mouth
Liver
Esophagus
Gallbladder
Stomach
Small intestine
Pancreas
Large intestine
Anus
The Components of the Digestive System

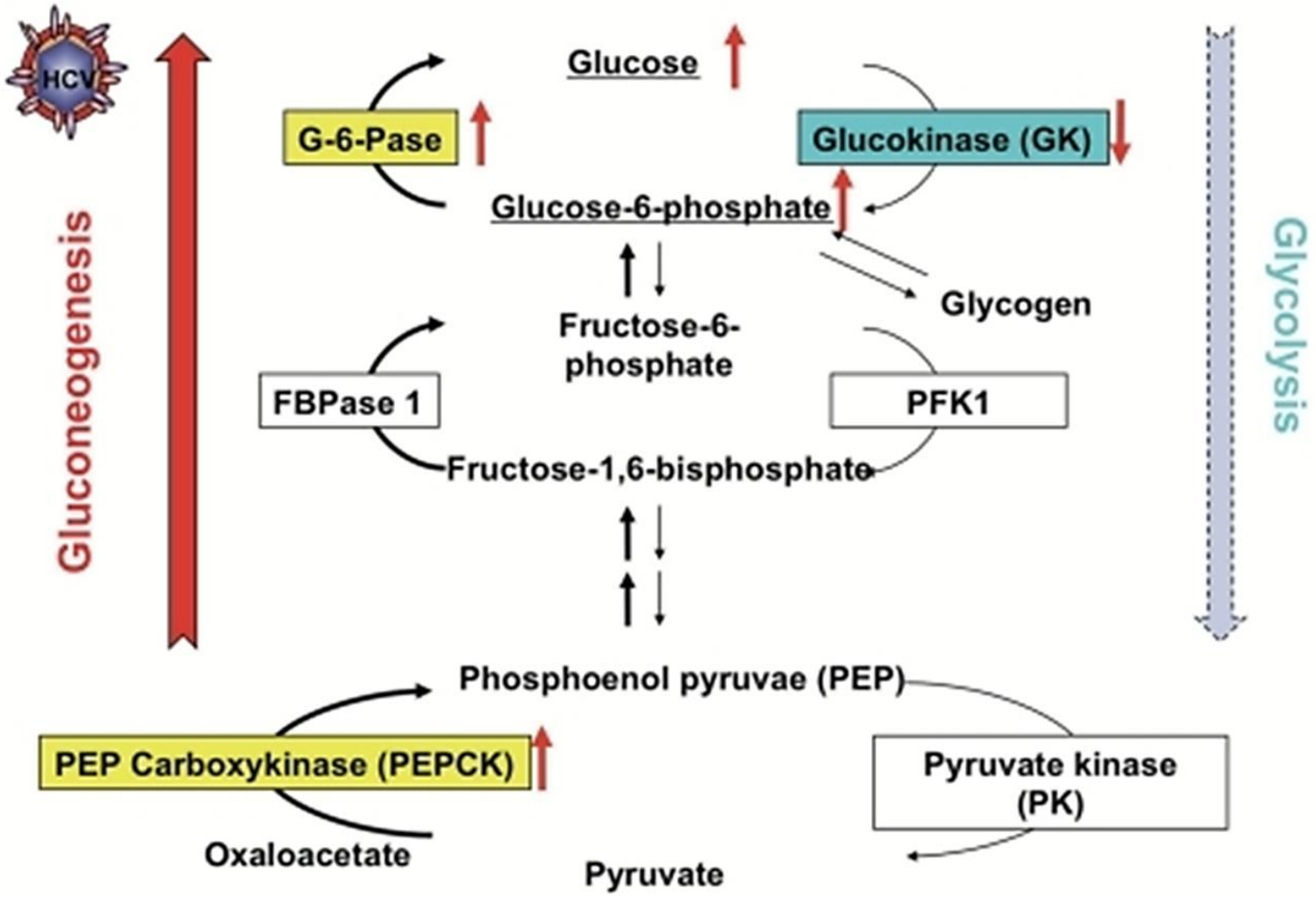
Carbohydrate Metabolism

- Glycolysis and Acetyl-CoA
- Krebs cycle
- Electron transfer

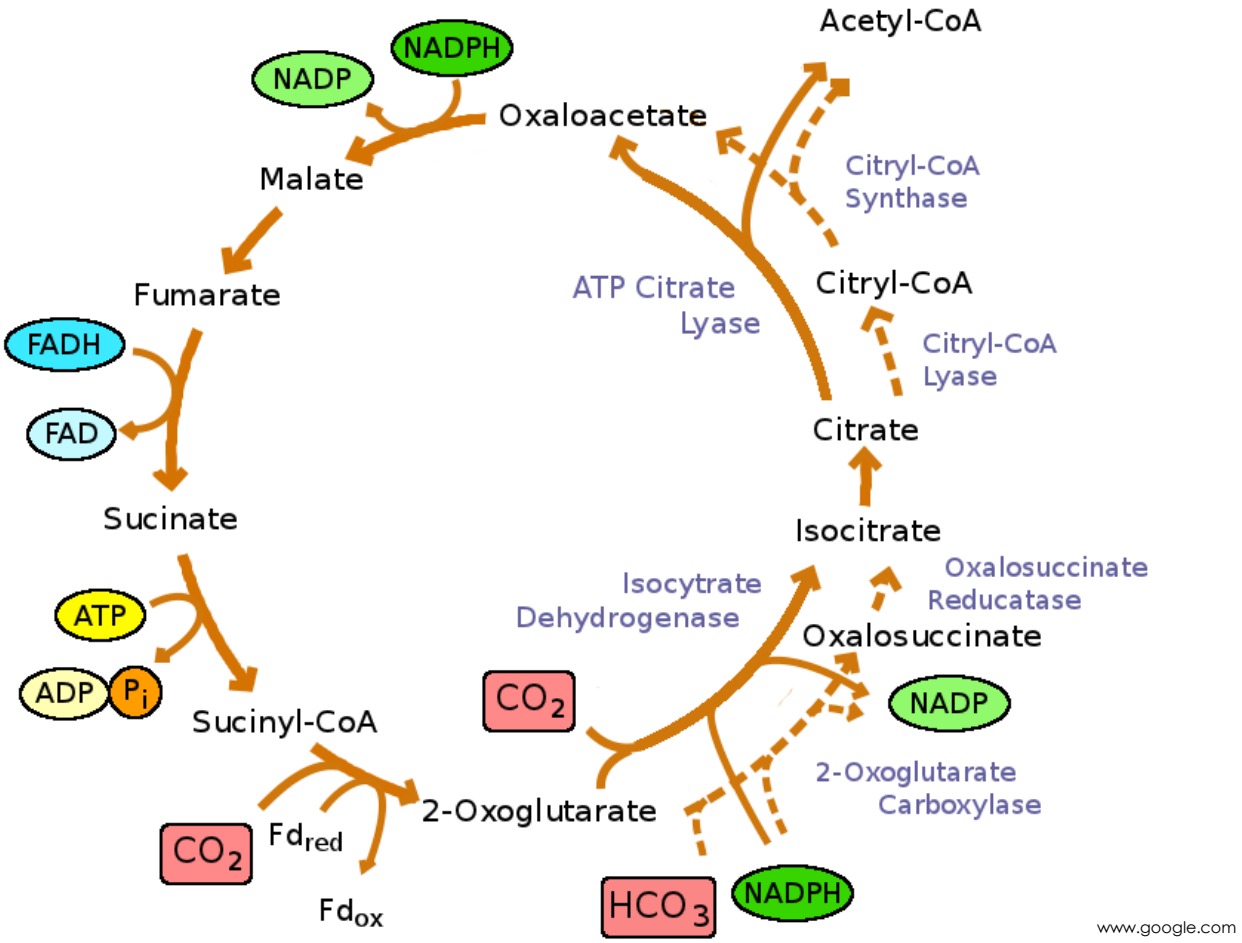
Summary equation of carbohydrate

$C_6H_{12}O_6 + 6\ O_2 \text{-----} > 6\ CO_2 + 6\ H_2O + \text{energy}$ (36ATP)

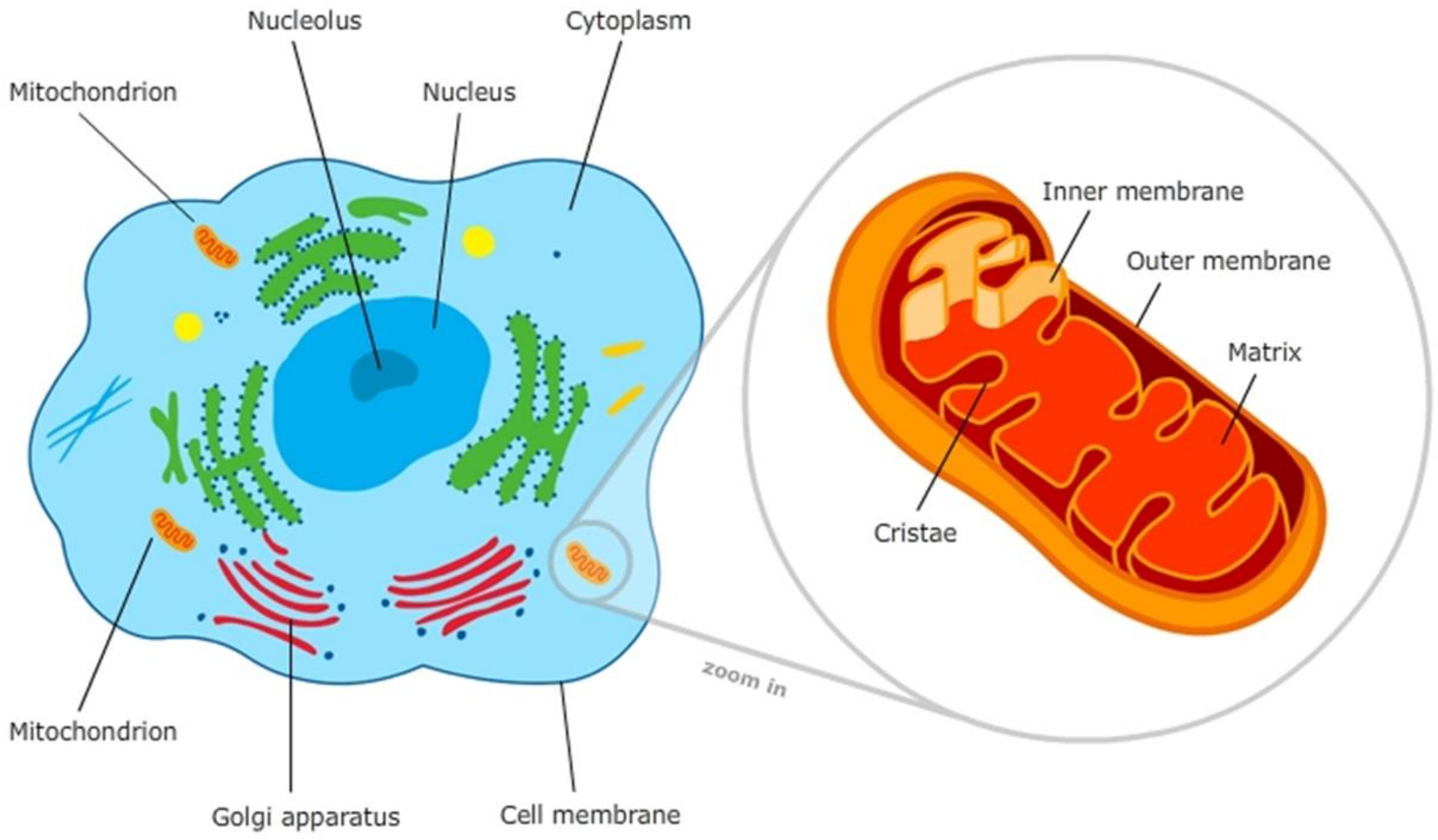
Gluconeogenesis and glycolysis



Krebs cycle



Isocitrate Dehydrogenase – important enzyme


Nucleolus
Cytoplasm
Mitochondrion
Nucleus
Inner membrane
Outer membrane
Matrix
Cristae
zoom in
Mitochondrion
Golgi apparatus
Cell membrane
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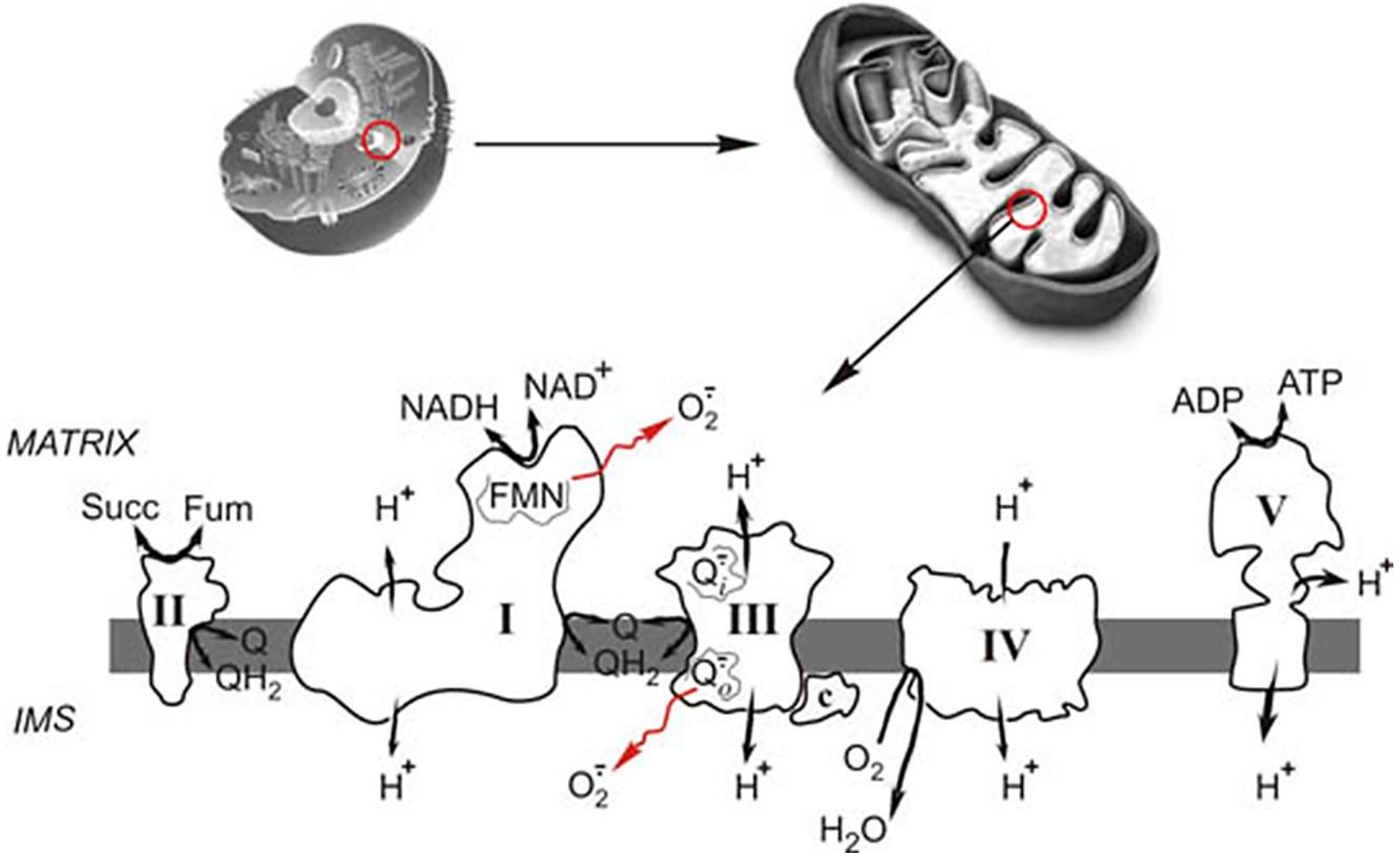
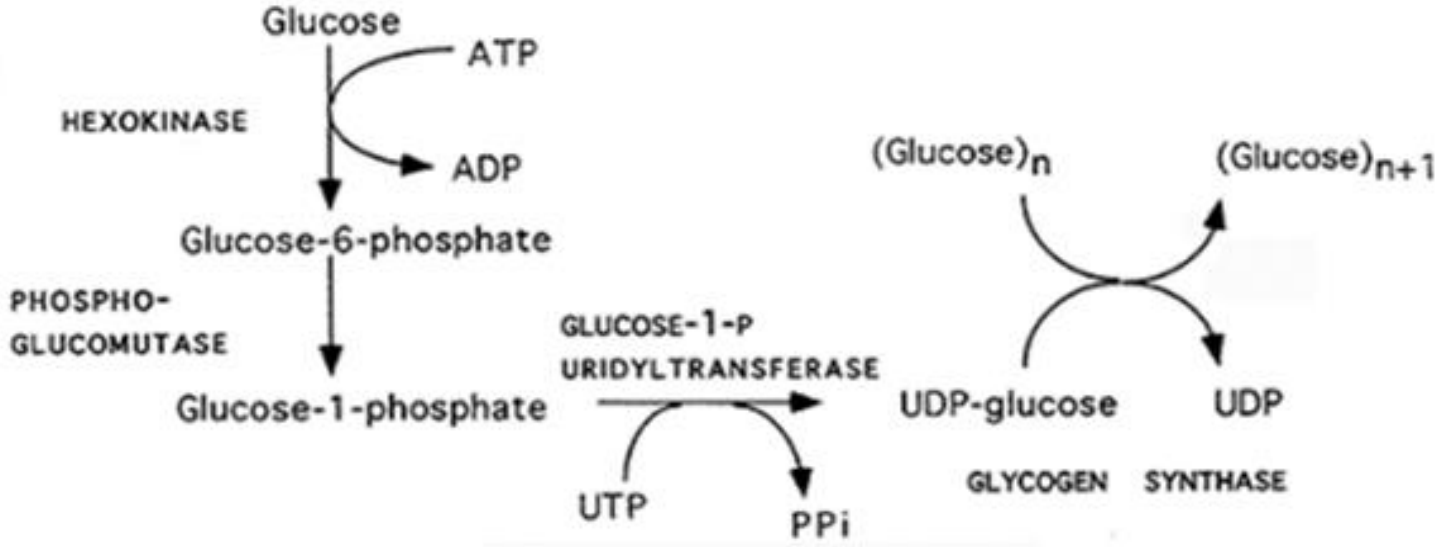
Electron transport system



