CHAPTER 3: Complications of Obesity

Part 1: Ectopic Fat and Type 2 Diabetes

References:

1. **Peter G. Kopelman, Ian D. Caterson, William H. Dietz - Clinical Obesity in Adults and Children 4e-Wiley-Blackwell (2022)**
2. **Sharon Akabas, Sally Ann Lederman, Barbara J. Moore - Textbook of obesity_ Biological, psychological and cultural influences-Wiley-Blackwell (2012)**

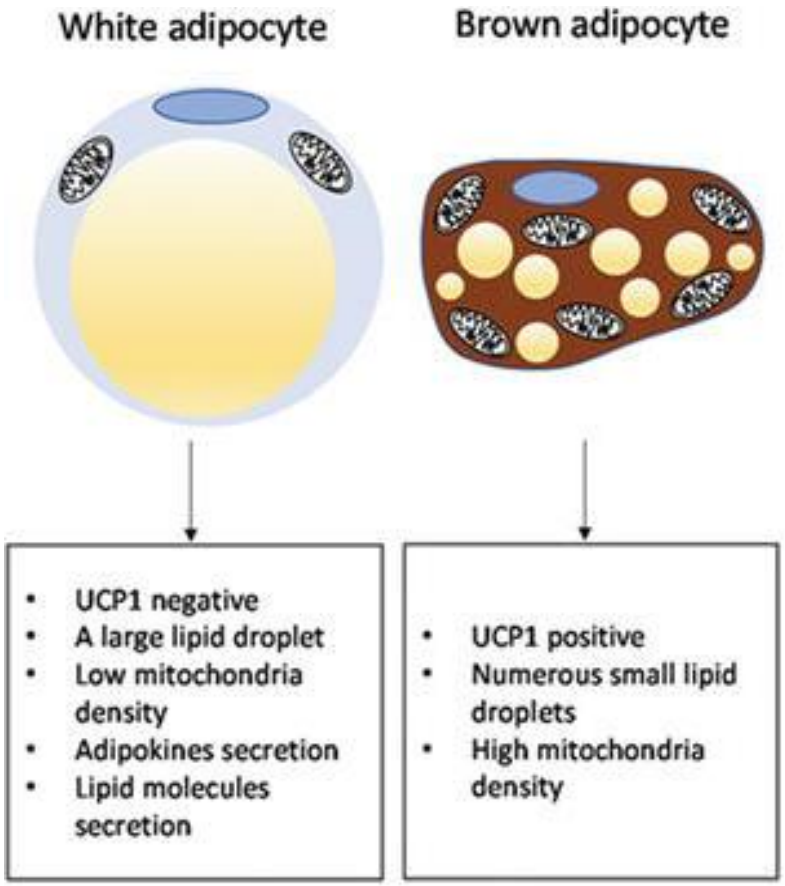
Outline

In this part, we will aim to:

1. Understand the biology of the adipose tissue
2. Understand what is ectopic fat accumulation
3. Link obesity with type 2 diabetes

What is Adipose Tissue?

- Adipose tissue is a dynamic organ that contributes to a broad range of physiological processes.
- Adipose tissue is found in mammals in two histologic forms: white adipose tissue (WAT) and brown adipose tissue (BAT).
  - WAT: Primary storage site for fat
  - BAT: Heat-producing tissue found in human fetuses and newborns (also identified in adults in specific areas)

