Metabolic syndrome

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ภาควิชาสรีรวิทยา

Objectives

- Describe endocrine, nutritional, and metabolic disease
- Describe metabolic and regulatory disorders
- Apply knowledge of preclinical sciences for diagnosis and management of obesity and metabolic syndrome

สำหรับตอบคำถาม/ซักถามในคาบเรียน

https://forms.gle/5GGfeL5rfJBdgj9L8

กิจกรรมในคาบเรียน

Mentimeter

https://www.menti.com/

Pretest

Which of the following factors increases the risk of Metabolic Syndrome?

- Choose 1 if the factor increases the risk
- Choose 2 if the factor does not increase the risk

Q1. Abdominal Obesity

Q2. Negative energy balance

Q3. Insulin Resistance

Q4. Sedentary lifestyle

Q5. Steroid drug use

Which of the following condition(s) fall(s) in the criteria of metabolic syndrome?

- Choose 1 if the factor falls in the criteria
- Choose 2 if the factor does not fall in the criteria

Q6. BMI 30.0 kg/m^2

Q7. BP 130/70 mmHg

Q8. Male waist circumference 81 cm

Q9. HDL-C 48 mg/dL in female

Q10. Diabetic patient with FPG 90 mg/dL

Case Study 1

Present history:

A 50-year-old male accountant presented with on and off fatigability and increased frequency of urination with increased thirst for 6 months.

Personal history:

- He prefers fried food and traditional Thai curry. He loves sweets especially fried banana or desserts with coconut milk. He also prefers fruits like jackfruit, rambutan, longan, durian, grape, chiko, dragon fruit, star fruit, and custard apple.
- His exercise of choice is playing pool once a week.
- Other physical activities are just going back and forth from his home to his workplace.
- He drinks 1-2 cans of beer 3-4 days a week, a carton of fruit juice or a bottle of green tea every day.

Personal history:

- He has been smoking a pack of cigarette per day since he was 18 years old.
- He recognized that he almost had an accident once because he dozed off while motorcycling on the way back home.
- His wife complains that he snores so loud lately.
- His mother has DM and HT for more than 10 years and has been on peritoneal dialysis for 3 years. His father passed away suddenly from an unknown cause at the age of 54.

Physical examination:

Height 170 cm, weight 100 kg, waist circumference 100 cm, hip 97 cm, BP 160/110 mmHg

Fundoscopic examination (Eyeground)

The patient's fundoscopic Finding

Normal fundoscopic examination

Other physical findings were within normal limits.

Laboratory investigation:

RPG* 280 mg/dL, total cholesterol 186 mg/dL, TG 300 mg/dL, calculated LDL-C 91 mg/dL, HDL-C 35 mg/dL**

***RPG = Random plasma glucose , ** TG = Triglyceride**

1. List and group the problems in this patient.

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2. What is (are) your provisional diagnosis (es)?

2. What is (are) your provisional diagnosis(es)?

- **Metabolic syndrome (≥ 3 of 5 criteria are met)**
  - ❑ **Waist circumference ≥ 90 cm**
  - ❑ **FBS ≥ 100 mg/dL**
  - ❑ **HDL-C < 40 mg/dL**
  - ❑ **BP ≥ 130/85 mmHg**
  - ❑ **TG ≥ 150 mg/dL**

3. Describe pathophysiologic mechanisms for his conditions.

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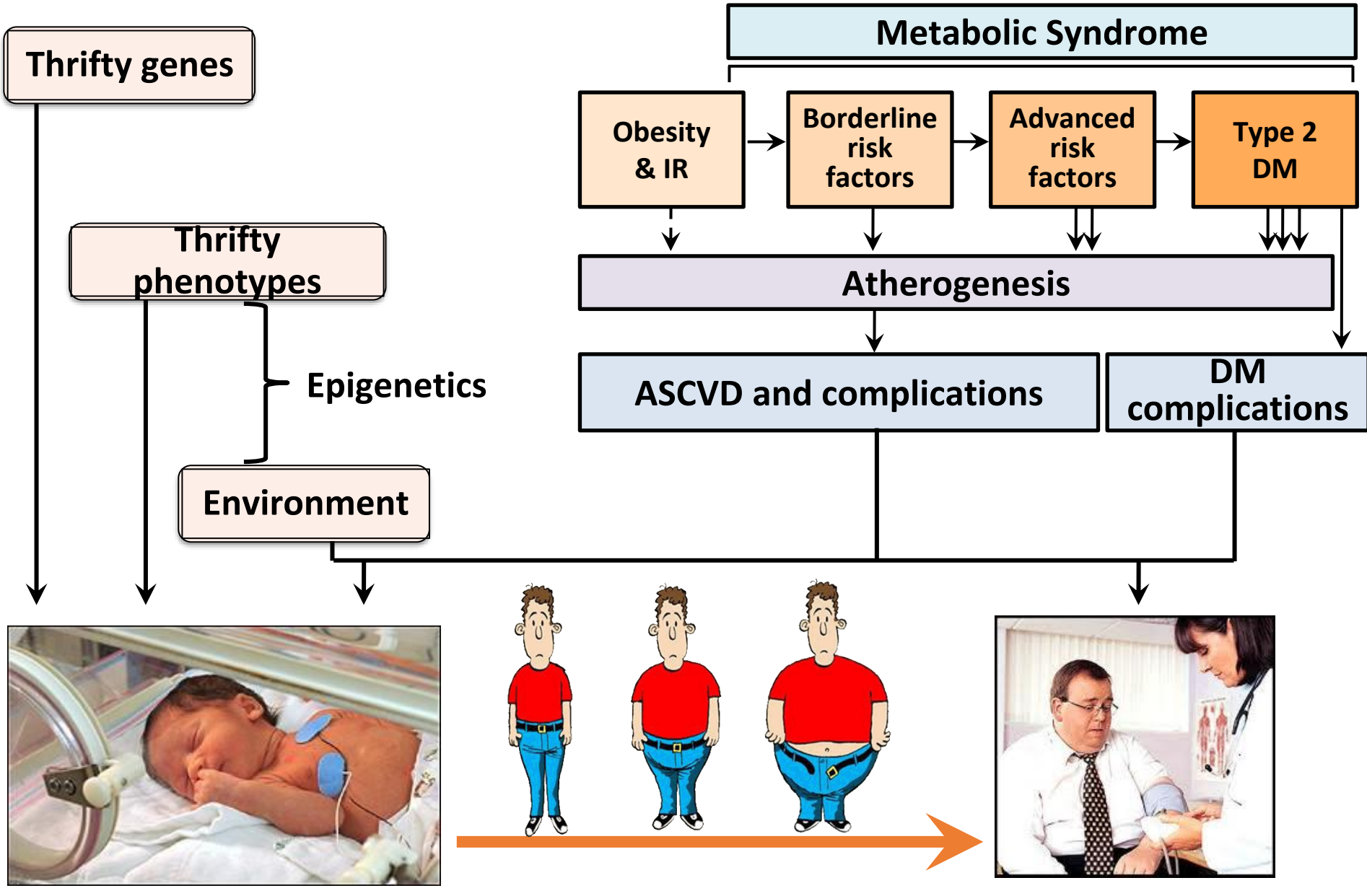
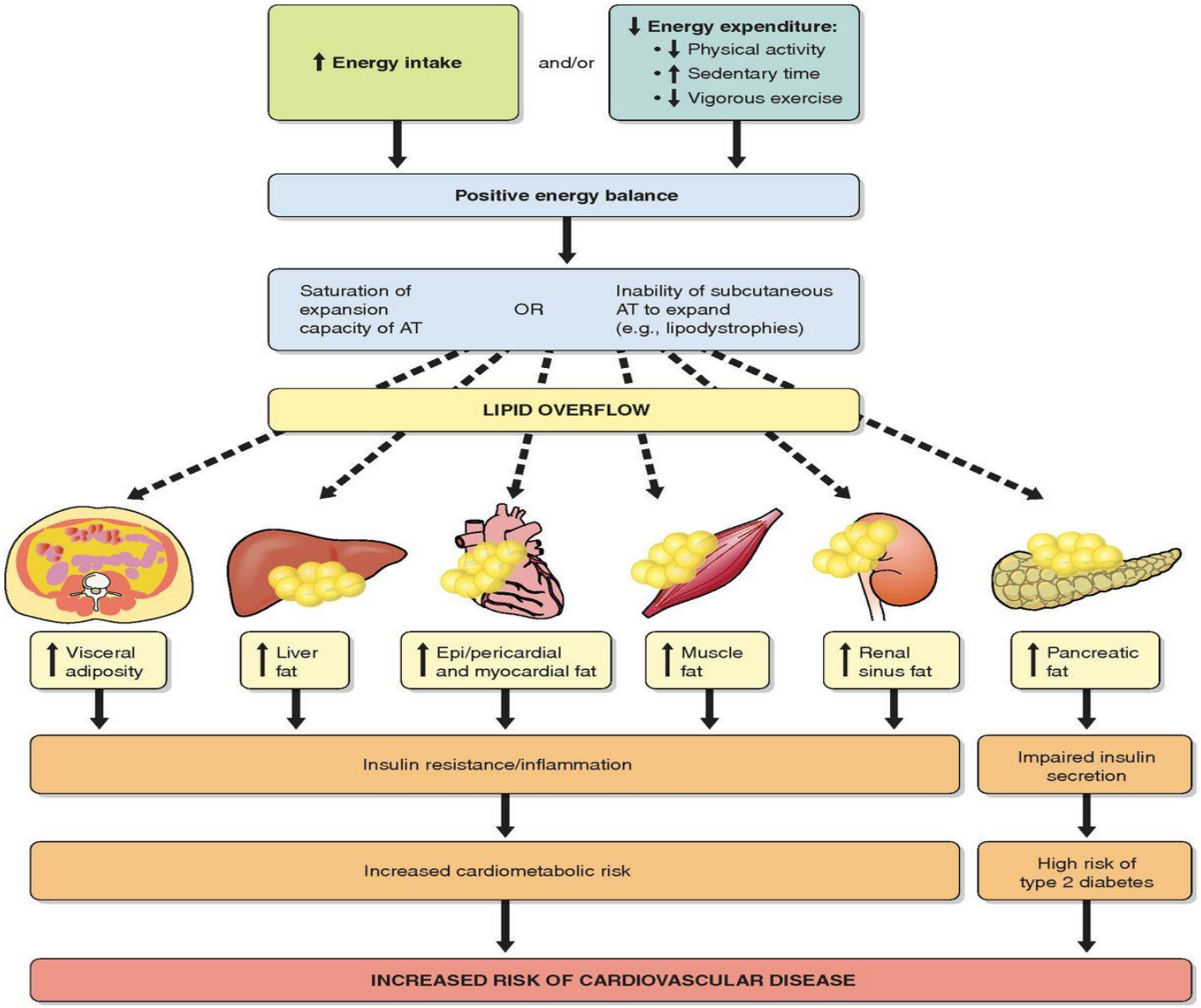
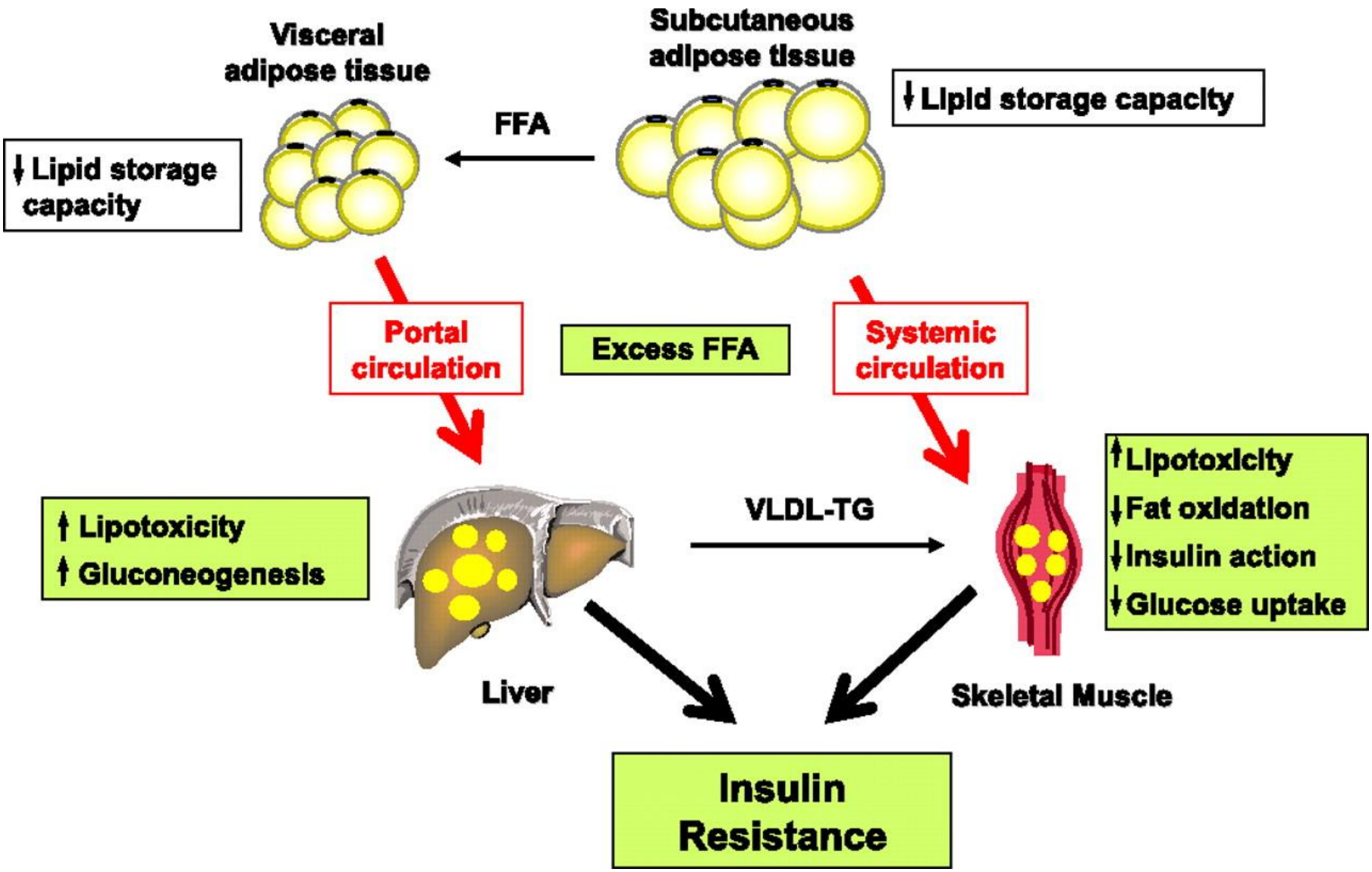