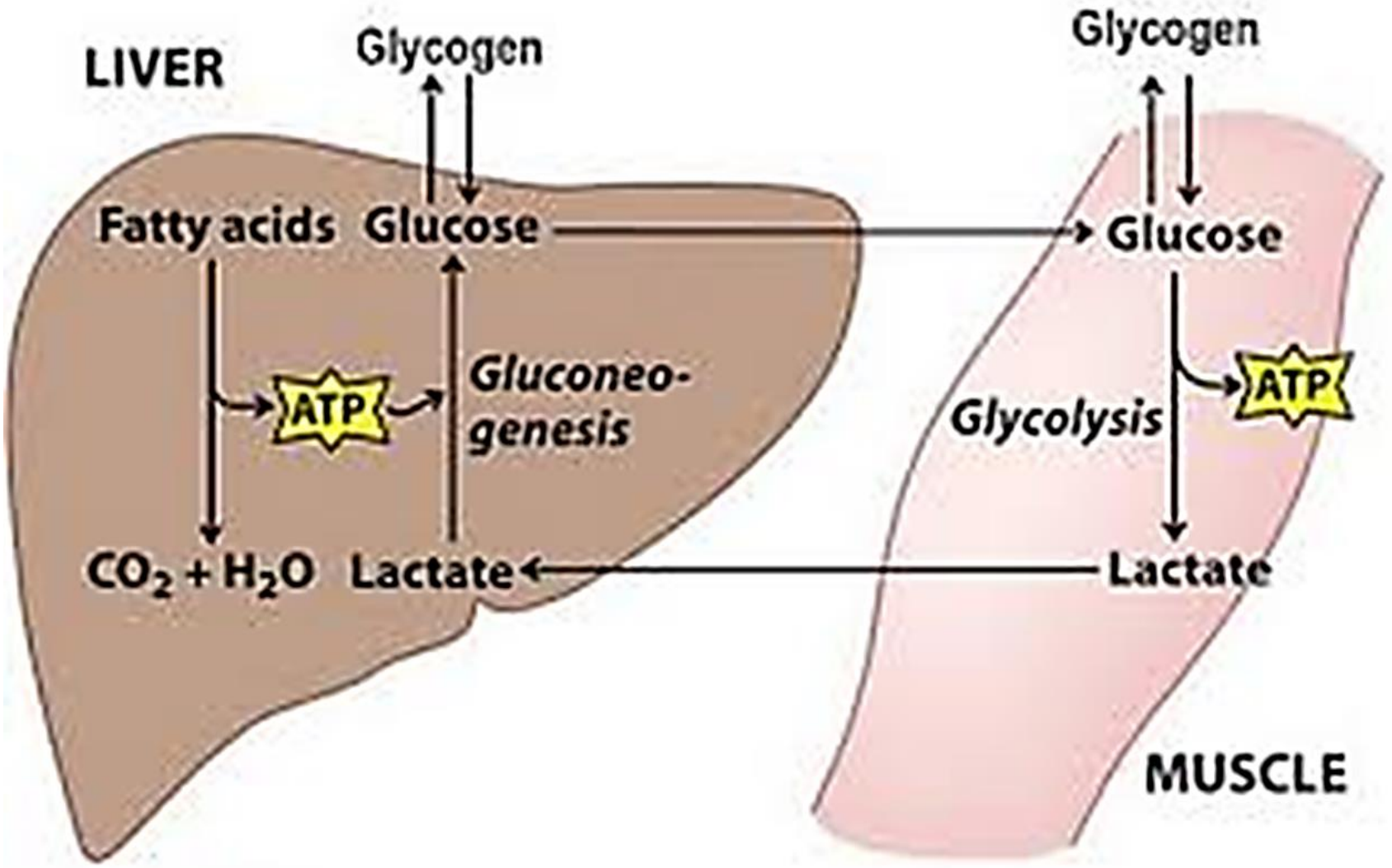
Carbohydrate storage

- Carbohydrate is stored mainly in the form of intramuscular glycogen in skeletal muscle and liver.
- Total mass of glycogen is relatively small, several hundred grams, and turnover is rapid.



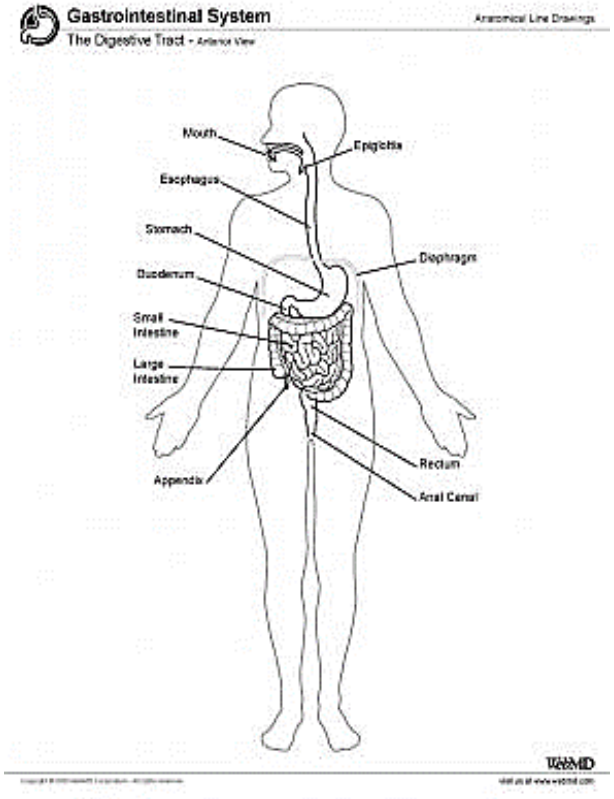
Glycogen synthase – important enzyme

Glycogen Synthesis

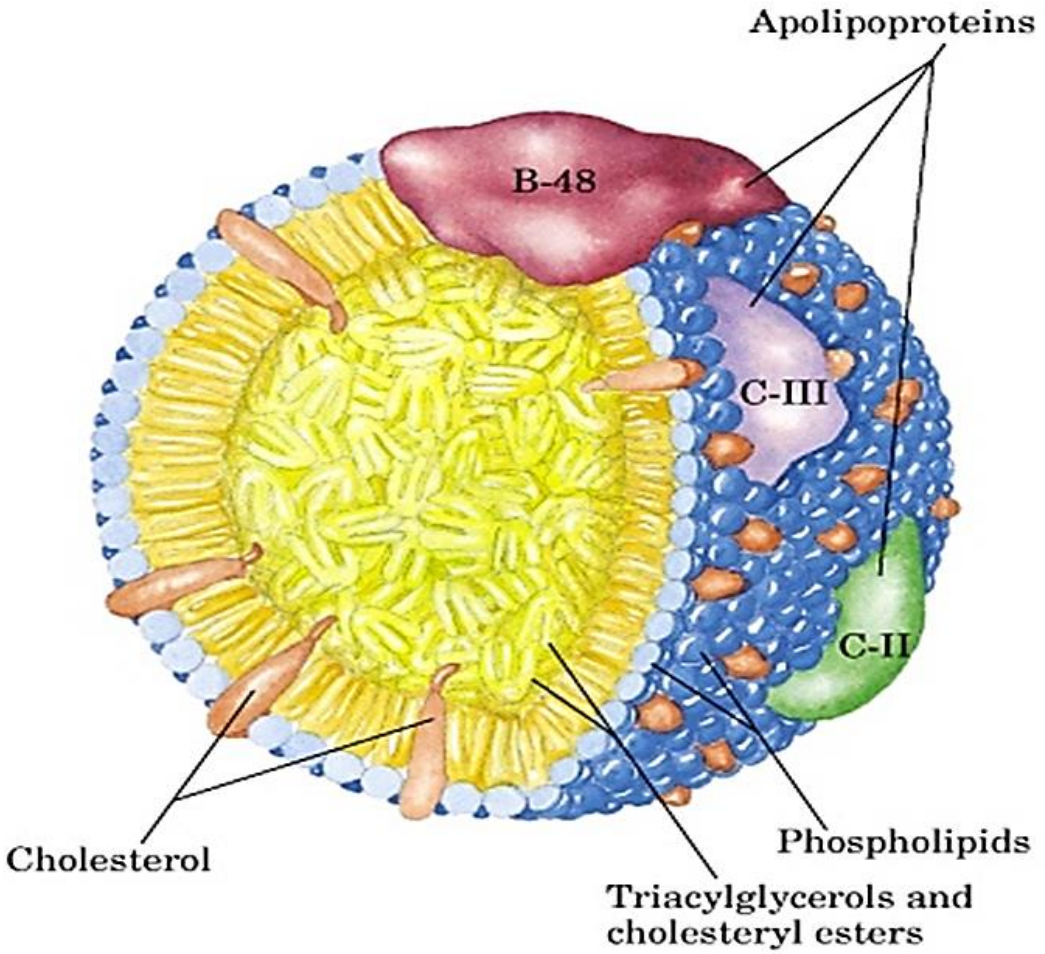


Lipid Metabolism

- After digestion, 2-monoacylglycerol, and free fatty acids are the main products in the intestinal lumen.
- In ER of the intestinal mucosal cells, fatty acids are activated to acyl-coenzyme A.
- These acyl-coenzyme A then react with 2-monoacylglycerol to form triglyceride (TG) again.



- In ER of the intestinal mucosal cells, TG are assembled into small fat droplet, known as chylomicrons.



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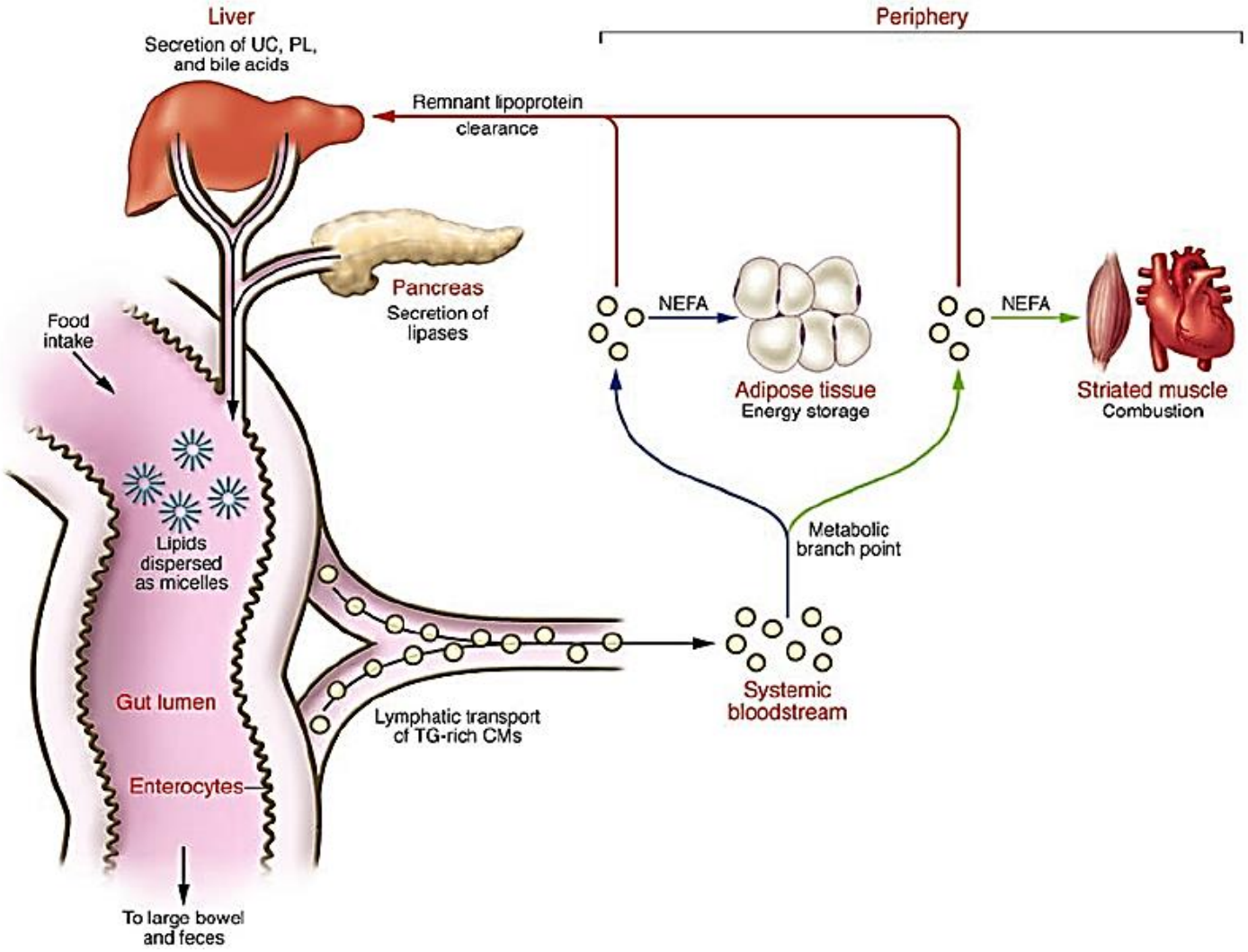
- Triglycerides in chylomicrons are utilized by adipose tissue, heart, skeletal muscle, lactating mammary glands, and to a lesser extent, spleen, lungs, kidneys, endocrine gland, and aorta. (not liver and brain).
- Because these tissues posses lipoprotein lipase (LPL).

Lipid Metabolism



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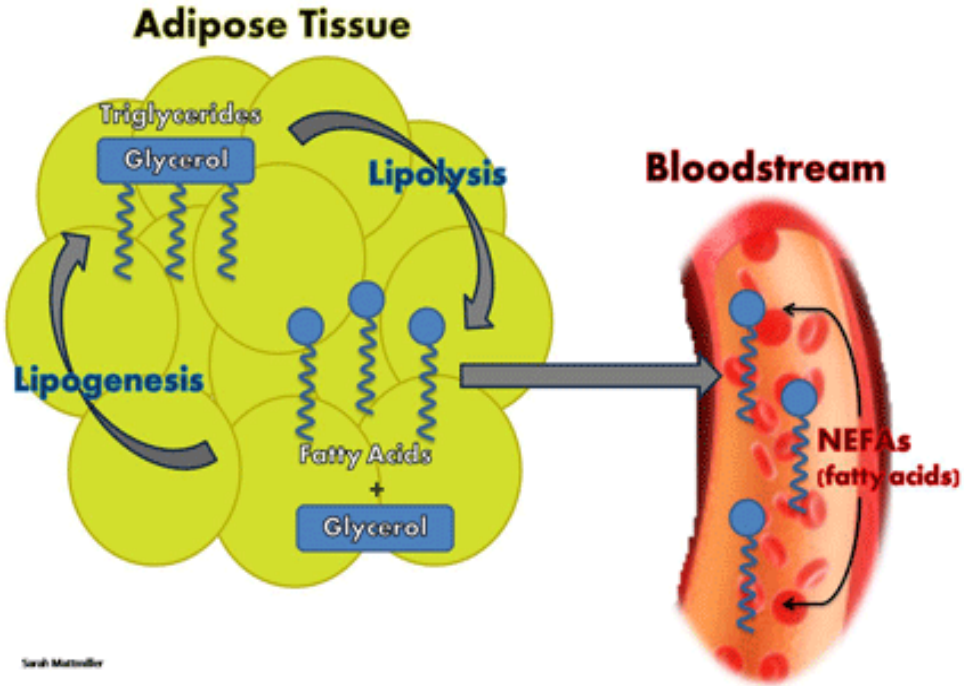
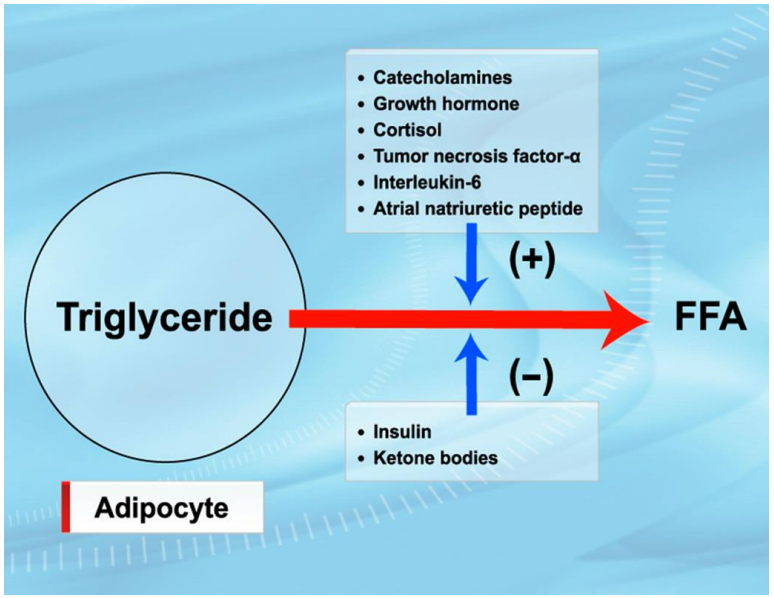
Adipose Tissue