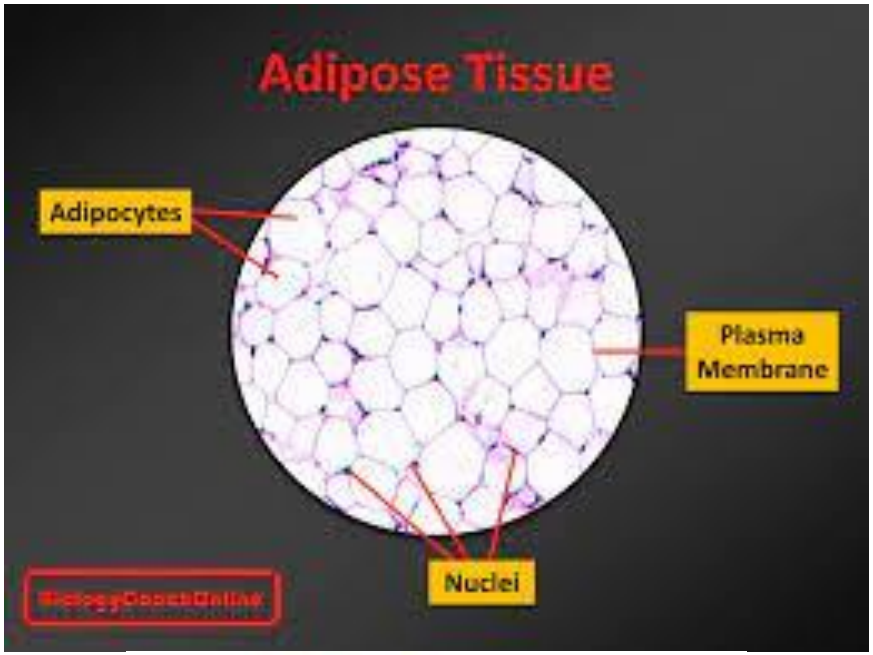


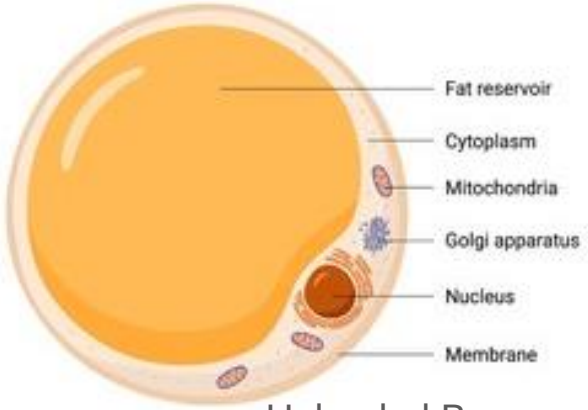
WAT vs BAT

	White fat	Brown fat
Function	Energy storage	Heat production
Morphology	Single lipid droplet Variable amount of mitochondria	Multiple small vacuolae Abundant mitochondria
Characteristic proteins	Leptin	UCP1
Human data	Large amounts are associated with increased risk of obesity-related disorders	Large amounts are associated with decreased risk of obesity-related disorders
Impact of aging	Increases with age relative to total body weight	Decreases with age

Features of Adipose Tissue

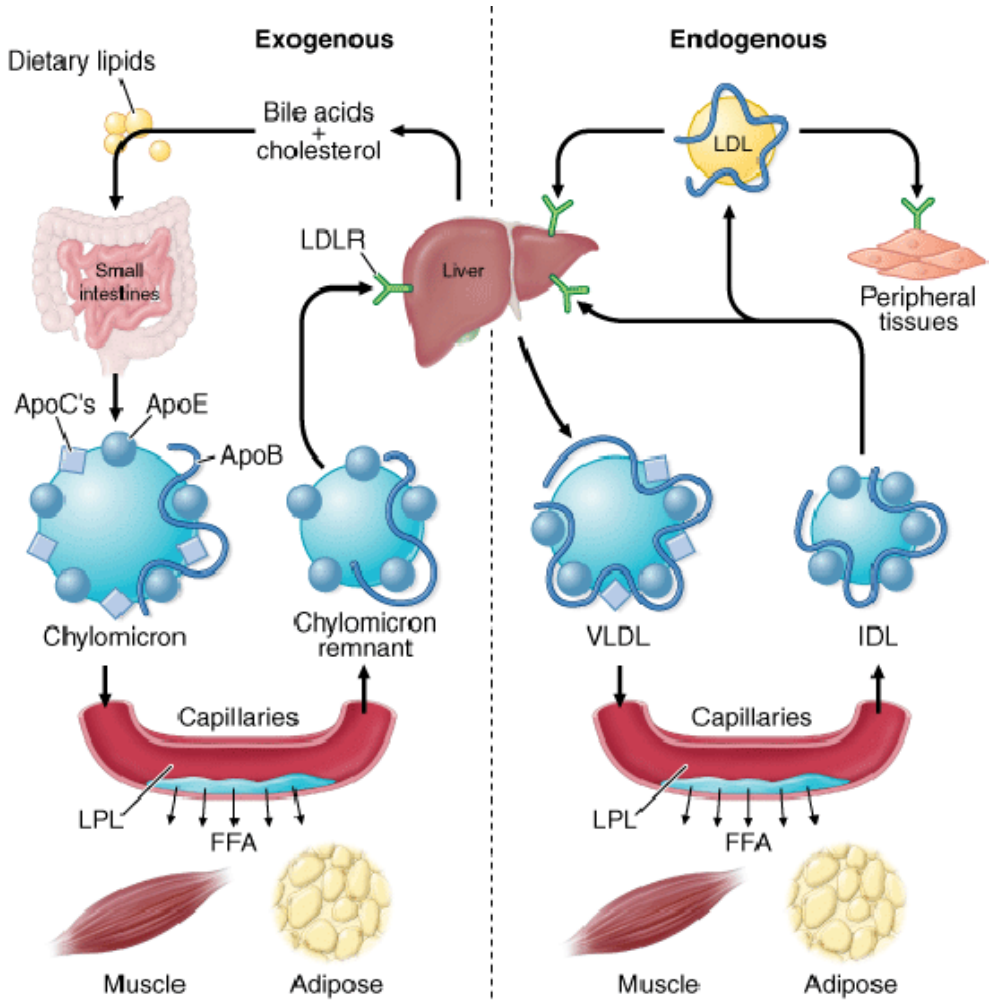
- Adipocytes: Primary storage sites in which excess consumed energy is stored as lipid.
- Adipocytes in WAT: large cells that typically contain a single lipid droplet.
- Size determined by the size of the lipid droplet (25 μm in a lean person to 200 μm in a morbidly obese person)