Pathophysiology of Human Visceral Obesity



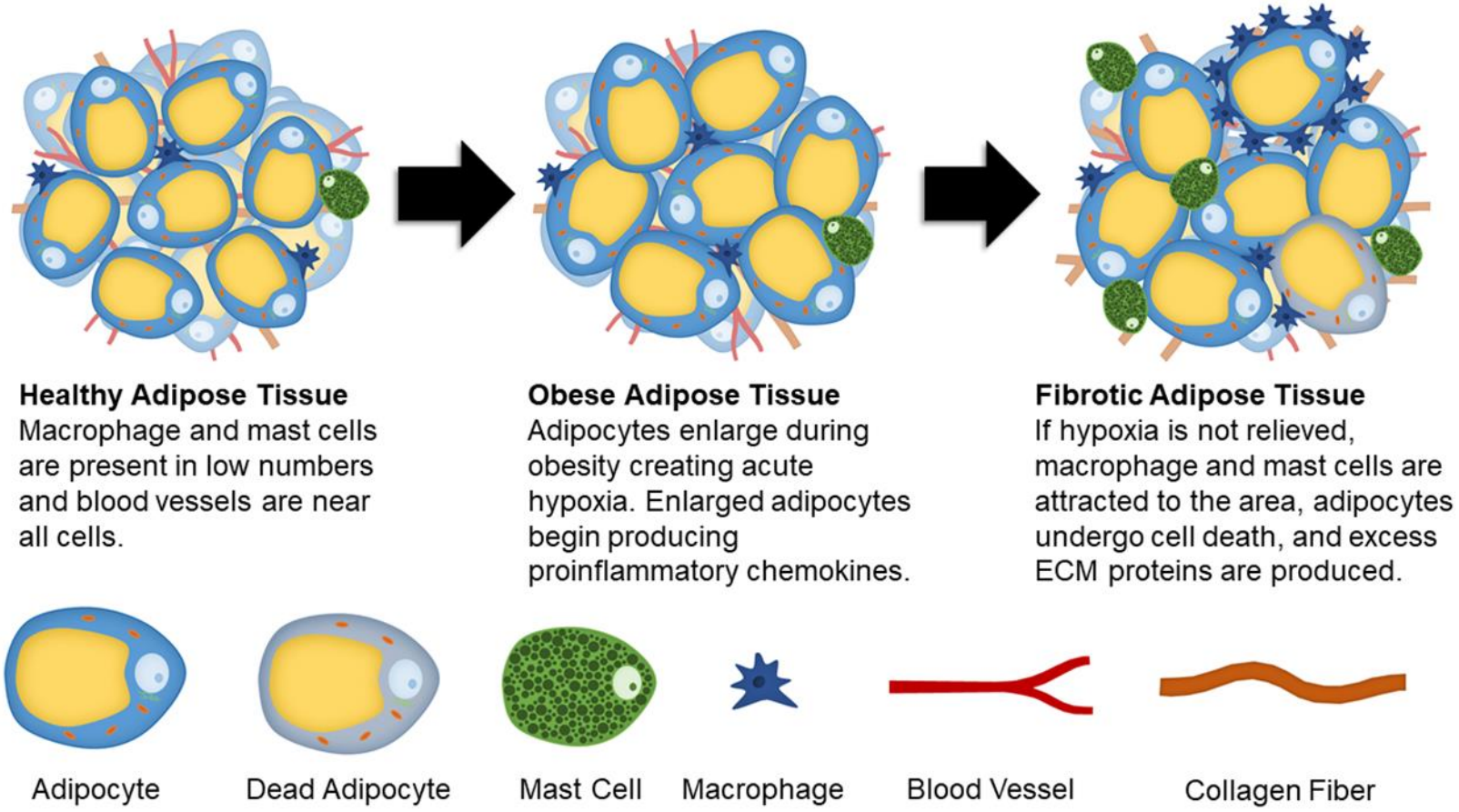
André Tchernof, et al. Physiological Reviews, 1 January 2013 Vol. 93