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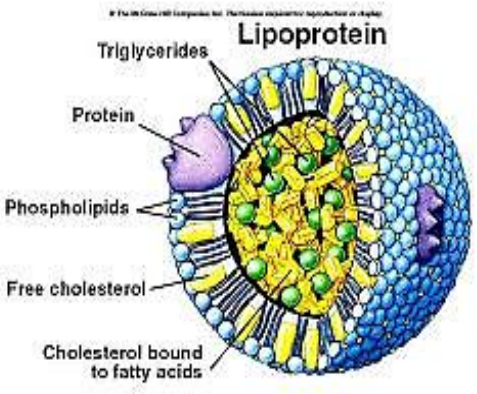
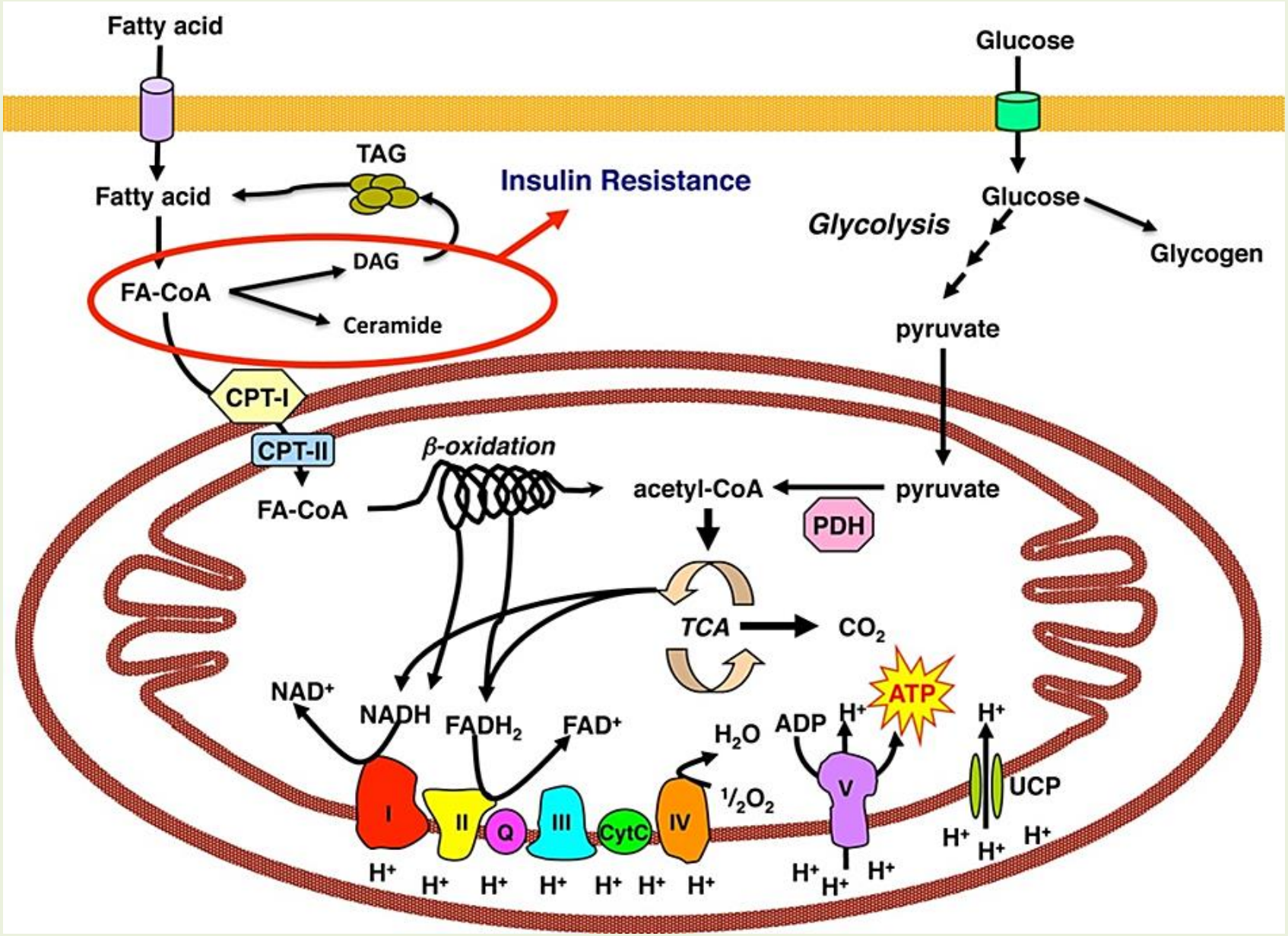
Lipoproteins

- Lipoproteins have characteristic lipid and protein compositions and can be separated by electrophoresis.



Class	Source	TG	PL	Chol es.	Chol.
Chylomicron	intestine	86	8	3	2
VLDL	liver	55	18	13	7
LDL	VLDL, IDL	9	20	40	8
HDL	Liver, intestine	5	33	17	5


Fatty acid
Glucose
TAG
Fatty acid
Insulin Resistance
Glycolysis
Glucose
Glycogen
DAG
FA-CoA
Ceramide
pyruvate
CPT-I
CPT-II
β-oxidation
FA-CoA
acetyl-CoA
pyruvate
PDH
TCA
CO2
NAD+
NADH
FADH2
FAD+
H2O
ADP
H+
ATP
H+
UCP
1/2O2
I
II
Q
III
CytC
IV
V
H+
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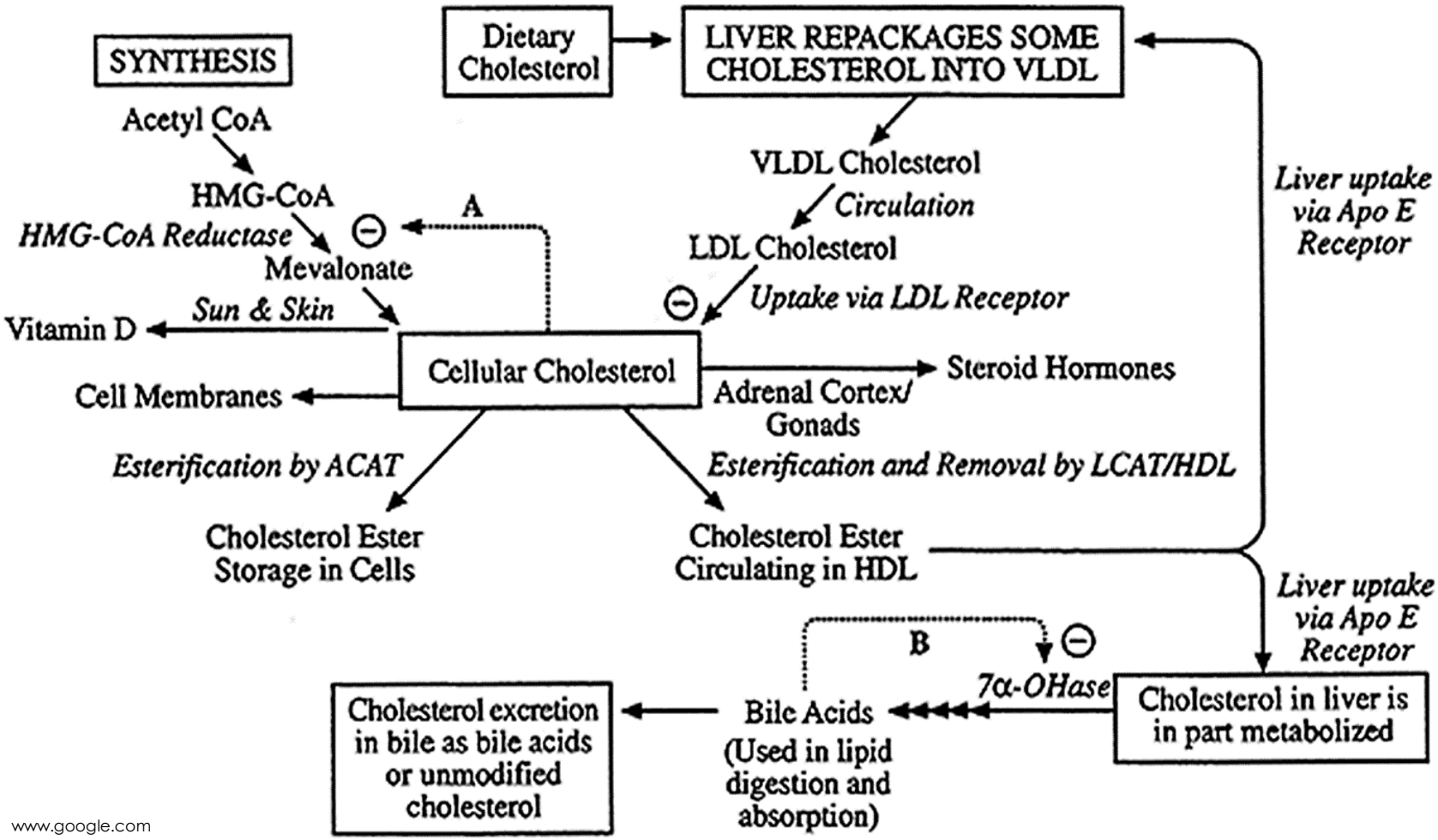
Lipid Metabolism



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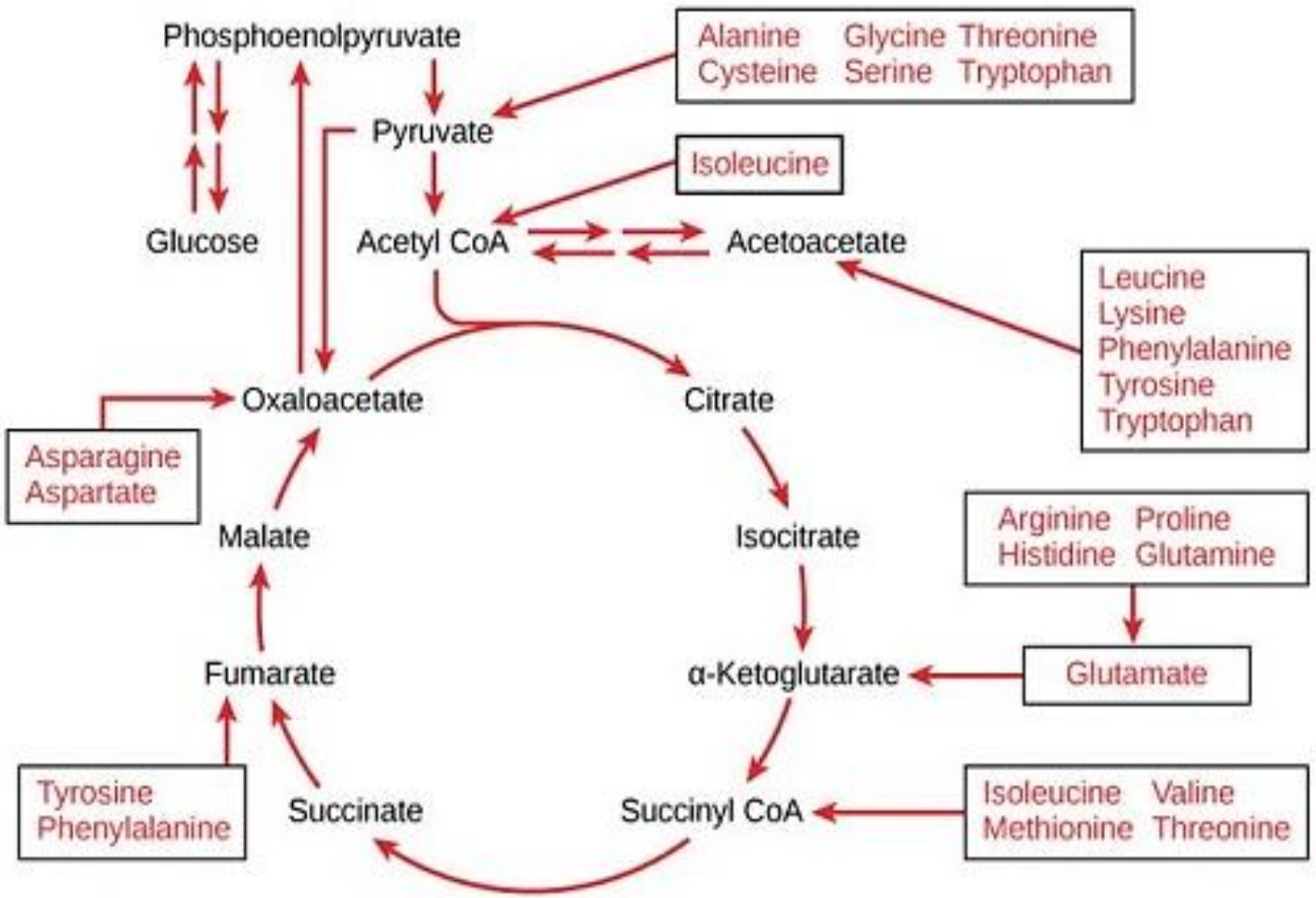
Protein Metabolism

Amino acids are used for 3 purposes:

- They are substrates for the generation of metabolic energy.
- They are substrate for protein synthesis.
- They are substrate for the synthesis of many products including heme, purines, pyrimidines, etc.

Amino Acids Metabolism



Regulation of Metabolic Processes

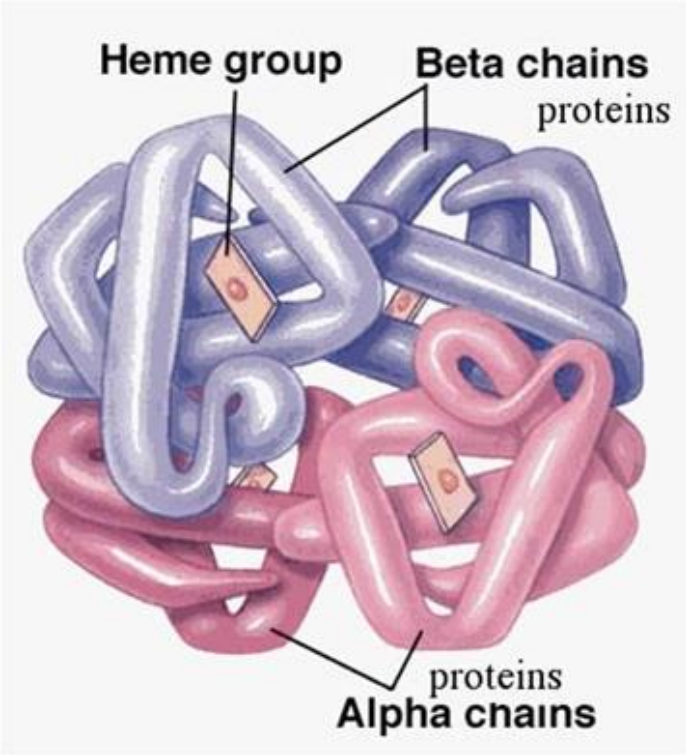
- ATP is energy currency in biological systems.
- A healthy cell must maintain an ATP/ADP ratio of about 10:1.
- The mammalian AMP-activated protein kinases (AMPK) that balance anabolic and catabolic pathways are based on the ratio of AMP/ATP.