Adipose tissue



Galgani J. E. et al, 2008

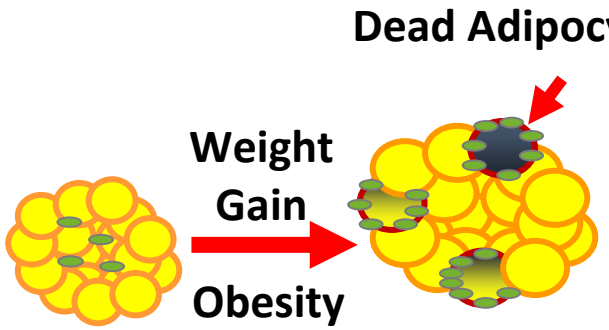
Obesity: Chronic inflammatory state



Proinflammatory chemokines: tumor necrosis factor-alpha (TNFα), inducible nitric oxide synthase (iNOS), interleukin 6 (IL-6), interleukin 8 (IL-8), hs C-reactive protein, transforming growth factor beta 1 (TGFβ1), soluble intercellular adhesion molecule (ICAM), and monocyte chemoattractant protein 1 (MCP-1)

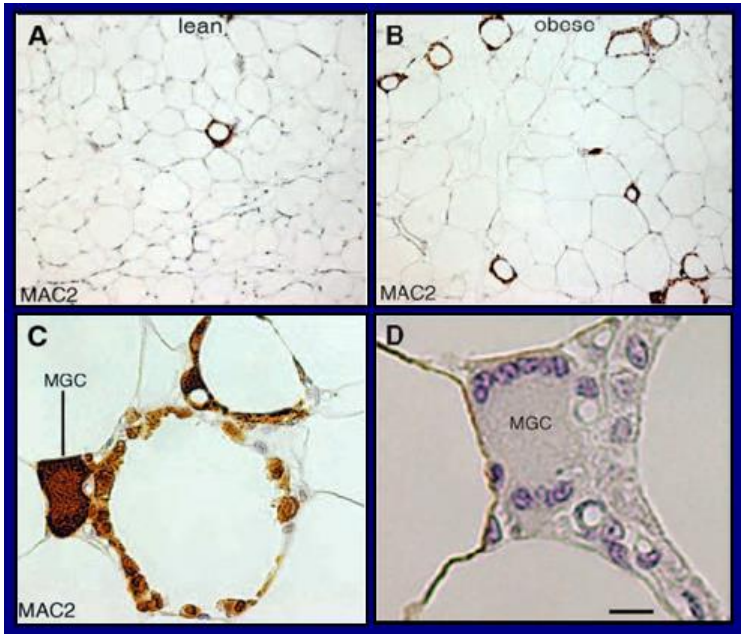
DeBari, M.K.; Abbott, R.D. Adipose Tissue Fibrosis: Mechanisms, Models, and Importance. *Int. J. Mol. Sci.* **2020**, *21*, 6030. https://doi.org/10.3390/ijms21176030

Macrophages Invade Visceral Adipose Tissue When Adipocytes Die



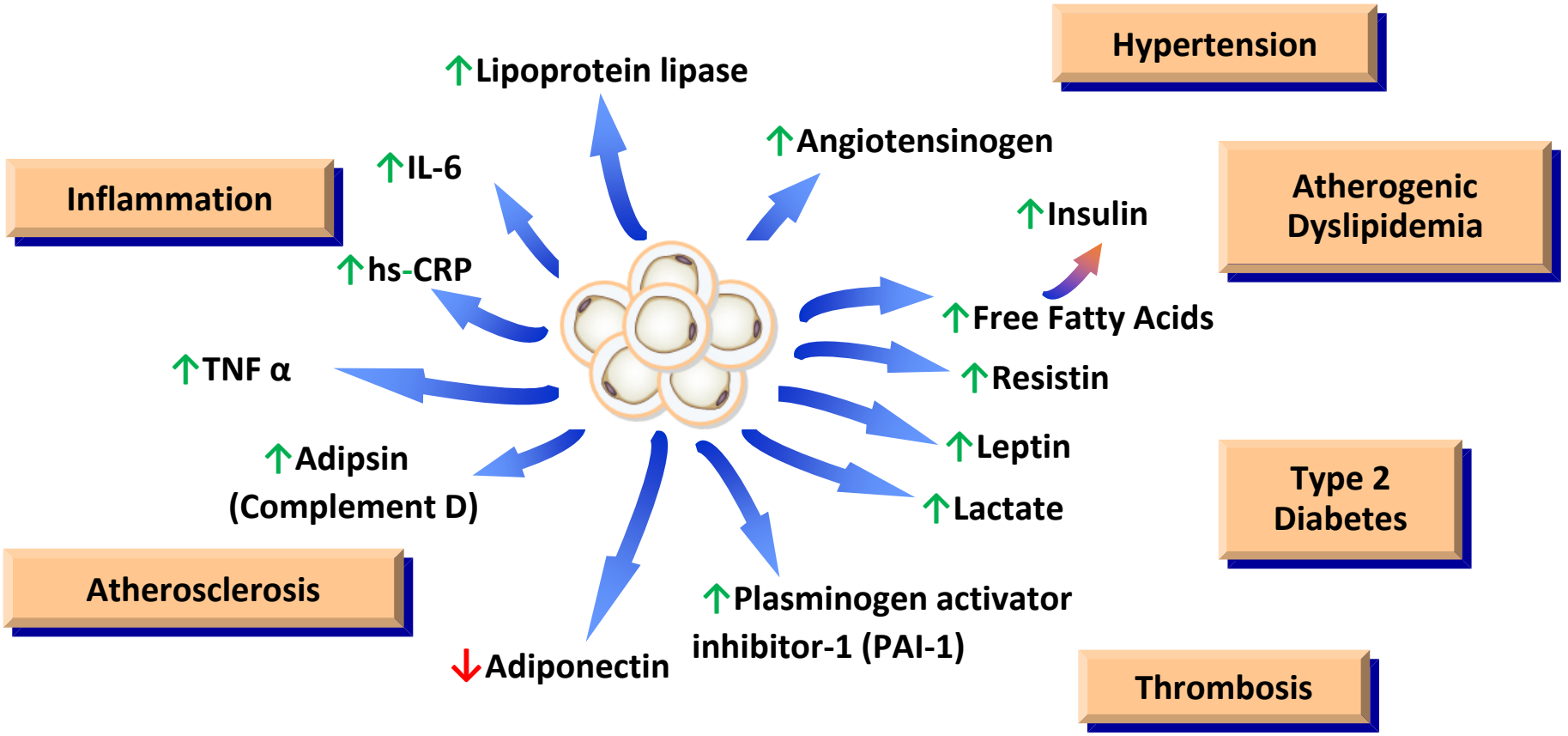
Lean Adipose Tissue (5% -10% of cells are macrophages)

Obese Adipose Tissue (Up to 50% of cells are macrophages)



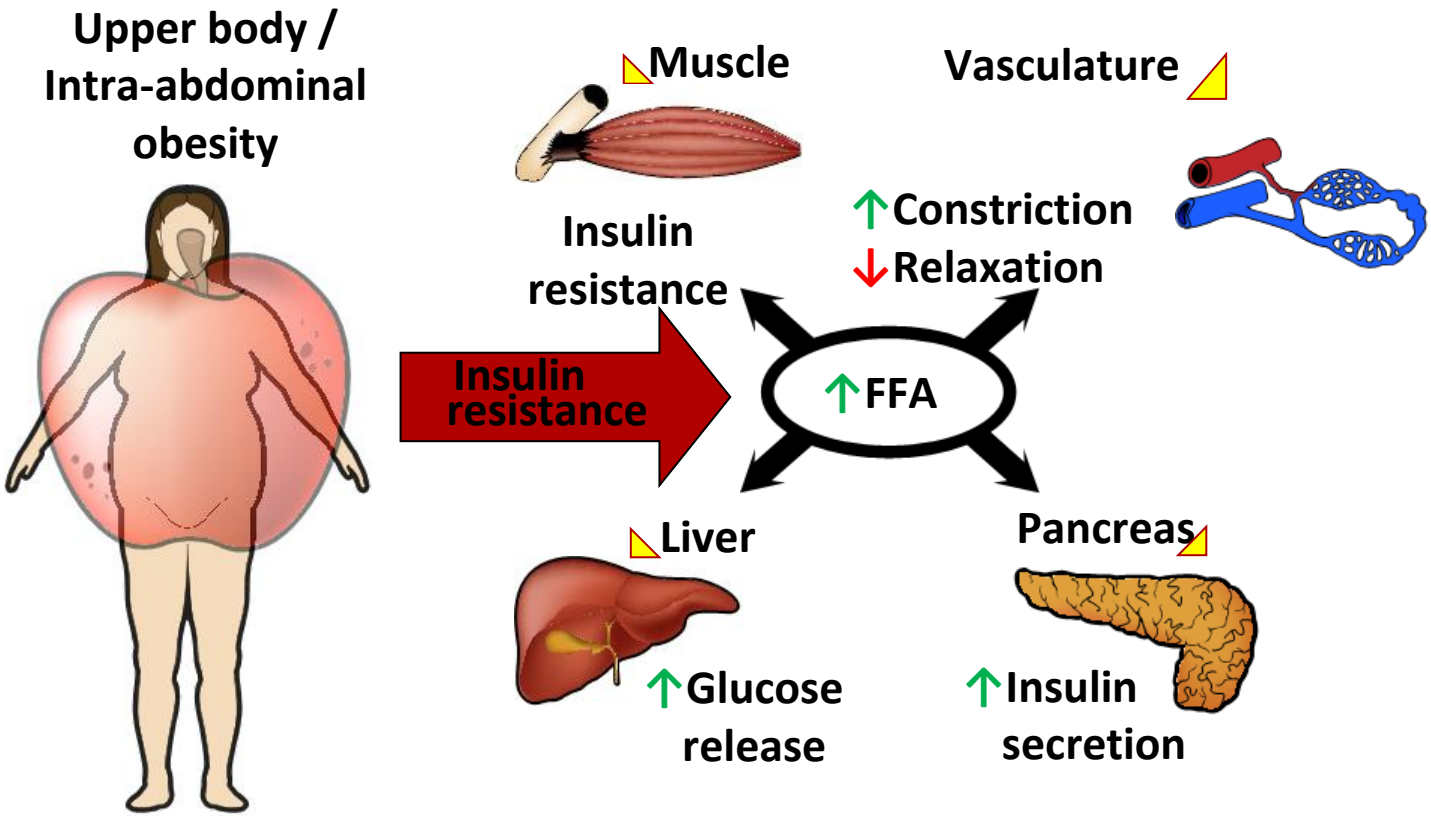
Cinti S, et al. *J Lipid Res.* 2005;46:2347–2355.