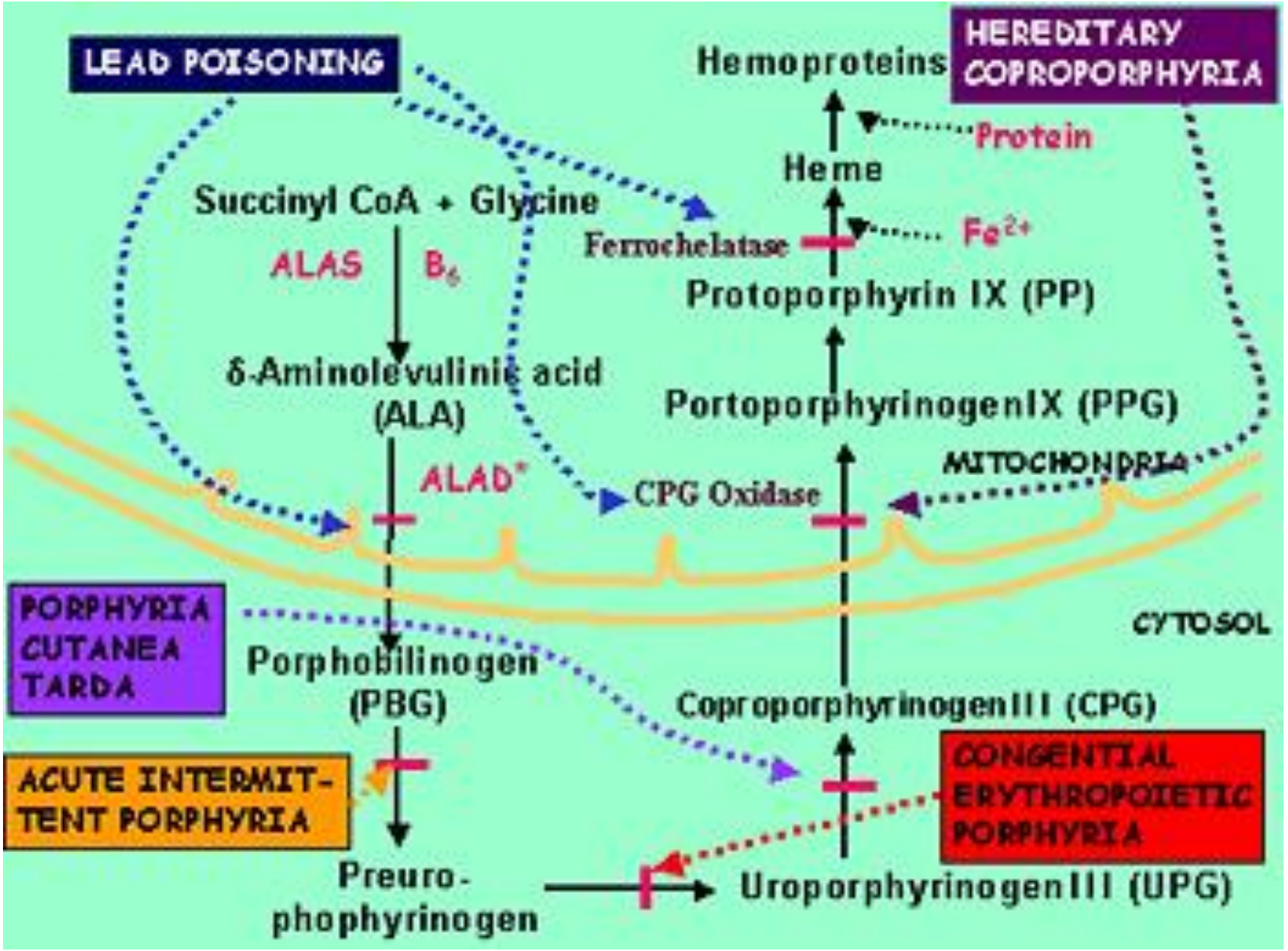
Metabolic Disorders

- Inherited metabolic syndrome
  - Porphyria
- Acquired metabolic disorders
  - Iron deficiency anemia
  - Metabolic syndrome
  - Diabetes mellitus
  - Hypo-hyperthyroidism

Porphyria

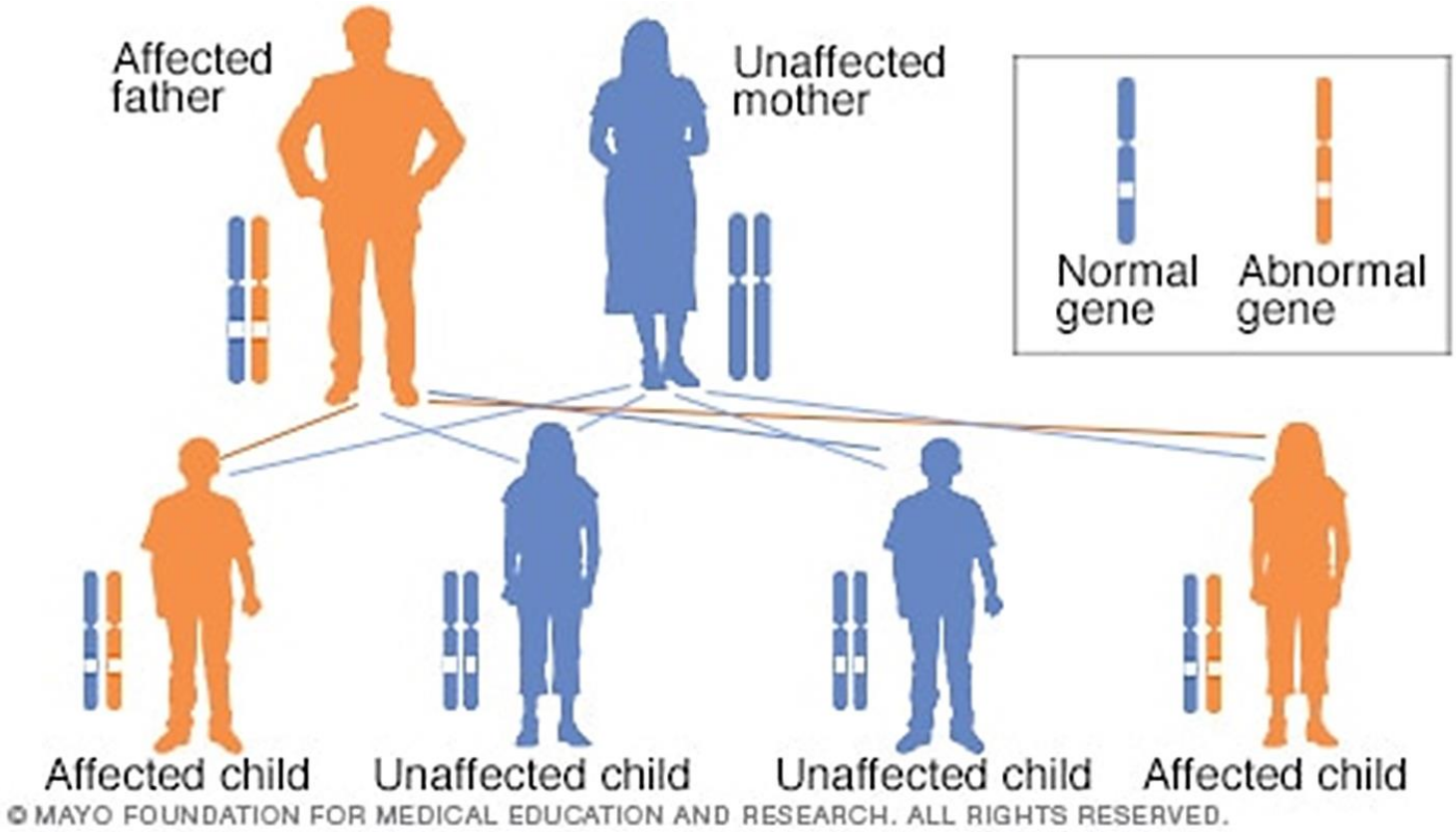
- Porphyria refers to a group of disorders that result from a buildup of natural chemicals that produce porphyrin in your body.
- Porphyrins are essential for the function of hemoglobin.




LEAD POISONING
HEREDITARY COPROPORPHYRIA
Hemoproteins
Protein
Heme
Succinyl CoA + Glycine
ALAS
B6
Ferrochelatase
Fe2+
Protoporphyrin IX (PP)
δ-Aminolevulinic acid (ALA)
PortoporphyrinogenIX (PPG)
MITOCHONDRIA
ALAD
CPG Oxidase
PORPHYRIA CUTANEA TARDA
CYTOSOL
Porphobilinogen (PBG)
CoproporphyrinogenIII (CPG)
CONGENITAL ERYTHROPOIETIC PORPHYRIA
ACUTE INTERMIT-TENT PORPHYRIA
Preuro-phophyrinogen
UroporphyrinogenIII (UPG)

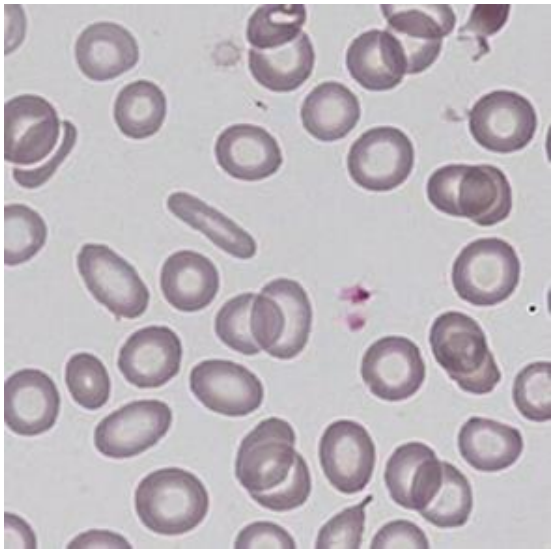
Pathophysiology of porphyria

- ALA synthase-2 enzyme



Iron deficiency anemia

- Bodys don’t have enough iron to produce hemoglobin
- Anemia due to – blood loss, inadequate iron diet, inability of absorb iron, pregnancy.
- Blood smear show pathognomonic features of pencil shaped red blood cell.

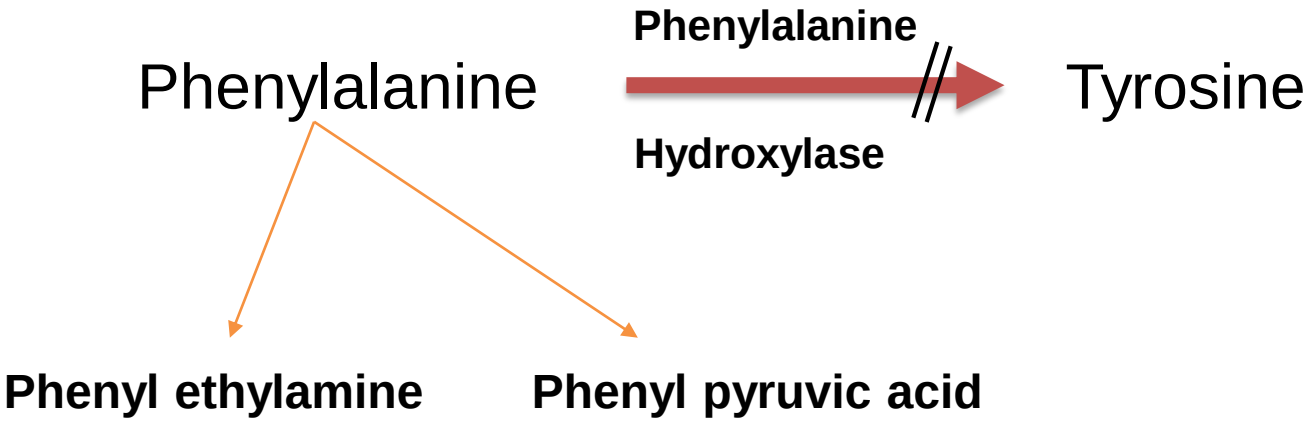


Amino Acid Disorders

- Phenylketonuria (PKU) – most common
- Absence of phenylalanine hydroxylase enzyme
- Inability to convert phenylalanine to tyrosine
- Tyrosine becomes conditionally essential

Amino Acid Disorders

Phenyl Ketonuria (PKU)



Phenyl pyruvic acid is what gives the urine its smell because its ketonic and acidic.

Phenyl Ketonuria (PKU)

CLINICAL FEATURES

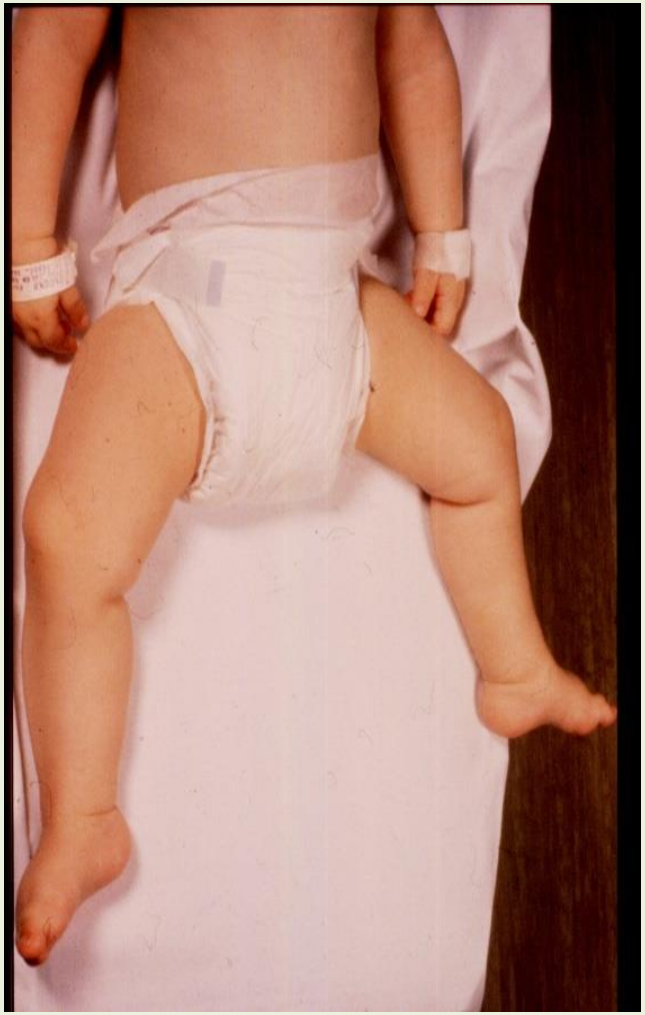
1. Hyperactivity, athetosis, vomiting.
2. Blond.
3. Seborric dermatitis or eczema skin.
4. Hypertonia.
5. Seizures.
6. Severe mental retardation.
7. Unpleasant odor of phenyl acetic acid.

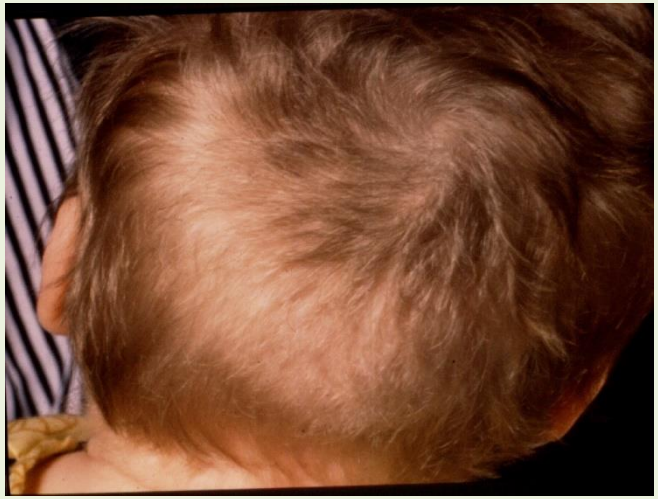
DIAGNOSIS

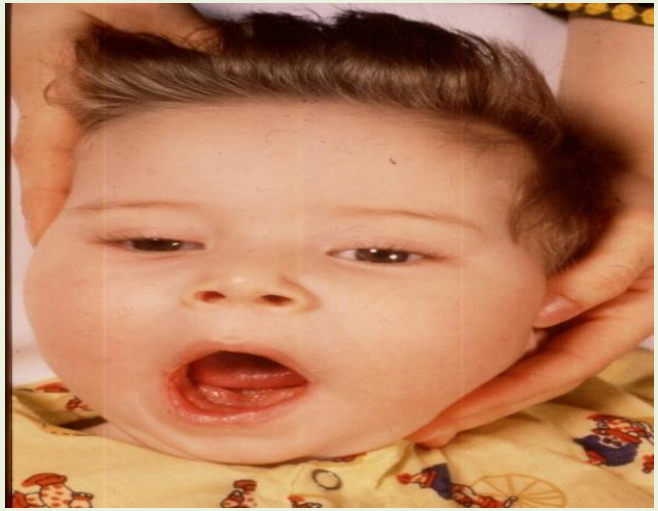
- Screening : Guthrie Test.
- High Phenylalanine > 20 mg/dl.
- High Phenyl pyruvic acid.

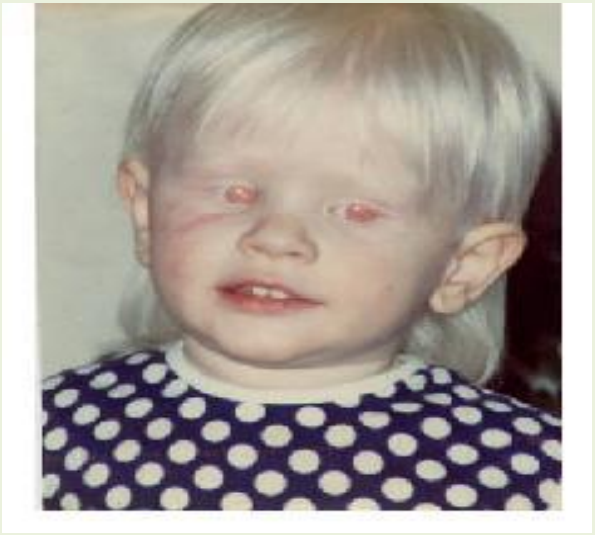
TREATMENT

- DIET.
- BH4 (Tetrahydrobiopterin).
- L – dopa and 5- hydroxytryptophan.









Iris had fibrous tissue, and it’s colourless and is red due to vessels.

Amino Acid Disorders

- **Phenylketonuria (PKU)**
  - Results in metal retardation, severe behavioral problems, seizures, eczema
  - Musty or mousy odor
  - Toxic to brain – demyelination of white matter
  - Decreased production of serotonin, epinephrine, norepinephrine, dopamine, GABA

Amino Acid Disorders

- **PKU – Nutrition Interventions**
  - Restriction of dietary protein
  - Synthetic formula supplying all essential amino acids except offending amino acids
  - Blood phenylalanine target levels more restrictive for children up to age 12

Amino Acid Disorders

- **PKU – Nutrition Interventions**
  - Assess kcal and protein needs
  - Amount of allowed phenylalanine determined by enzymatic activity and blood levels
  - Allow as much protein as possible for adequate growth from fruits, vegetables, limited amounts of grains
  - Balance provided by metabolic formulas

Amino Acid Disorders

- **PKU – Nutritional Concerns**
  - Risk for nutritional deficiencies
  - Growth retardation
  - Bone status
  - Amino acid deficiencies
  - Overrestriction
  - Metabolic control during pregnancy

Amino Acid Disorders

- **PKU – Adjunct Therapies**
  - Antibiotics
  - Carnitine
  - Sodium benzoate
  - Sodium phenylbutyrate

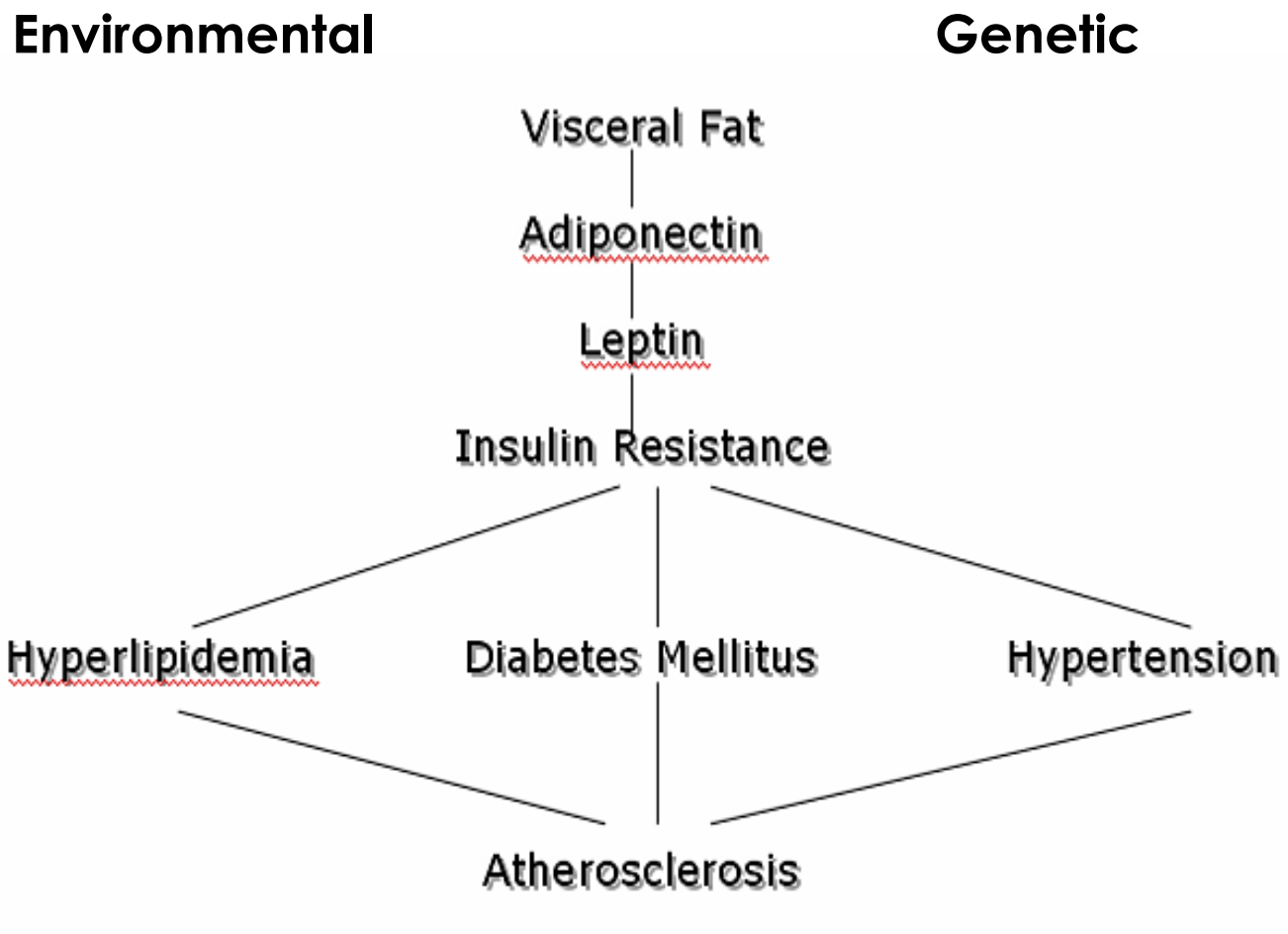
Pathophysiology of iron deficiency anemia

- Iron is needed for the synthesis of hemoglobin and new DNA.
- It is the component of various enzymes, especially cytochrome group.
- Body requires iron for transport of oxygen.
- 60% of body iron is in hemoglobin, 15% in myoglobin, and other in some protein and enzymes.

Metabolic Syndrome (American Heart Association)

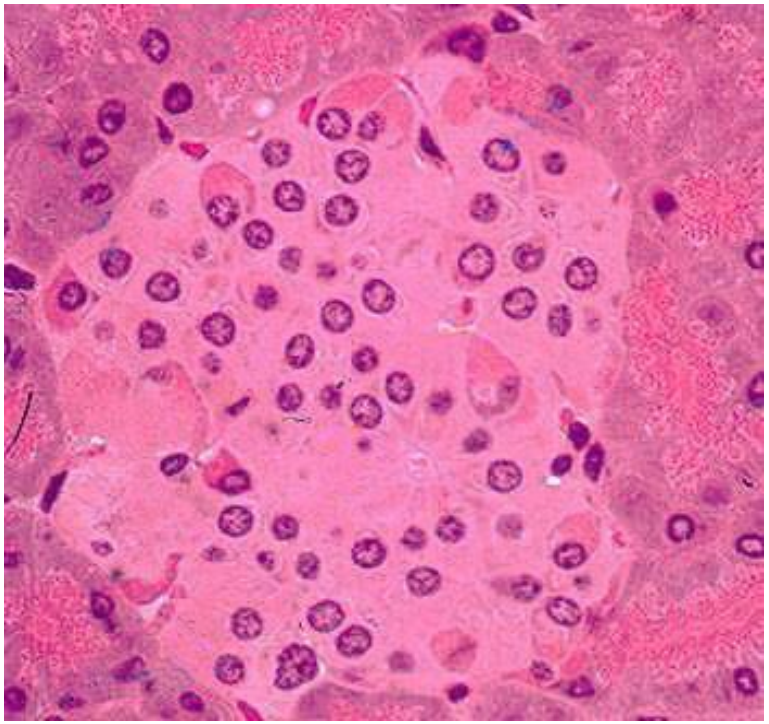
- **Metabolic syndrome may be diagnosed if you have 3 or more of the following:**
  - being very overweight or having too much fat around your waist, >40 inches in men, and >35 inches in women.
  - high triglyceride (TG) levels >150 mg/dL and low levels of HDL <40 mg/dL in men, and < 50 mg/dL in women.
  - high blood pressure that's consistently 135/85 mmHg or higher
  - an inability to control blood sugar levels (insulin resistance) FBS >100 mg/dL

The Metabolic Syndrome

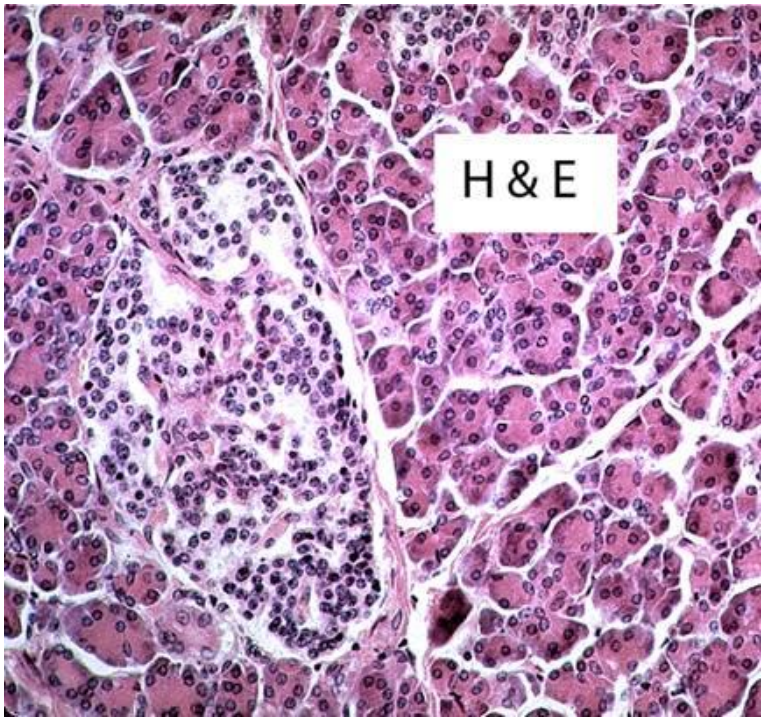


Acini and islets of Langerhans

The parenchyma of the exocrine pancreas is composed of dark-staining serous cells arranged in acini. "Dark" refers to H&E which of course is hemotoxylin-eosin--purple and rose-orange--basic vs acidic. Interspersed among these many acini is the endocrine component of the pancreas, ovoid groups of islet cells.



Islet of Langerhans



Islet with acinar cells

The actions of insulin include:

- Membrane transport of glucose, amino acids and certain ions;
- Increased storage of glycogen;
- Formation of triglycerides;
- Stimulation of DNA, RNA and protein synthesis.

Three other peptide hormones are produced in the islets of Langerhans in the pancreas:

- Glucagon, consisting of 29 amino acids
- Somatostatin, a cyclic 14 amino acids
- Pancreatic polypeptide, 36 amino acids with an amide C terminus

Leptin

Leptin is a 16 kiloDalton protein hormone regulating energy input and utilization. It decreases appetite and increases metabolism. In 1994, leptin was discovered in mice by Jeffrey M Friedman and coworkers at Rockefeller University, NYC.

The obesity *Ob* gene in mice is called the *Lep* gene in humans. Leptin is produced by adipose tissue, having 6 different types of receptors.

Adiponectin

Adiponectin is a protein hormone that regulates glucose and fatty acid catabolism. Produced by adipocytes, it can be involved in vascular deterioration.

It was discovered in 1997 by Yuji M Matsuzawa and his coworkers. Its APM1 gene maps to chromosome 3q27. Among other actions, adiponectin inhibits the myelo-monocytic lineage cells. It is a negative regulation in the hemotopoiesis and immune system, thus anti-inflamatory.

Obesity

Over eating and then overweight often lead to diabetes.
Note that regular exercise maintains and improves health.

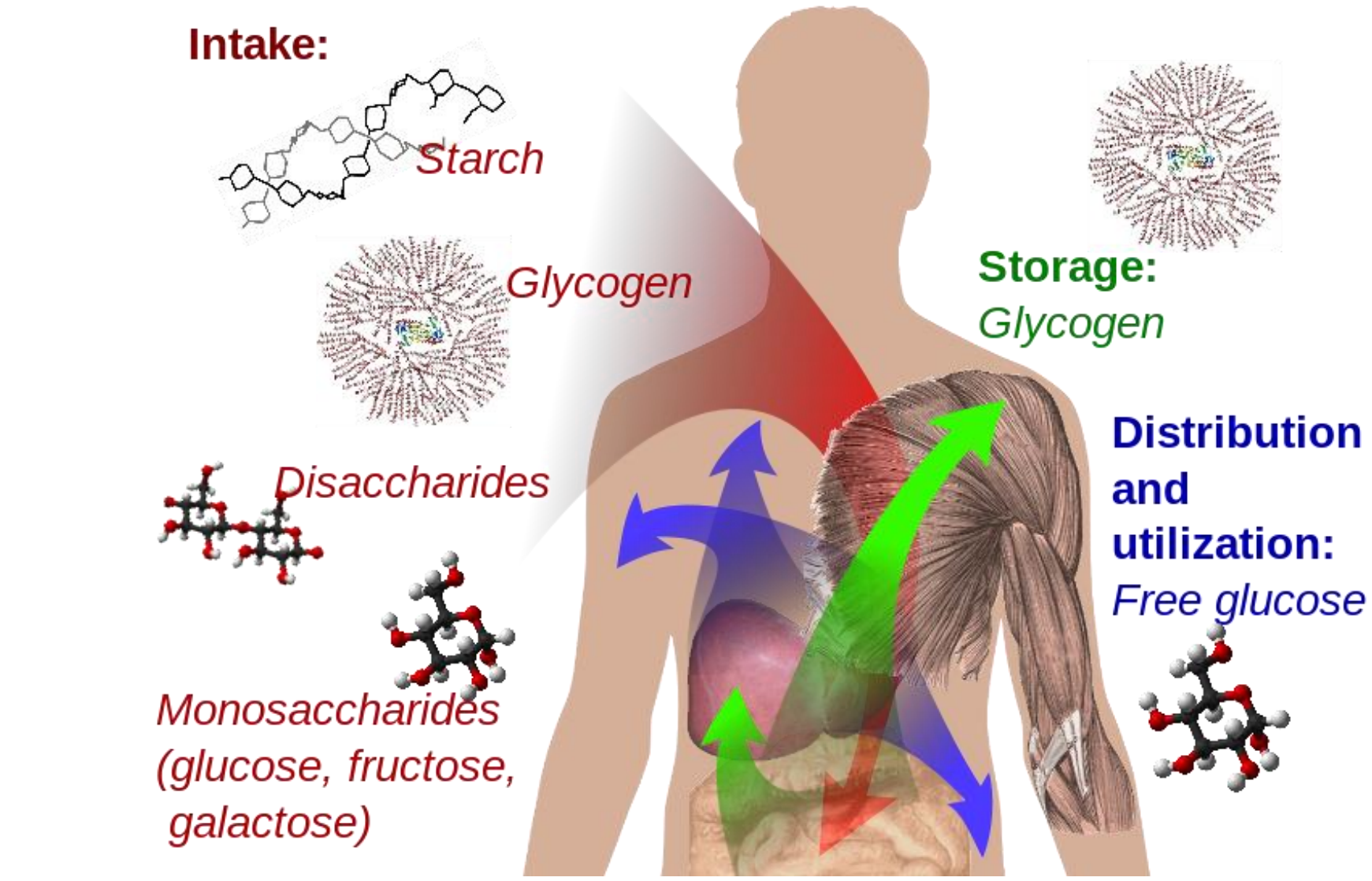
This worldwide social problem began by the 1980s via sedentary life, fast foods and other changes in life style.

Obese persons are more likely to suffer from one or more of several disorders.

These include:

- diabetes mellitus, type 2
- high blood pressure
- high levels of cholesterol and triglycerides
- Gout
- gall bladder and urinary calculus
- osteoarthritis in the back, knees and feet
- coronary heart disease
- Stroke
- cancer of the colon and prostate in men, and of the breasts, uterus and polycystic ovaries in women

Glucose metabolism



Diabetes Type 1

Type I diabetes mellitus is insulin-dependent, autoimmune disease. The disease is organ-specific resulting in pancreatic islet cell destruction.

Evidence of cellular destruction includes autoantibodies to
1) islet cells (ICA),
2) antibodies to insulin (IAA) and
3) glutamic acid decarboxylase autoantibodies (GAD Ab)

ICA (as detected on thin frozen sections of human pancreas by indirect immunofluorescence) are present in about 80 % of newly diagnosed patients. ICA, GAD Ab and IAA are each helpful in screening first-degree relatives of patients with IDDM.

Diabetes Type 2

Type 2 is also caused by insulin deficiency, even though the pancreas is producing it.

The cause of morbidity is insulin resistance with consequent hyperglycemia.

While diabetes cannot be cured, it can be controlled by insulin, diet, weight control and physical fitness by running, walking and sports. Overeating can sometimes result in diabetes.

Glucose Tolerance Test

After an overnight fast, a sample of blood is drawn.
Then 75 g of glucose dissolved in about 200-300 ml of water is drunk. Two hours later another blood sample is taken.

Account is taken of the fact that the concentration of glucose measured in plasma is 10 % higher than in whole blood.

Diabetes is present when the fasting blood sample is over 6.7 mmol/L or the level in plasma is over 7.8 mmol/L, or the second sample has 10 mmol/L of blood.

In healthy persons, the glucose concentration rises to about twice the normal level within the first hour and returns to normal within 2 hours.