Function of Adipose Tissue in Health and Disease



Trayhurn P, Wood IS. *Br J Nutr.* 2004;92:347–355. Eckel RH, et al. *Lancet.* 2005;365:1415–1428. Lyon CJ, et al. *Endocrinology.* 2003;144:2195–2200.

Upper Body / Abdominal (Visceral) Obesity and Insulin Resistance



Why is Obstructive Sleep Apnea (OSA) so common in obesity and the metabolic syndrome?

- **Enlargement of soft tissue within/surrounding airway → pharyngeal airway narrowing**
- **Reduction of lung volume decrease longitudinal tracheal traction forces and pharyngeal wall tension → narrowing of the airway**
- **Obesity-related leptin resistance may impair neuroanatomical interactions necessary for stable breathing**

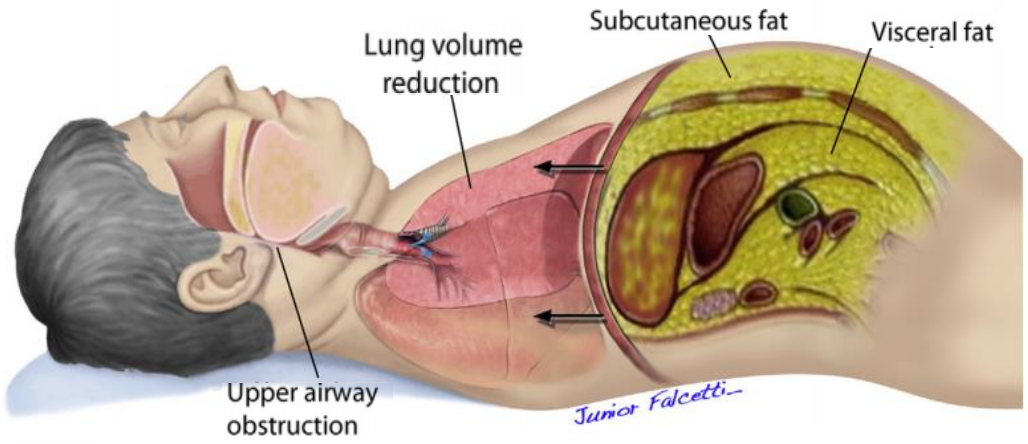


Figure 1 Obesity Predisposes to Obstructive Sleep Apnea

Obstructive Sleep ApneaA Cardiometabolic Risk in Obesity and the Metabolic Syndrome. J Am Coll Cardiol. 2013;62(7):569-576.

Further laboratory investigation

- AST 60 U/L (reference range <40)
- ALT 120 U/L (reference range <41)
- Creatinine 1.12 mg/dL (reference range 0.67-1.17)
- Urinalysis - sp.gr. 1.020 with protein 1+ glucose 2+

4. From additional information, which condition should be considered in this patient?

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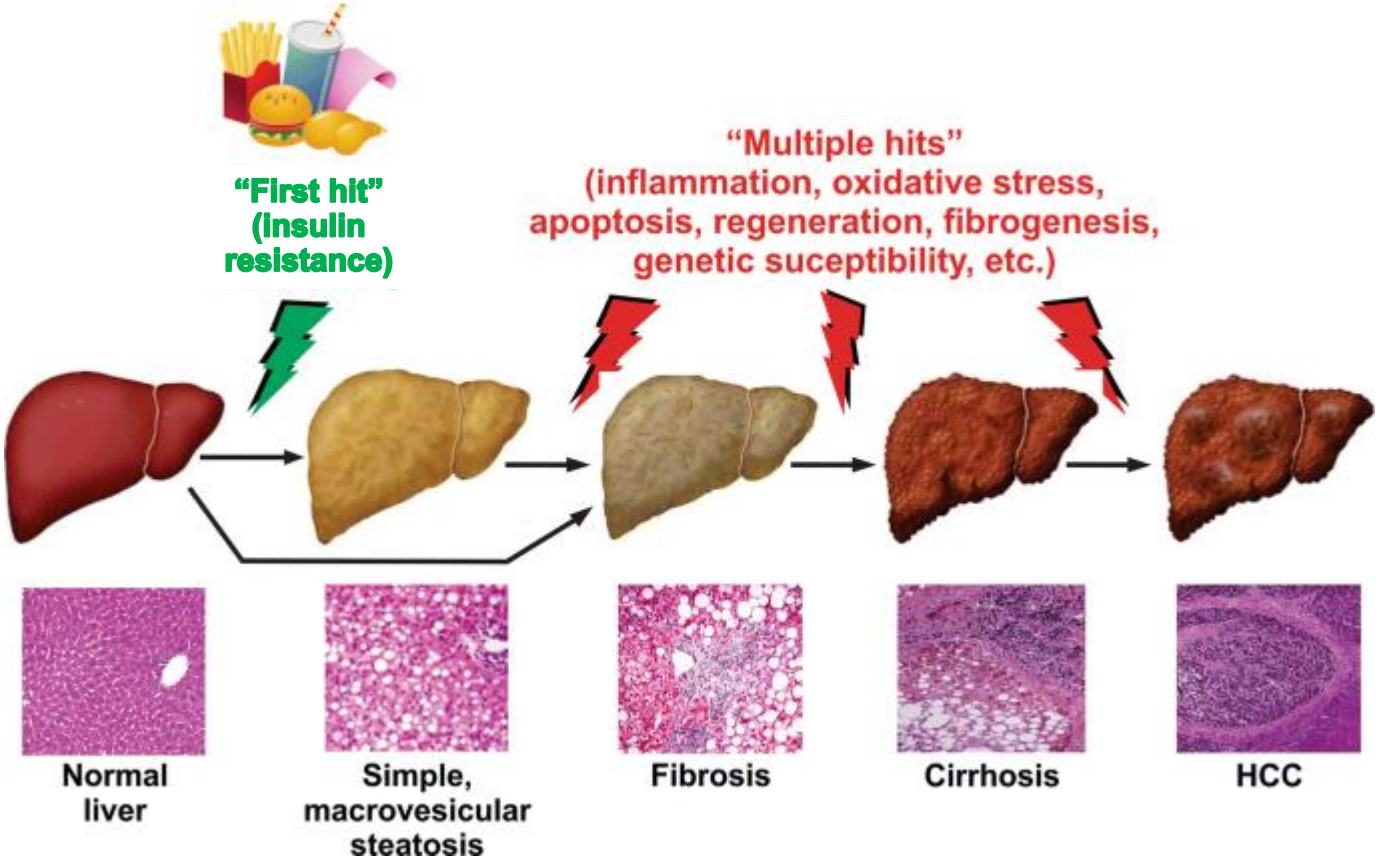
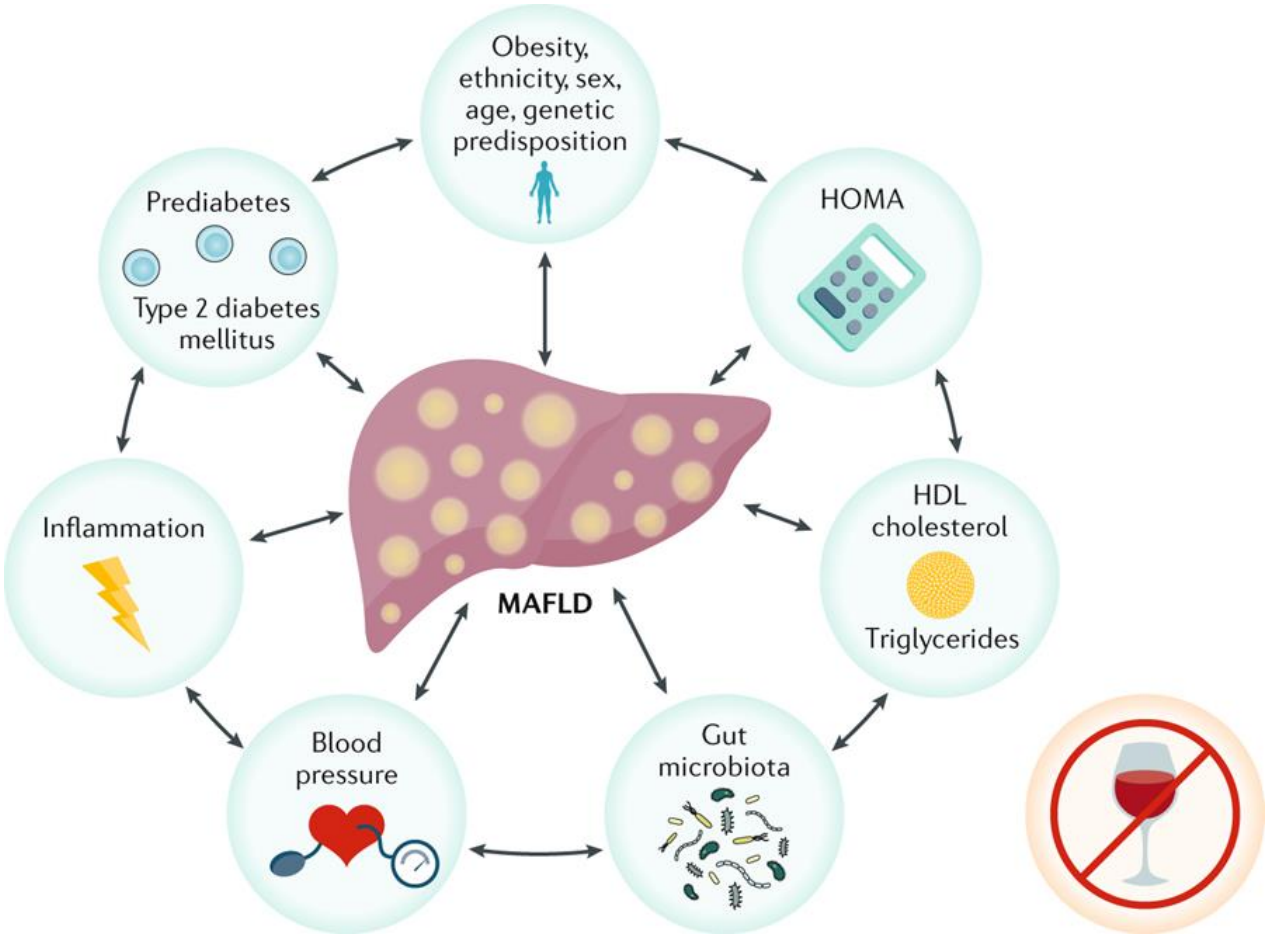
- Nonalcoholic fatty liver disease (NAFLD): fatty infiltration in liver
- New proposed nomenclature: MAFLD – Metabolic Associated Fatty Liver Disease