Cholesterol test

- Cholesterols and triglyceride are types of fats called lipids.
- Too much fat increases your risk of a heart attack or vascular diseases.
- Heart disease is the # 1 killer of both men and women.
- Low density lipoprotein (LDL) cholesterol at abnormally high levels can cause fatty deposits in the arteries which is defined as atheroscelosis,
- High density lipoprotein (HDL) cholesterol can help carry away LDLs, keeping arteries open. Some triglycerides may result from extra calories.

Hypoglycaemia

- May be the end result of a metabolic disease - sick
- May be the primary symptom
- What is the timing of hypo
  - Fasting
  - Postprandial
  - Inter-current illness
- Hepatomegaly?
  - Permanent
  - Transient
- Ketosis?
- Lactate++?
- Liver dysfunction?
- Short stature?

ความชุกของภาวะเมตาบอลิกซินโดรมในประชากร ต.ท่ามะปราง อ.แก่งคอย จ.สระบุรี

Prevalence of Metabolic Syndrome in the Population of Ta-Maprang Sub-district, Kangkoi District, Saraburi Province

พิศิษฐ์ นามจันทรา* พัชริยา พรรณศิลป์ เครือวัลย์ คุ้มครอง วรางคณา เล็กตระกูล และ สุดาภรณ์ เก่งการ

Pisit Namjuntra* Phatchariya Phannasil Khurawan Kumkrong Warangkana Lektrakul and Sudaporn Kengkarn

คณะเทคนิคการแพทย์ มหาวิทยาลัยรังสิต

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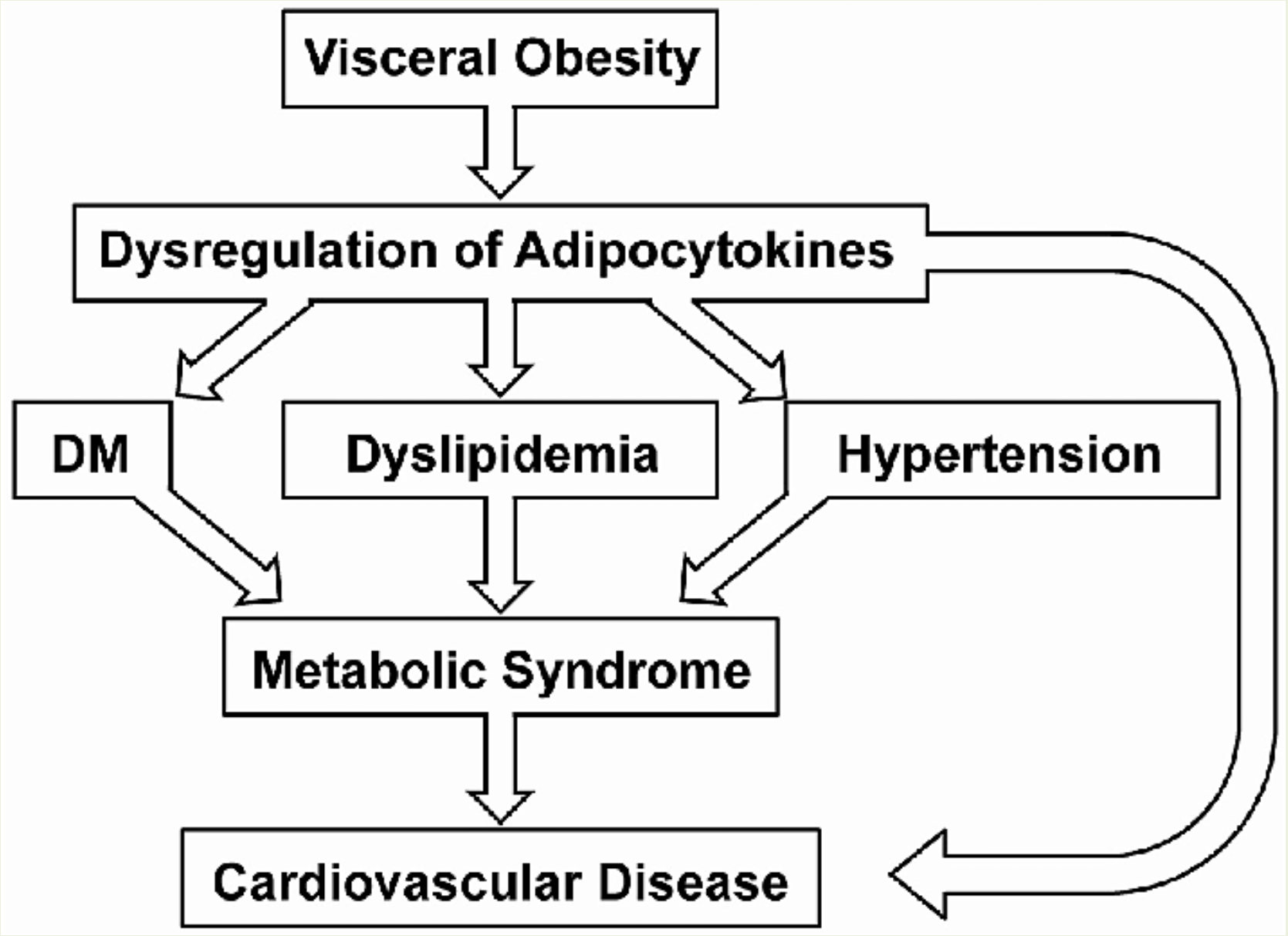
Risk factors

- Age
- Ethnicity

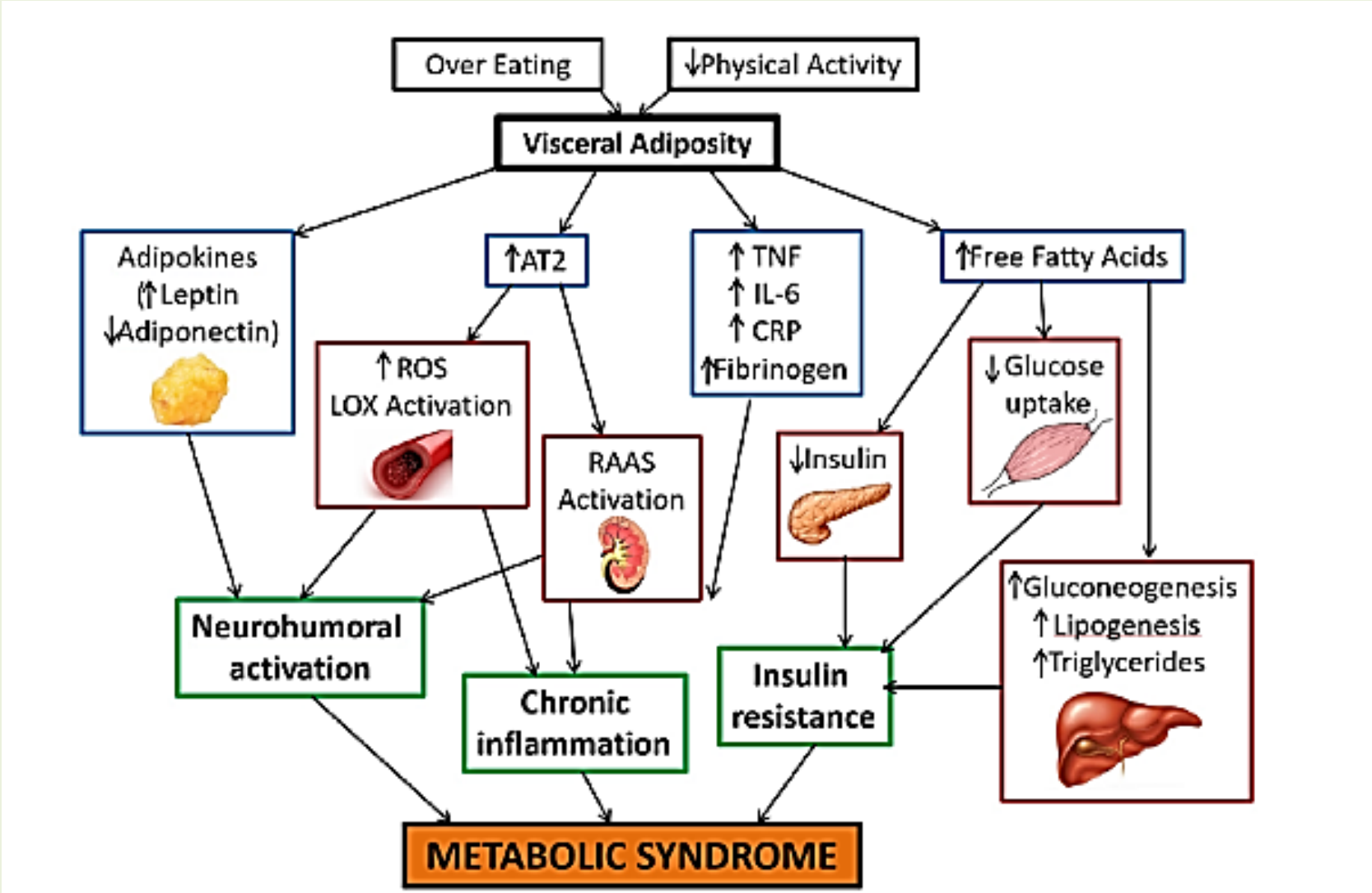
In the United States, Hispanics — especially Hispanic women.

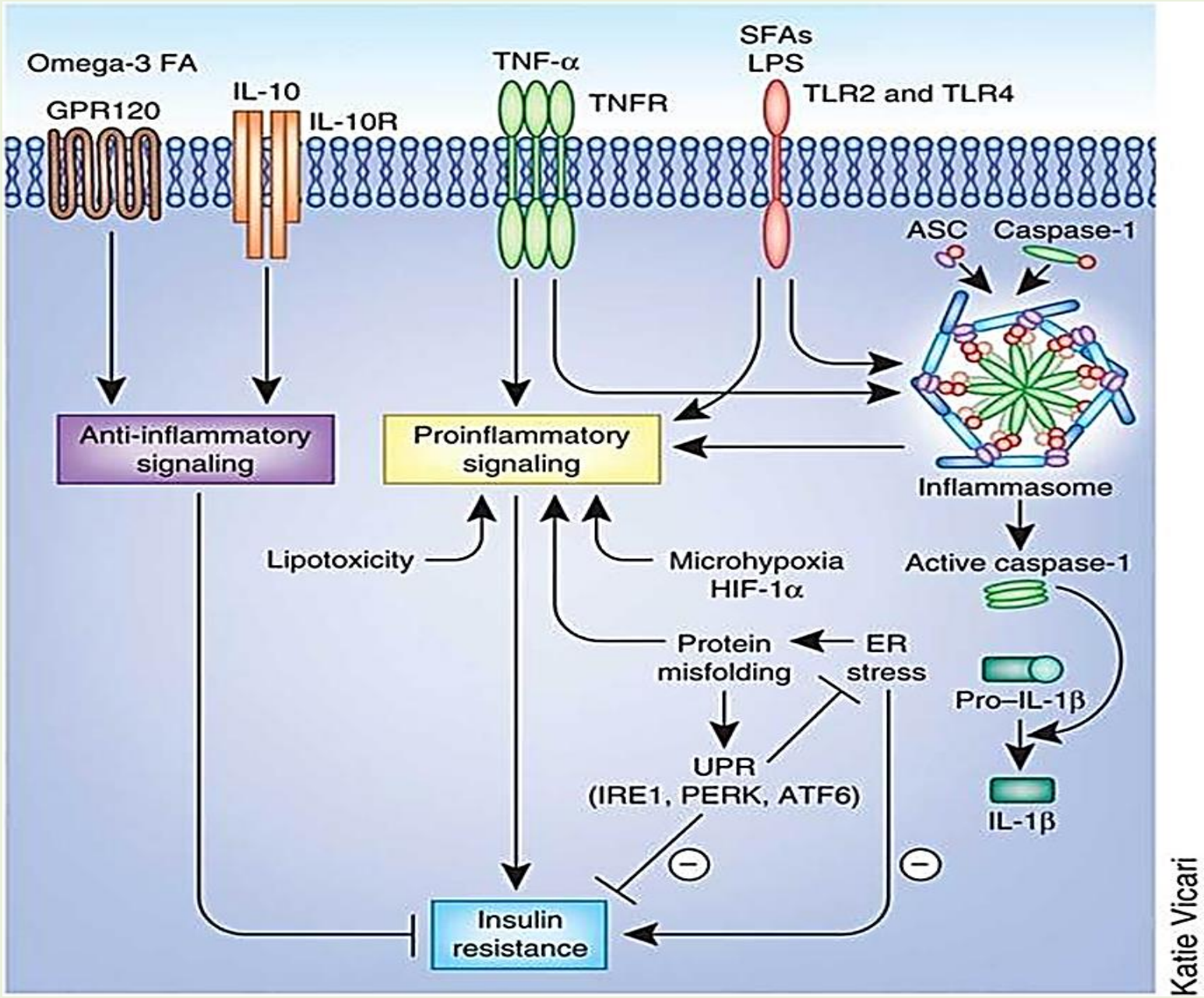
- Obesity
- Diabetes
- Other diseases

Nonalcoholic fatty liver disease, polycystic ovary syndrome or sleep apnea.

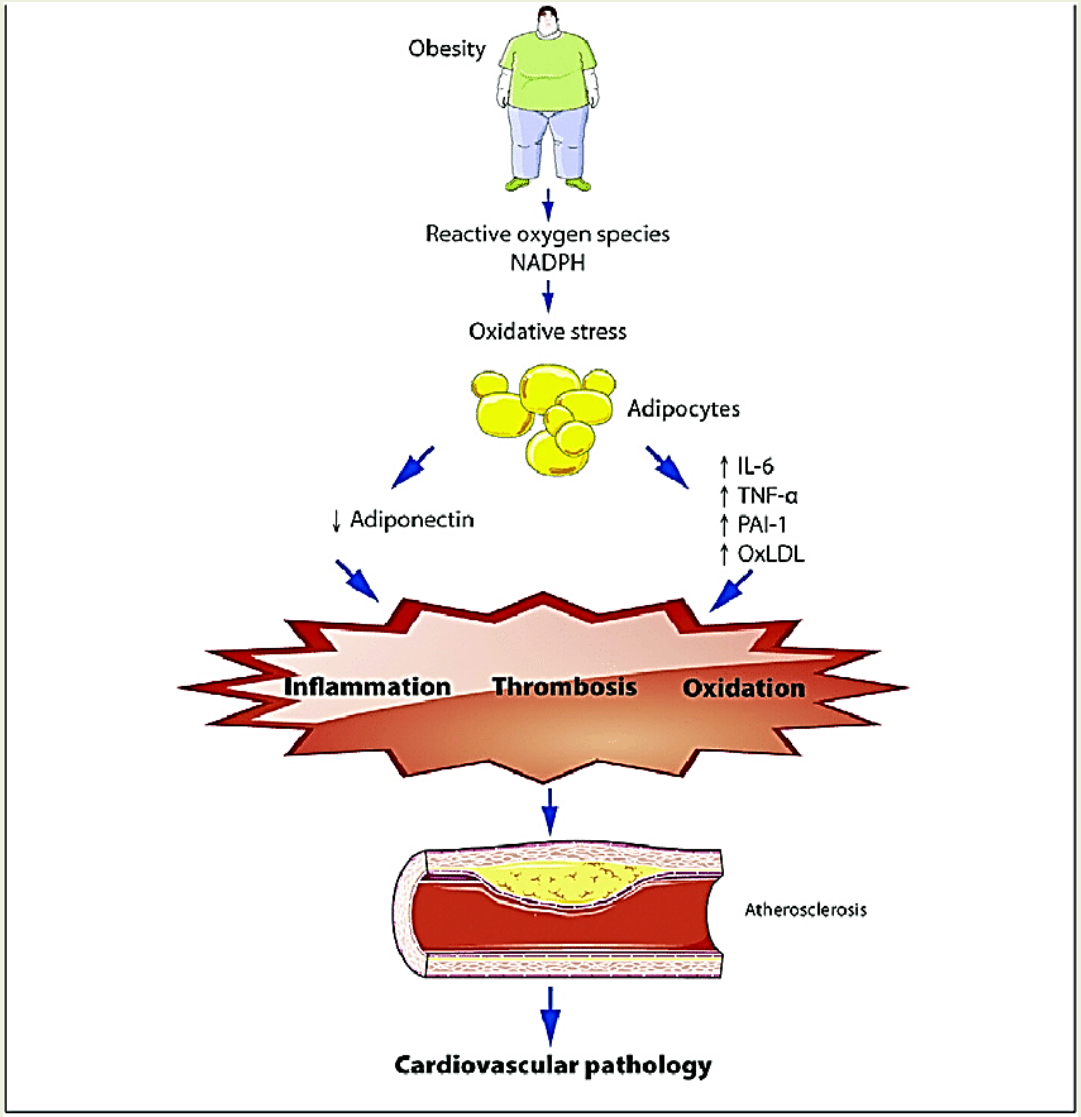

Visceral Obesity
Dysregulation of Adipocytokines
DM
Dyslipidemia
Hypertension
Metabolic Syndrome
Cardiovascular Disease

Pathophysiology of metabolic syndrome

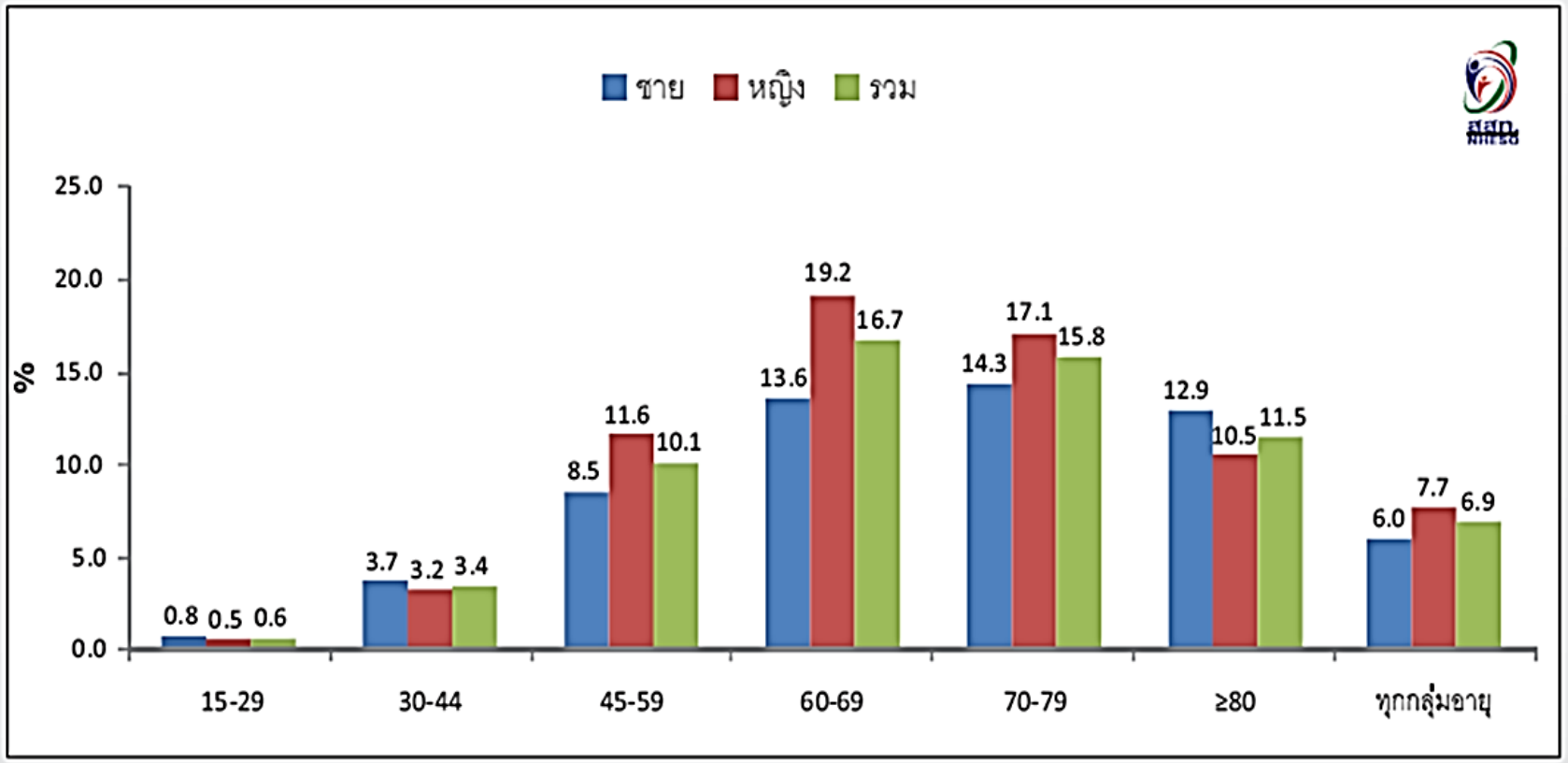


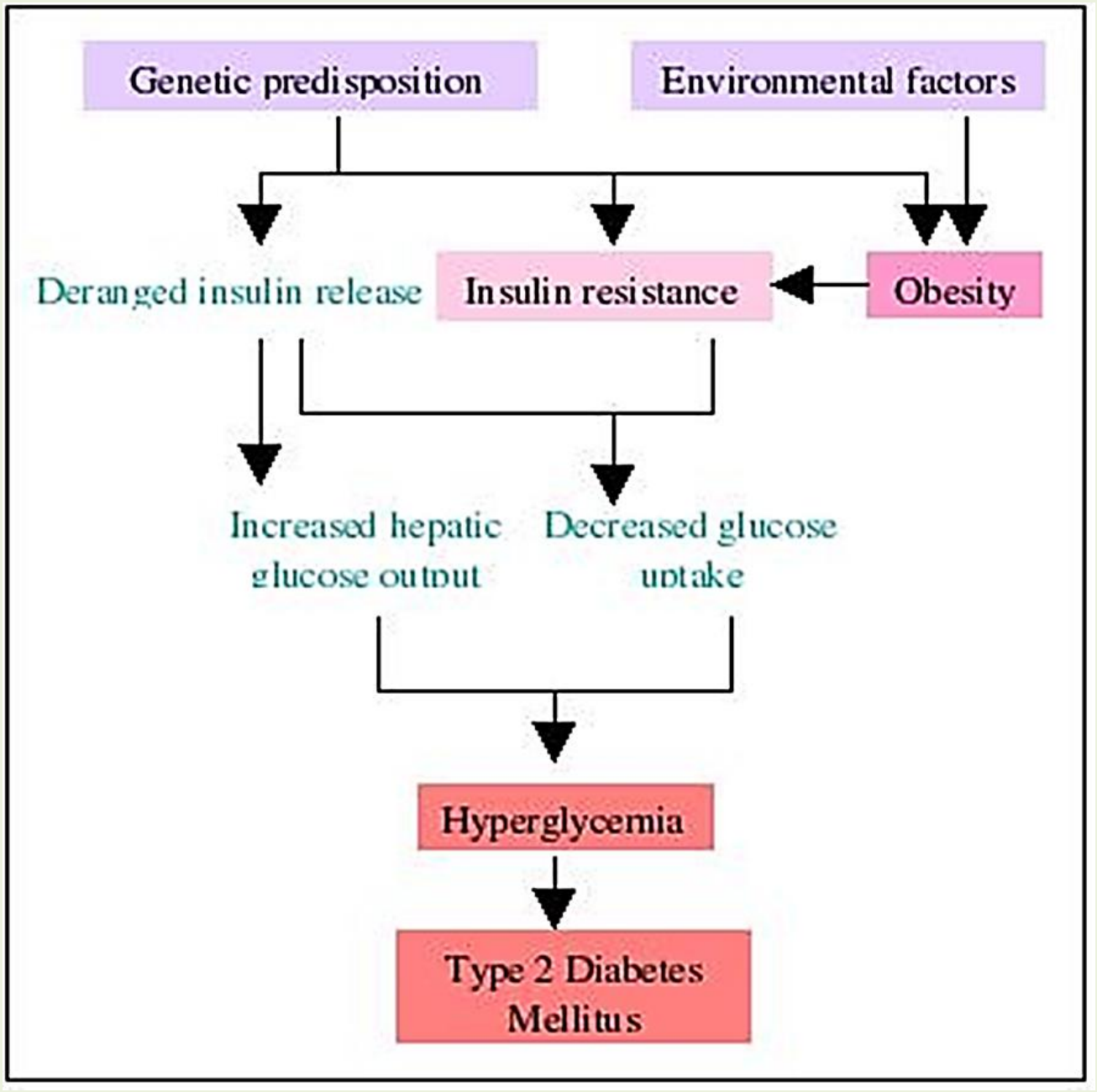

Omega-3 FA
GPR120
IL-10
IL-10R
TNF-α
TNFR
SFAs
LPS
TLR2 and TLR4
ASC
Caspase-1
Anti-inflammatory signaling
Proinflammatory signaling
Inflammasome
Lipotoxicity
Microhypoxia
HIF-1α
Active caspase-1
Protein misfolding
ER stress
Pro–IL-1β
UPR
(IRE1, PERK, ATF6)
IL-1β
Insulin resistance
Katie Vicari

Pathophysiology of atherosclerosis in metabolic syndrome



Type 2 Diabetes mellitus




Genetic predisposition
Environmental factors
Deranged insulin release
Insulin resistance
Obesity
Increased hepatic glucose output
Decreased glucose uptake
Hyperglycemia
Type 2 Diabetes Mellitus

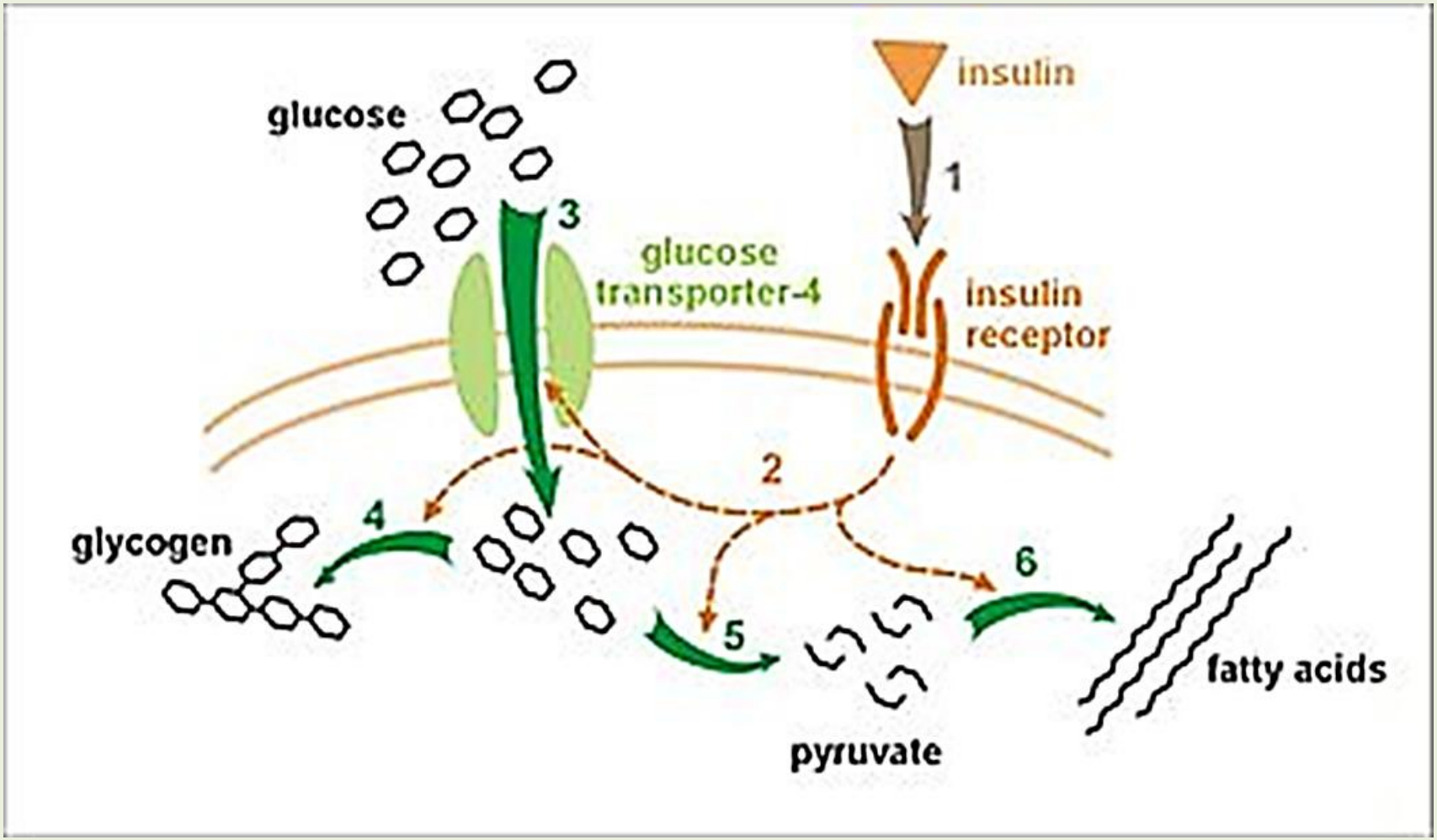
Environmental factors and DM

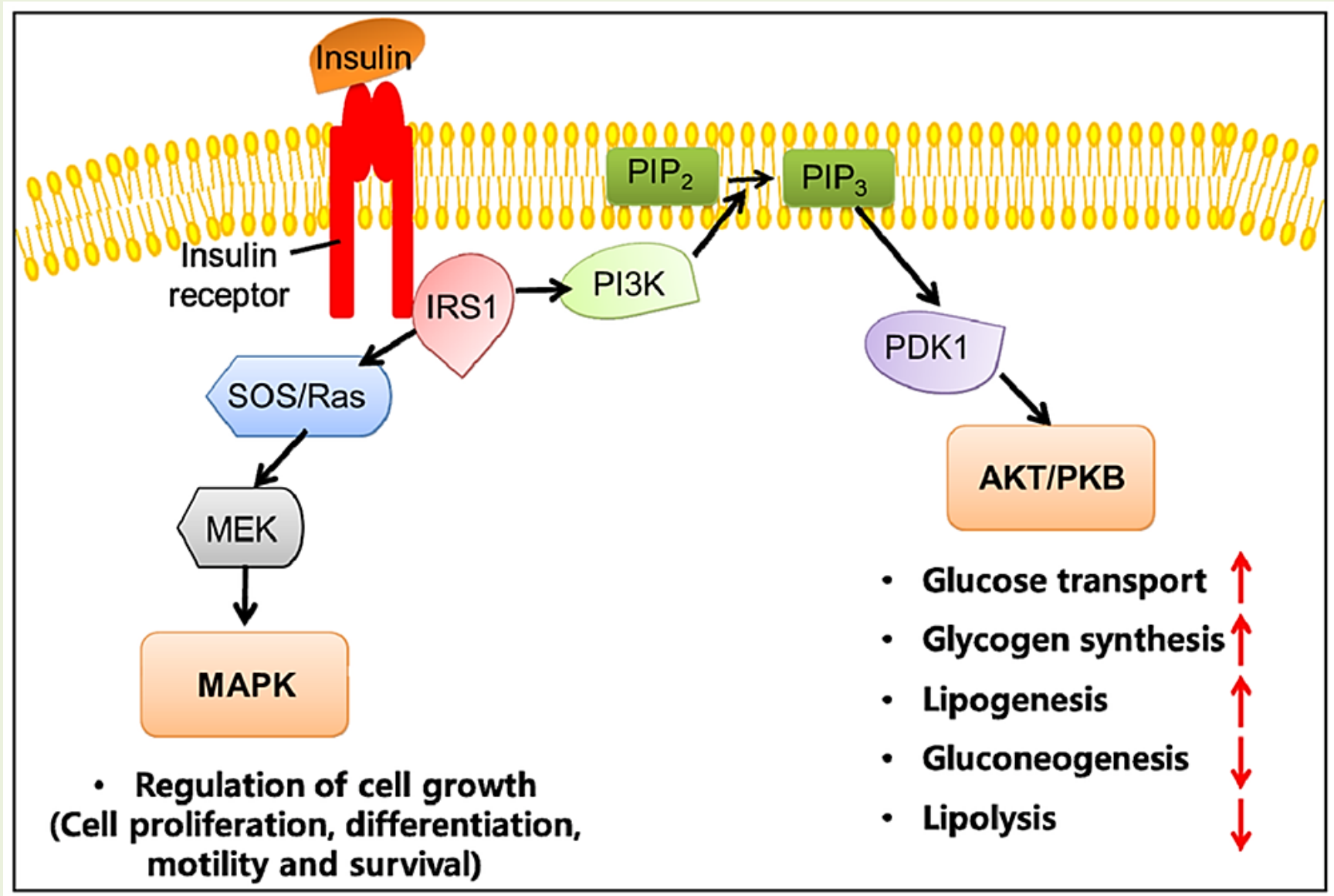
- Infections such as periodontal disease.
- The chronic inflammation such as viral hepatitis.
- Environmental pollutants can also trigger inflammation such as chronic exposure to inorganic arsenic, organochlorine pesticide.
- Smoking.
- Emotional stress.