Bessone F, et al. Cell. Mol. Life Sci. 76, 99–128 (2019). https://doi.org/10.1007/s00018-018-2947-0

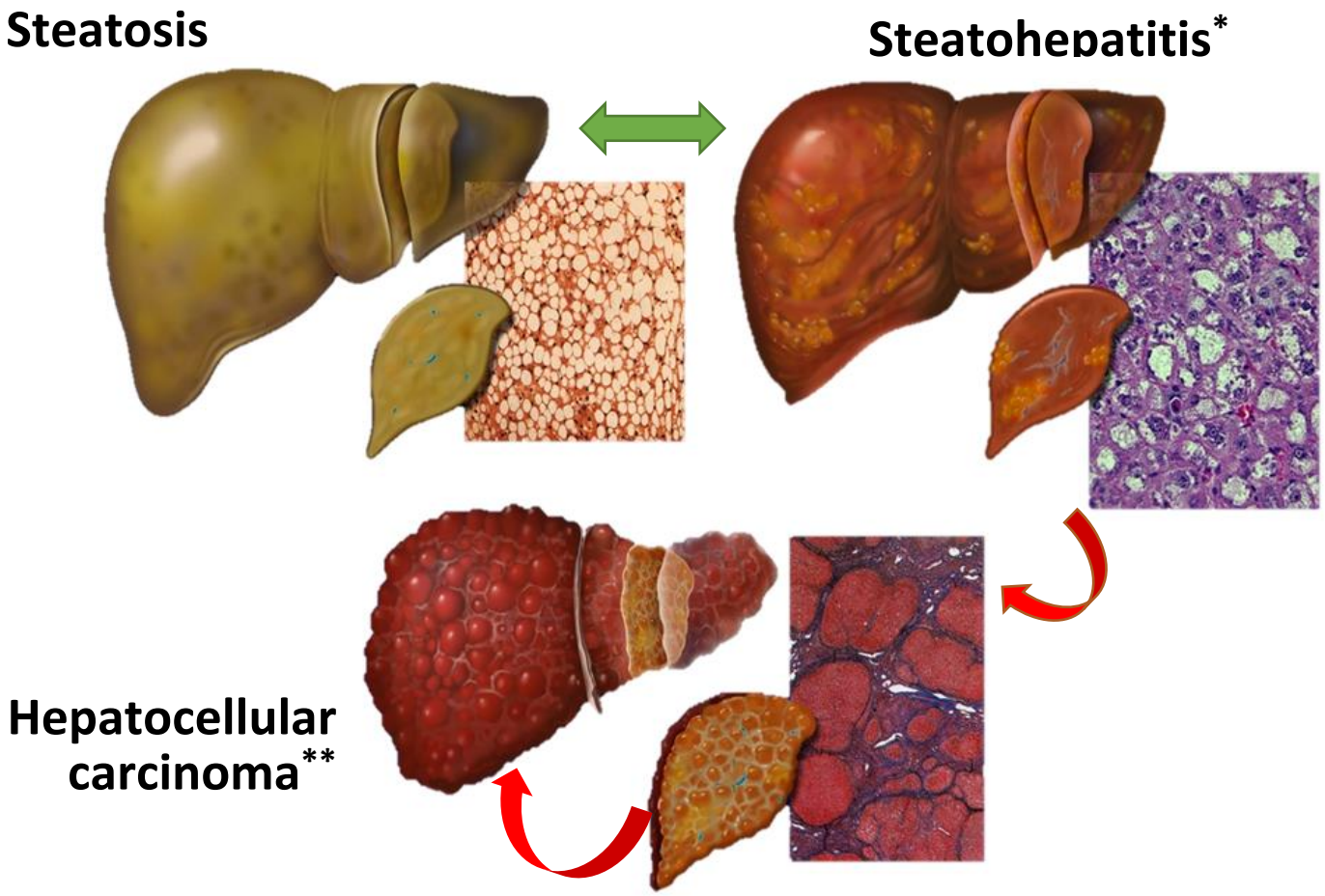
NAFLD/MAFLD



Heterogeneous factors lead to MAFLD, including ethnicity, sex, dietary habits, genetic predisposition, age, gut microbiota and metabolic status.

Tilg H, Effenberger M. Nature Reviews | Gastroenterology & Hepatology 2020;17:387

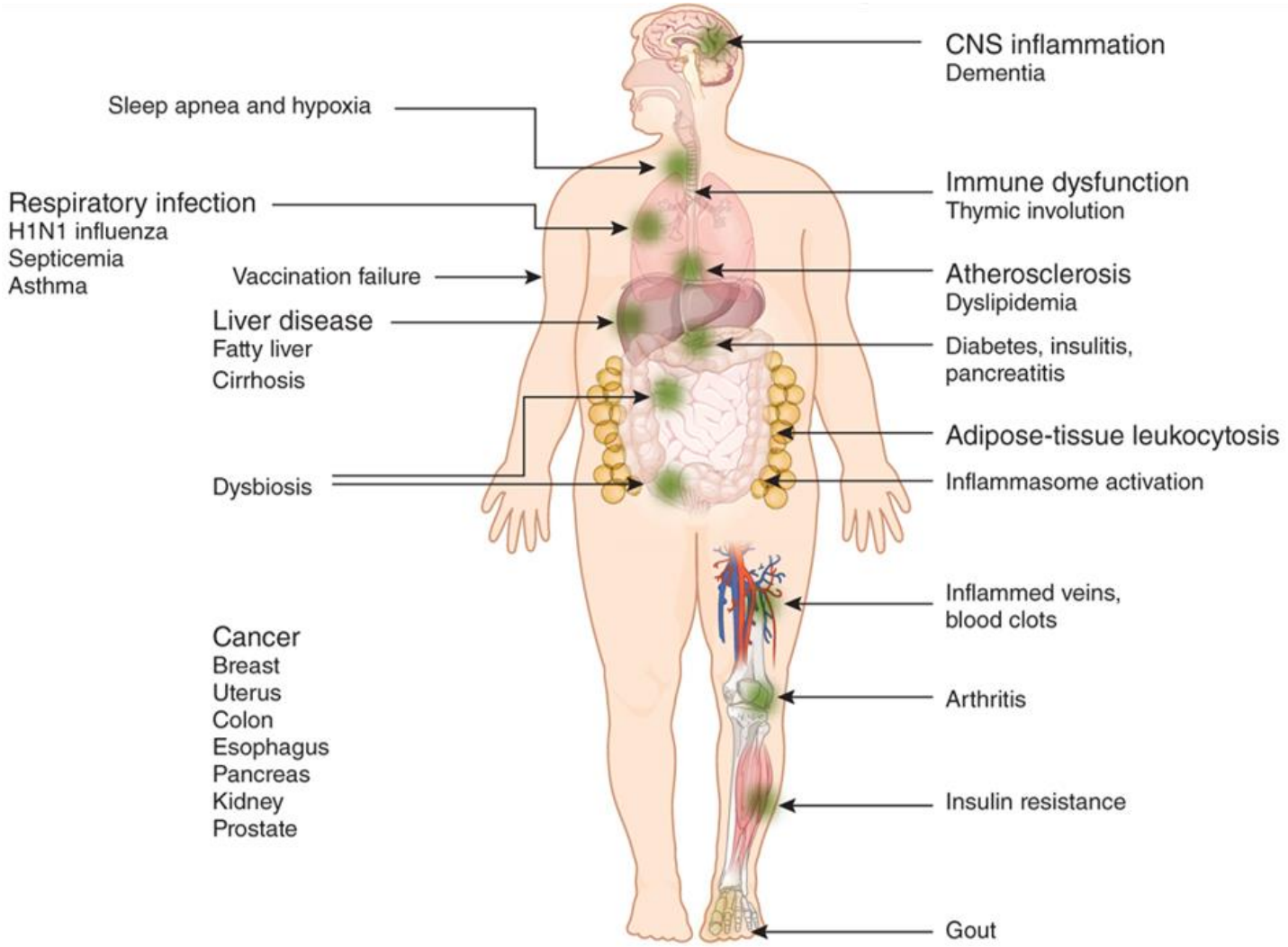
NAFLD/MAFLD: Chronic Inflammatory State



*NASH: Non-alcoholic steatohepatitis

**HCC: Hepatocellular carcinoma

Complications of obesity



Immunological complications of obesity. Nature Immunology 13, 707–712(2012)

Case Study 2

Present history:

- A 50-year-old Thai male patient came to your clinic with a chief complaint of an unhealed wound which has lasted for 1 month.
- 1 month ago, he stepped on a thorny stick while working in his rice field. It caused him a small puncture wound on his sole of which he felt no pain. He washed the wound with water and soap after arriving home.
- Despite the wound, he could walk well with some numbness at both feet.
- One week later, his wife noticed that the wound had increased in size with swelling and some yellowish discharge. She brought him to the nearby health-promoting hospital where he has been receiving wound dressing every other day without any improvement.

- His urination seemed to be more frequent for the 1-2 months.
- He has gained 2 kg. of weight during the last 6 months.
- He has earned his living by growing rice since he was young. He had been in good health except for some tiredness with knee and back pain from his work.
- Six months ago, his neighbor told him about an herbal drug that could help for knee and back pain. He tried it and felt a lot better. Not only relieving of pain, he also had increased appetite and general well-being. Therefore, he took it regularly ½ - 1 glass everyday.

Physical examination:

BT 37° Celsius, Heart Rate 80/min, BP150/80 mmHg, Respiratory Rate 14 /min
BW 90 kg, Height 170 cm, Waist circumference 100 cm
General appearance: as shown

Before **After**

Face

Abdomen

Wound at left foot

Cardiovascular system: normal S1 & S2, no murmurs
Respiratory system: normal breath sound, no adventitious sound
Nervous system: motor power grade IV+/V both deltoids and quadriceps, others grade V/V

Laboratory investigations:

• FPG	160 mg/dL	(74-99)
• Total cholesterol	220 mg/dL	(<200)
• Triglyceride	160 mg/dL	(<150)
• HDL-C	25 mg/dL	(>40)
• BUN	52 mg/dL	(6-20)
• Creatinine	2.4 mg/dL	(0.67-1.17)

1. What is the most likely diagnosis in this patient?

1. What is the most likely diagnosis in this patient?

2. Which condition should be considered in this patient?

2. Which condition should be considered in this patient?

Metabolic syndrome

≥ 3 of 5 criteria are met

- ❑ **Waist circumference ≥ 90 cm**
- ❑ **BP ≥ 130/85 mmHg**
- ❑ **FBS ≥ 100 mg/dL**
- ❑ **TG ≥ 150 mg/dL**
- ❑ **HDL-C < 40 mg/dL**

Obesity (BMI ≥ 25 kg/m^2 for Asians)

Abdominal obesity (waist circumference ≥90 cm in men)

ยากษัยเส้นปู่แดง

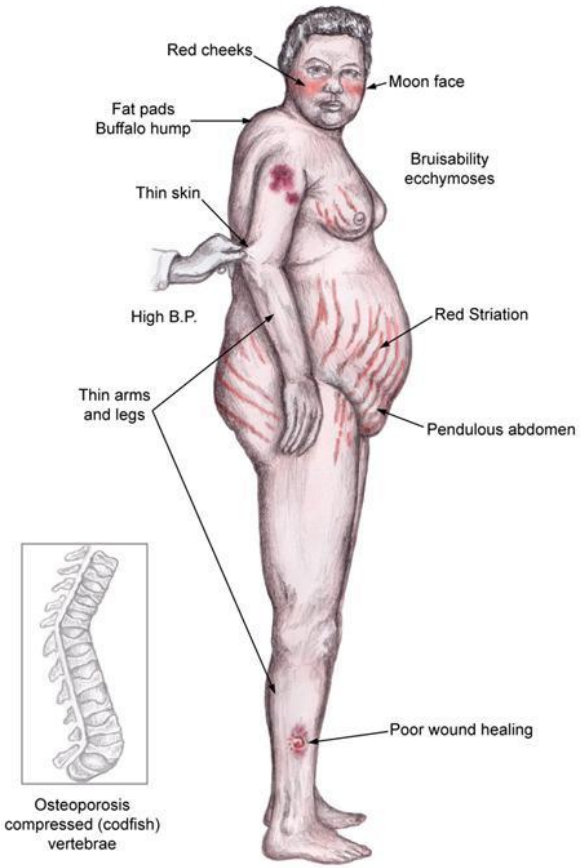
โดยมีการแพร่ระบาดของผลิตภัณฑ์ดังกล่าว ที่ตรวจสอบพบสารสเตียรอยด์ในหลายพื้นที่ ซึ่ง สสจ.เชียงใหม่และ สสจ.เลยได้แจ้งเตือนให้ผู้บริโภคทราบถึงอันตรายของผลิตภัณฑ์ดังกล่าวแล้ว และประสานไปยัง อย. ก่อนจะพบว่ามีการลักลอบผลิตตามบ้านและโกดังในพื้นที่จังหวัดขอนแก่น และขายผ่านแพลตฟอร์มออนไลน์ส่งทั้งในไทยและประเทศเพื่อนบ้านเป็นจำนวนมาก

จึงได้นำหมายค้นศาลจังหวัดพลเข้าตรวจค้นสถานที่ผลิตและเก็บอาหารและผลิตภัณฑ์สมุนไพรผิดกฎหมายในพื้นที่จังหวัดขอนแก่น จำนวน 4 จุด พบของกลางนำสมุนไพร กว่า 20,000 ขวด, ยาเม็ดในกลุ่ม สเตียรอยด์ จำนวนกว่า 2,092,000 เม็ด, ยาเม็ดแก้ปวดไม่มีทะเบียน จำนวนกว่า 2,224,000 เม็ด ยาเม็ดแก้แพ้ จำนวนกว่า 5,000 เม็ด รวมมูลค่ากว่า 10 ล้านบาท พร้อมตรวจยึดอุปกรณ์การผลิตจำนวนมาก

ขณะที่เพจกรมสอบสวนกลาง ระบุว่า จากการตรวจสอบนำสมุนไพรดังกล่าว 1 ขวด จะผสมยาสเตียรอยด์ 70 เม็ด และยาแก้อักเสบ 30 เม็ด รวม 100 เม็ด

https://www.prachachat.net/marketing/news-894153

Cushing's Syndrome



- Moon face
- Facial plethora
- Dorsocervical & supraclavicular fat pad
- Thin skin and easy bruisability
- Wide-purplish striae
- Truncal obesity
- Delayed wound healing
- Muscle weakness
- Osteoporosis
- High blood pressure
- Hyperglycemia
- Immunocompromised state

Physiologic Effects of Glucocorticoids

Metabolism	•↓ muscle protein and increases nitrogen excretion •↑ gluconeogenesis and plasma glucose levels •↑ hepatic glycogen synthesis •↓ glucose utilization (anti-insulin action) •↓ amino acid utilization •↑ fat mobilization •Redistributes fat •Permissive effects on glucagon and catecholamine effects •Maintains vascular integrity and reactivity
Hemodynamic	•Maintains responsiveness to catecholamine pressor effects •Maintains fluid volume
Immune function	•↑ antiinflammatory cytokine production •↓ proinflammatory cytokine production •↓ inflammation by inhibiting prostaglandin and leukotriene production •↓ bradykinin and serotonin inflammatory effects •↓ circulating eosinophil, basophil, and lymphocyte counts (redistribution effect) •Impairs cell-mediated immunity •↑ neutrophil, platelet, and red blood cell counts
Central nervous system	•Modulates perception and emotion •↓ CRH and ACTH release

Case Study 3

Present history:

- **A 20-year-old medical student presented to Dermatology clinic for consultation of her acne which she had suffered since she was 15 years old.**

- **She also had irregular menses since menarche. She stated that on average, she had 1 period every 3-4 months which she thought that it might be from her stress in school. When she did have her period, she bled very heavily, passing large clots, and had a lot of abdominal cramping.**

Additional history

- She also complained about excessive facial hair, which requires her to shave at least once every several days, and a lot of hair on her abdomen and arms.

- She denied any headache, blurred vision, or discharge from her nipples. She did not take any medication and had never used hormones nor oral contraceptives for her acne.