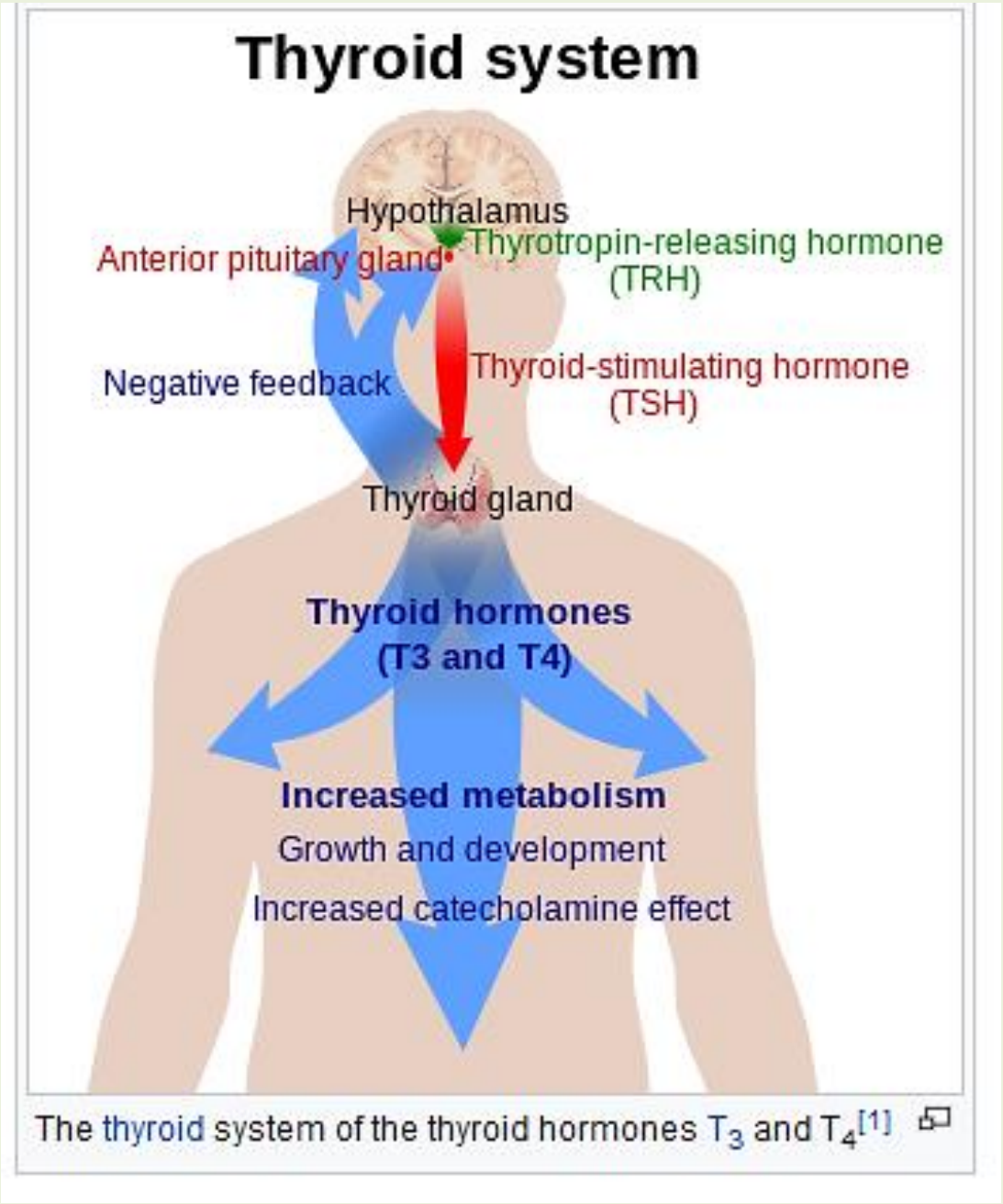
Pathophysiology of DM: Actions of insulin

- Increases glucose uptake of the cells.
- Decreases protein breakdown.
- Decreases gluconeogenesis in the liver.
- Increases fatty acid uptake and triglyceride synthesis in fat cells.
- Regulates many cytokines and other hormones.
- Activates numerous enzymes.
- Influences DNA transcription, vascular tone, and brain chemistry.

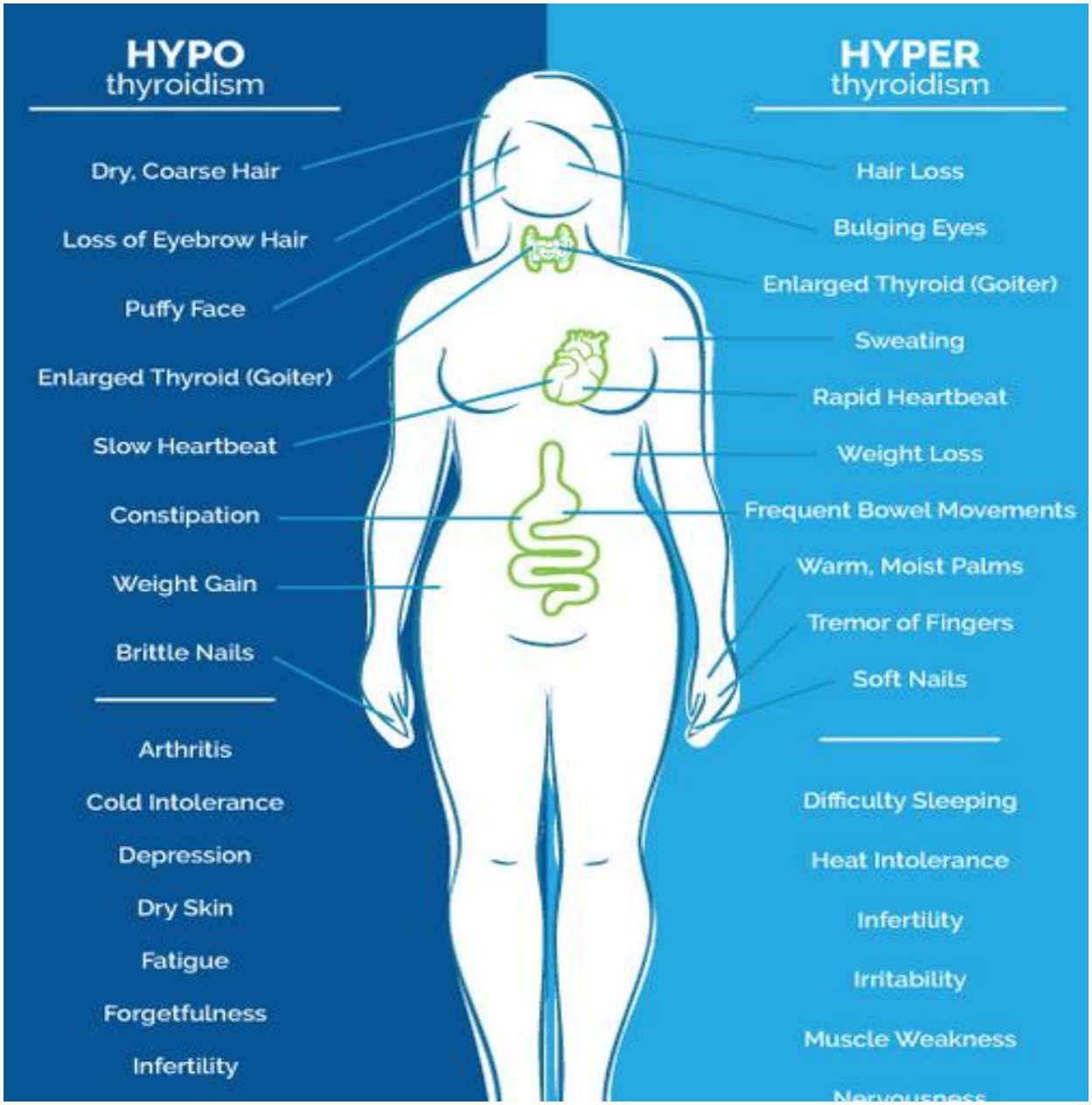
The primary defect that is most widely associated with T2DM is insulin resistance.




Insulin
Insulin receptor
IRS1
PI3K
PIP2
PIP3
PDK1
AKT/PKB
SOS/Ras
MEK
MAPK
• Glucose transport
• Glycogen synthesis
• Lipogenesis
• Gluconeogenesis
• Lipolysis
• Regulation of cell growth (Cell proliferation, differentiation, motility and survival)



The thyroid system of the thyroid hormones T_3 and T_4[1]



- Hyperthyroidism accelerates body's metabolism, contrary to hypothyroidism.

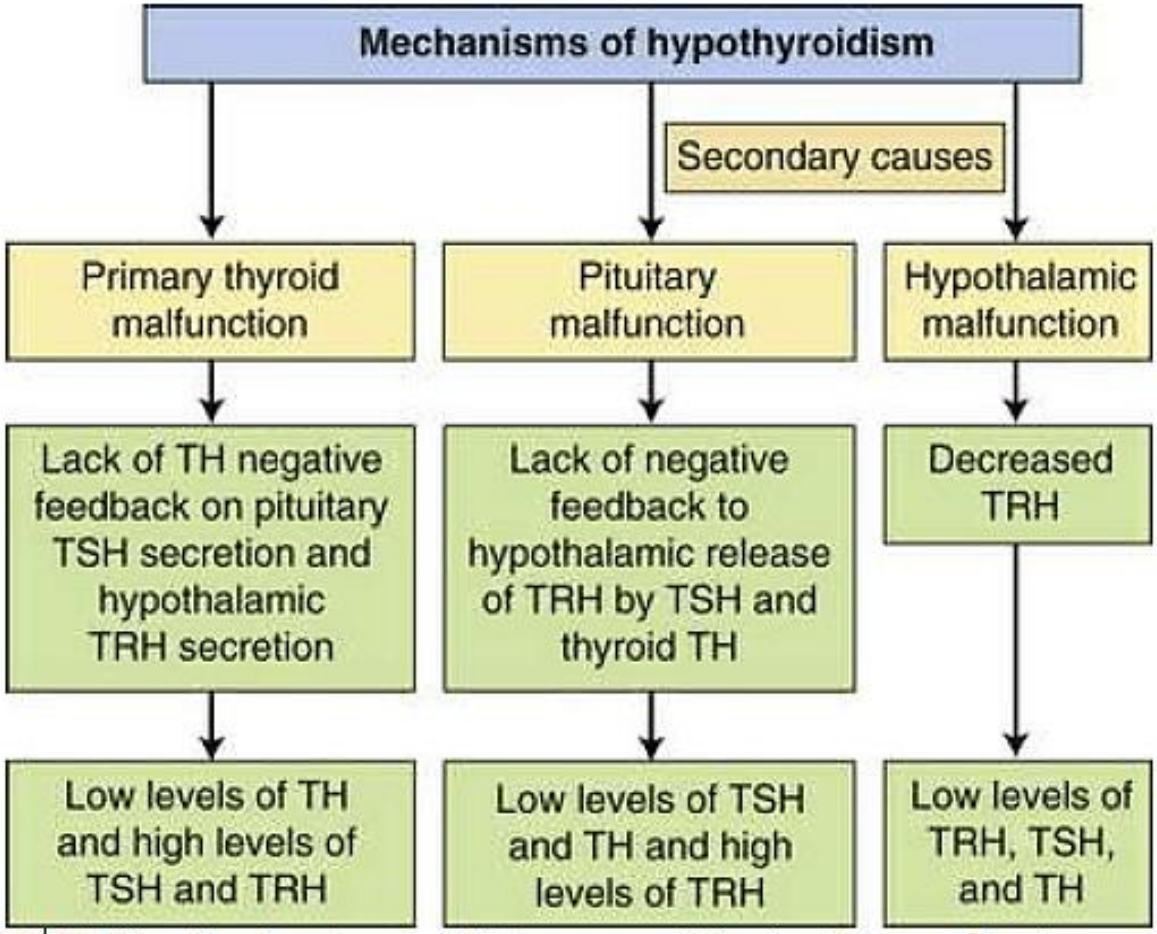
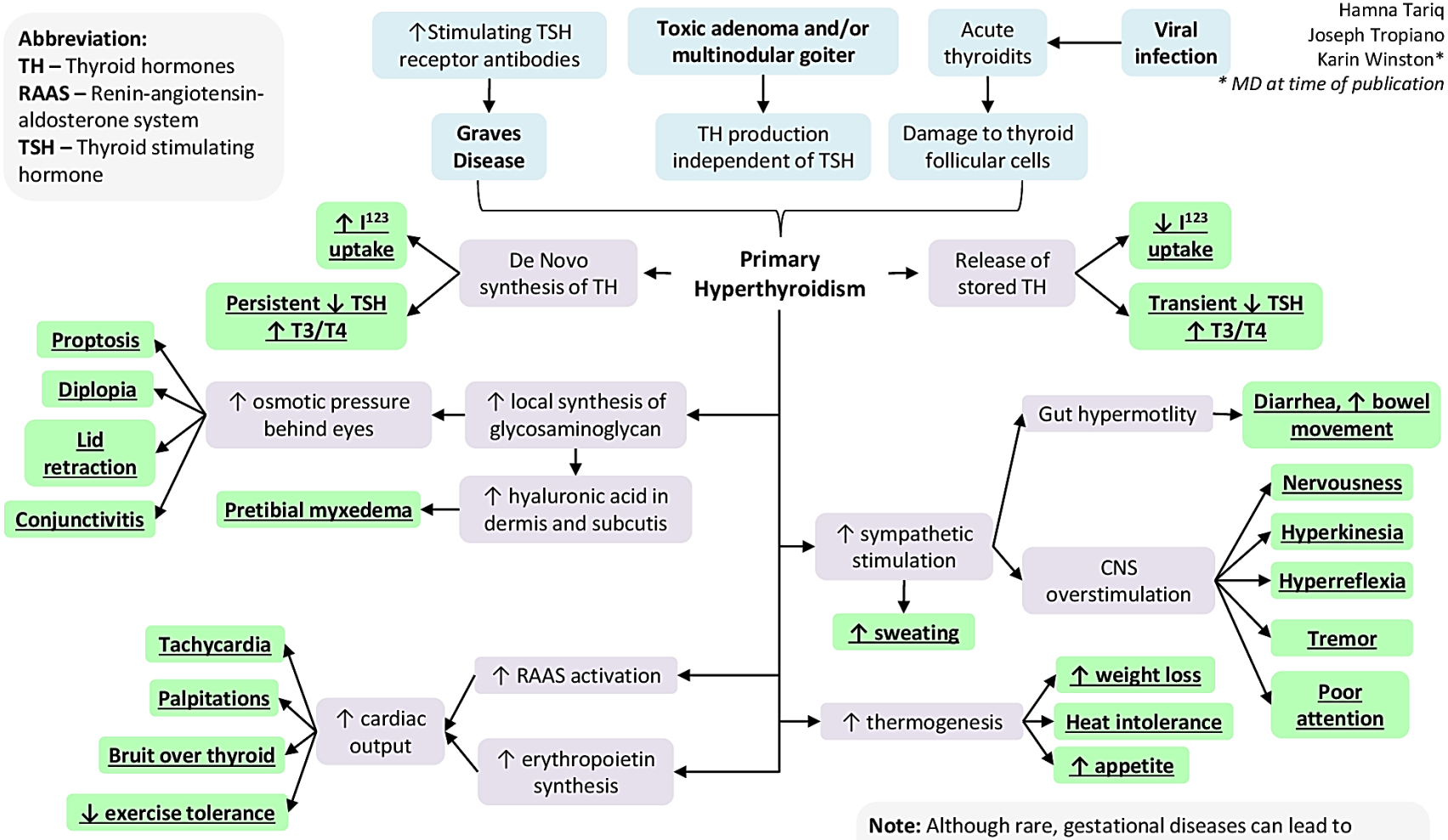


FIGURE 22.10 Mechanisms of Primary and Central (Secondary) Hypothyroidism. ***TH,*** **Thyroid hormone;** ***TRH,*** **thyroid-releasing hormone;** ***TSH,*** **thyroid-stimulating hormone.**

Primary Hyperthyroidism: *Pathogenesis and clinical findings*

Authors:
David Deng
Reviewers:
Amyna Fidai
Hamna Tariq
Joseph Tropiano
Karin Winston*
** MD at time of publication*

Abbreviation:
TH – Thyroid hormones
RAAS – Renin-angiotensin-aldosterone system
TSH – Thyroid stimulating hormone



Note: Although rare, gestational diseases can lead to thyrotoxicosis due to excess secretion of hCG, which is structurally similar to TSH. Secondary hyperthyroidism due to excess TSH production by the pituitary can also occur.

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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First Steps in Metabolic Therapy for Inborn Error of Metabolism

- Reduce precursor substrate load
- Provide caloric support
- Provide fluid support
- Remove metabolites via dialysis
- Divert metabolites
- Supplement with cofactor(s)

Metabolic Disorders

- Approaches to Treatment
  - Acute therapy
    - Correction of acid-base balance and hydration of immediate importance
    - Maintenance of adequate kcal to prevent tissue catabolism
    - Offending metabolites restricted

Metabolic Disorders

- Approaches to Treatment
  - Chronic Therapy
    - Restriction of precursors
    - Replacement of end products
    - Providing alternate substrates for metabolism
    - Use of scavenger drugs to remove toxic by-products
    - Supplementation of vitamins or other cofactors

MANAGEMENT OF IEM

Genetic:

- Establish diagno
- Carrier testing.
- Pedigree analysis, risk counseling.
- Consideration of Prenatal diagnosis for pregnancies at risk.

MANAGEMENT OF IEM

PSYCHOSOCIAL , EDUCATIONAL , FAMILIAL

- **Family counseling and support.**
- **Education to promote increased compliance with special form of therapy such as Protein – restricted diet.**
- **Assessment of community resources and support groups.**

Therapeutic Measures for IEM

- D/C oral intake temporarily
- Usually IVF's with glucose to give 12-15 mg/kg/min glucose and at least 60 kcal/kg to prevent catabolism (may worsen pyruvate dehydrogenase deficiency)
- Bicarb/citrate, Carnitine/glycine
- Na Benzoate/arginine/citrulline
- Dialysis--not exchange transfusion
- Vitamins--often given in cocktails after labs drawn before dx is known
  - Biotin, B6, B12, riboflavin, thiamine, folate

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