Physical examination:

- **Height 165 cm, weight 63 kg, waist 85 cm, hip 90 cm, BP 140/85 mmHg**

- **Skin findings were as shown:**



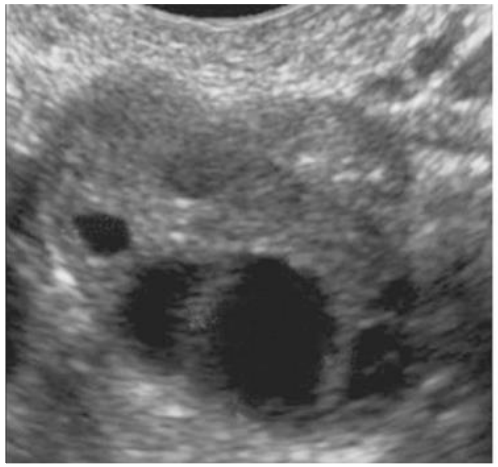

Physical examination:

Skin findings were as shown:

Laboratory investigation:

- FPG 120 mg/dL
- 2-hour PG (glucose tolerance test) 233 mg/dL,
- Fasting insulin level 36 µU/mL (reference range 2.6-24.9)
- Total cholesterol 200 mg/dL
- Triglyceride 160 mg/dL
- HDL-C 45 mg/dL

- Pelvis ultrasound



Normal ovary

The patient's ovary

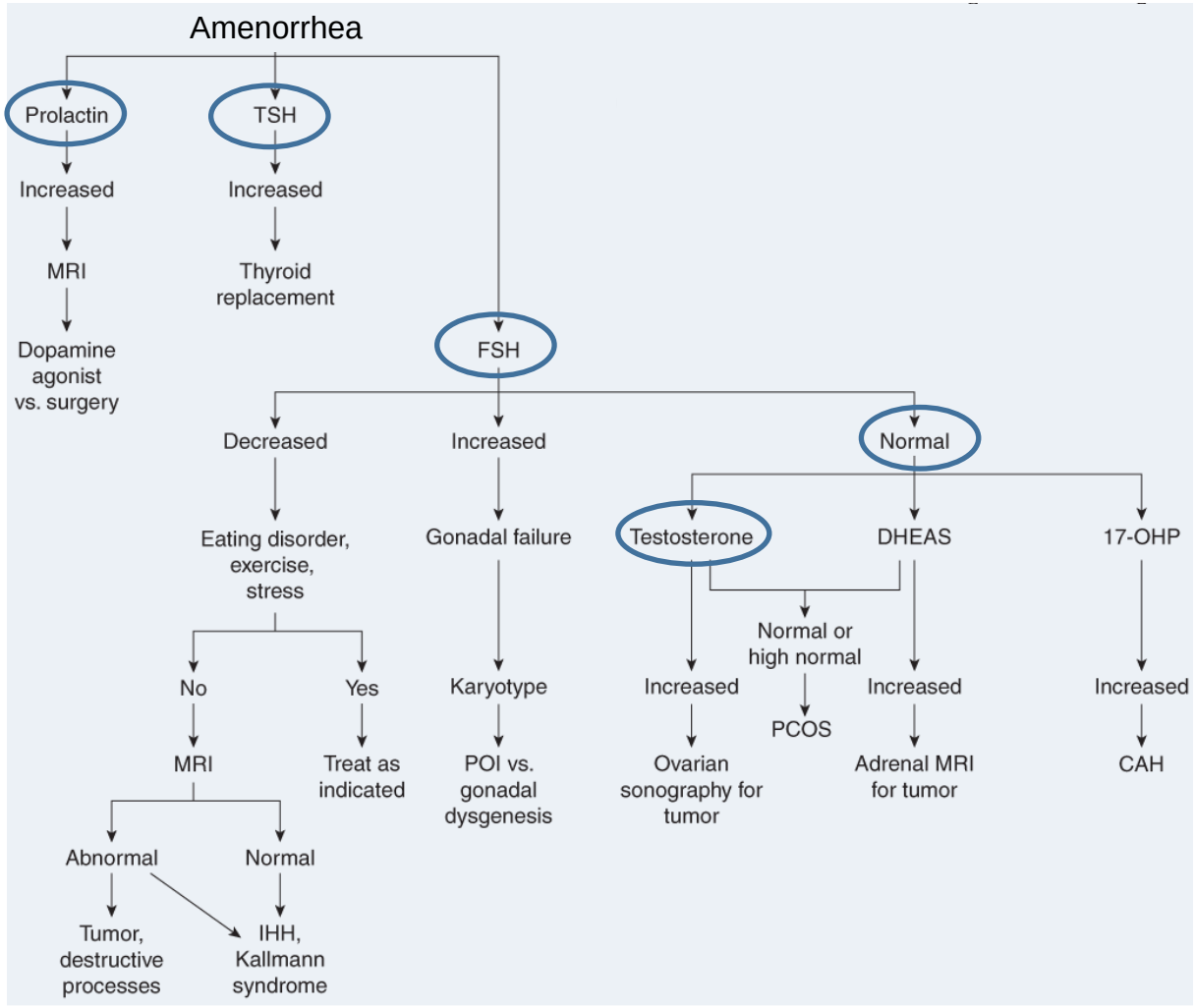
1. List and group the problems in this patient.

Problem List:

Further laboratory investigation:

- FSH 6 mIU/mL (follicular: 3.5-12.5, luteal 1.7-7.7)
- LH 20 mIU/mL (follicular: 2.4-12.6, luteal 1.0-11.4)
- LH:FSH >3
- TSH 2.4 uIU/L (reference range: 0.27-4.20 uIU/L)
- Prolactin 20 ng/mL (reference range: 4.79-23.30 ng/mL)
- Total testosterone 0.502 ng/dL (reference range for women 20-49 yr: 0.084-0.481 ng/dL)
- 17OH-progesterone 0.72 ng/mL (follicular: 0.32-0.82 ng/mL, luteal: 0.79-3.29 ng/mL)
- DHEAS at 150 ug/dL (for women 20-24 years: 148-407 ug/dL) - normal, rule-out excess sex hormone from adrenal origin

Diagnostic algorithm to evaluate amenorrhea/oligomenorrhea



2. What is the most likely diagnosis in this patient?

2. What is the most likely diagnosis in this patient?

3. Which condition(s) is/are related with the diagnosis?

3. Which condition should be considered in this patient?

Metabolic syndrome

≥ 3 of 5 criteria are met

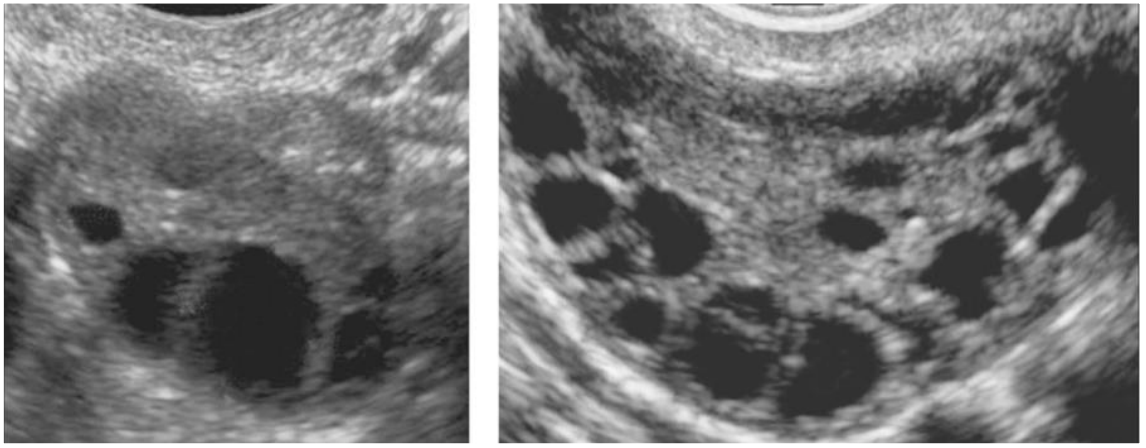
- ❑ Waist circumference ≥ 80 cm
- ❑ BP ≥ 130/85 mmHg
- ❑ FBS ≥ 100 mg/dL
- ❑ TG ≥ 150 mg/dL
- ❑ HDL-C < 50 mg/dL

Overweight (BMI ≥ 23 kg/m^2 for Asians)

Abdominal obesity (waist circumference ≥80 cm in women)

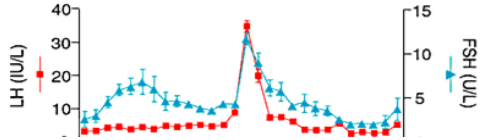
Polycystic ovary syndrome (PCOS)

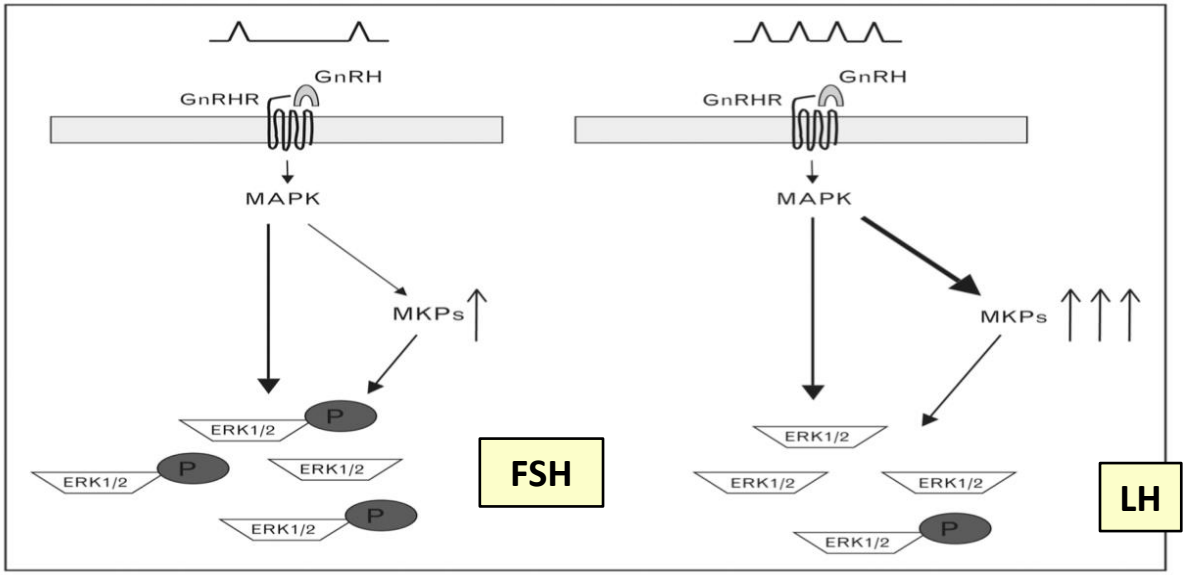
- **Widespread reproductive and endocrinologic disorder that encompasses many associated healthy conditions and has an impact on various metabolic processes.**



Normal ovary **The patient's ovary**

Polycystic ovary syndrome (PCOS)



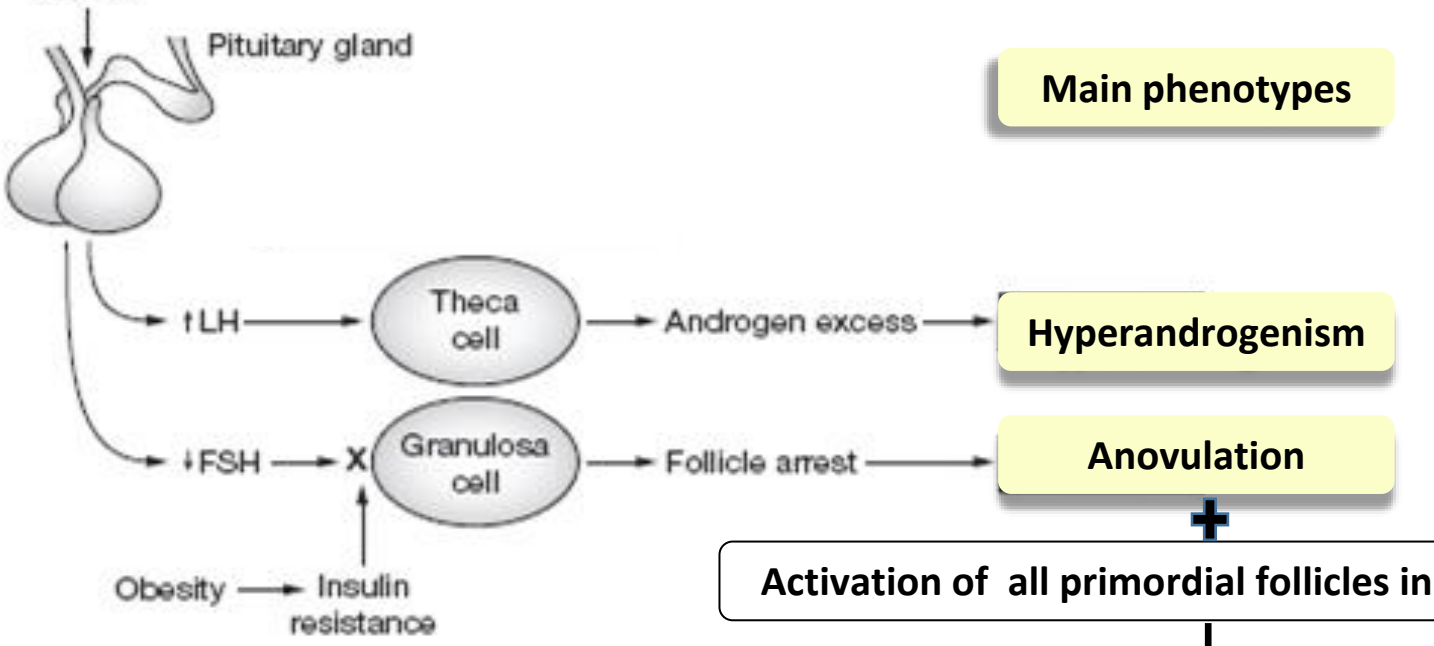


MAPK: mitogen-activated protein kinase
MKPs: MAPK phosphorytases
ERK ½: Extracellular signal regulated kinase
GnRH: Gonadotropin releasing hormone
LH: Lutenizing hormone
FSH: Follicle stimulating hormone

Nick A. Ciccone et al. 2009

Polycystic ovary syndrome (PCOS)

↑Frequency of pulsatile GnRH release



Main phenotypes

Hyperandrogenism

Anovulation

+

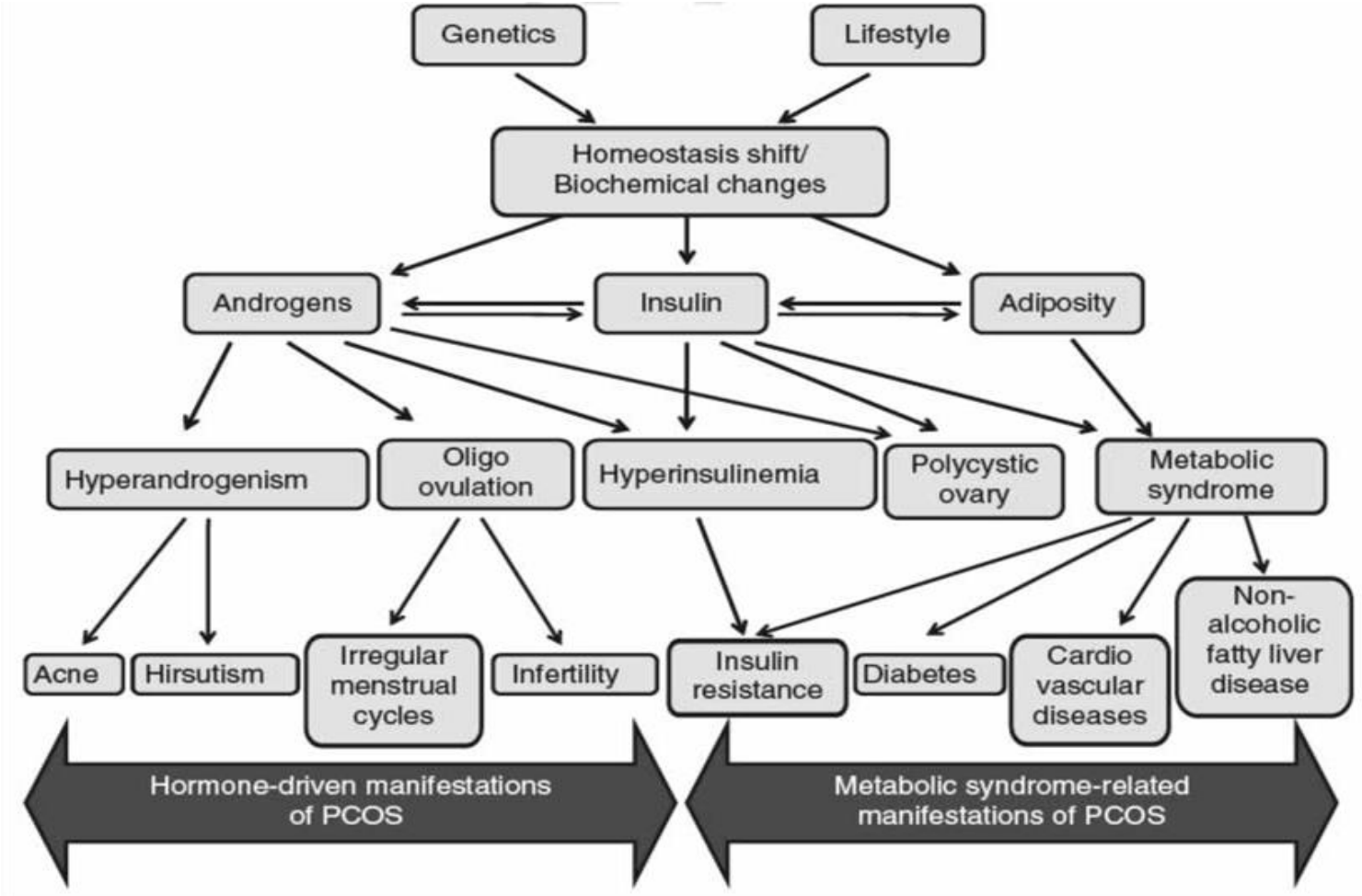
Activation of all primordial follicles in the pool

Polycystic ovaries

GnRH: Gonadotropin releasing hormone
LH: Lutenizing hormone
FSH: Follicle stimulating hormone

http://www.ansci.wisc.edu/jjp1/ansci_repro/misc/project_websites_08/wed/pcos/Causes.html

Polycystic ovary syndrome (PCOS)



http://mason.gmu.edu/~abaranov/pages/ongoing%20project%20pages/ongoing-PCOS.html

สำหรับตอบคำถาม/ซักถามในคาบเรียน

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