TAG storage and release

- TAG may be synthesized from free fatty acids (FFAs) or from glucose or other substrates in a high-carbohydrate/low-fat diet

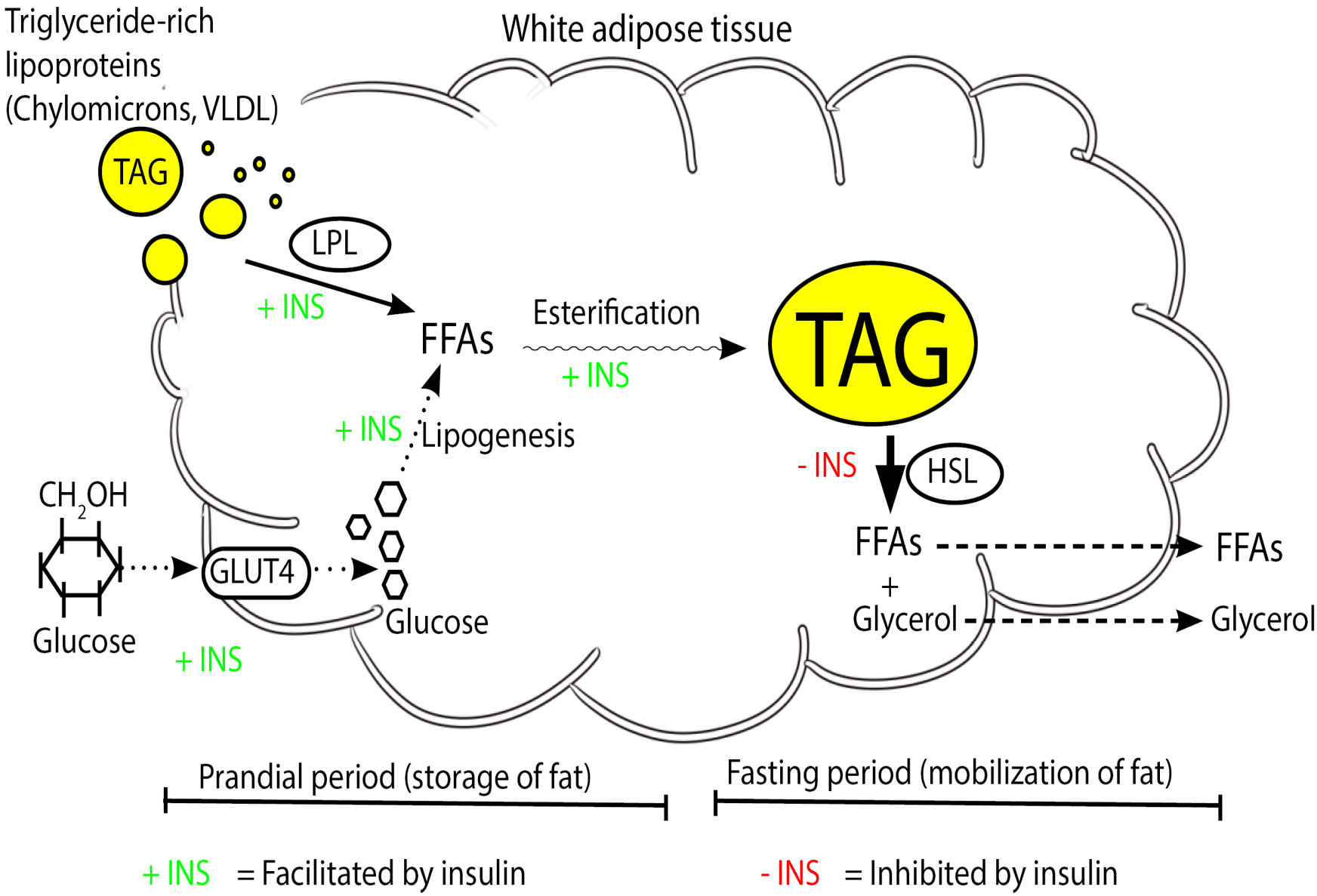


Physiology of Adipose Tissue

1. Energy Storage
2. Thermal/Mechanical Insulation
3. Metabolism of Steroid Hormones
4. Endocrine Functions

Energy Storage

- A central function of adipose tissue is energy storage.
- Triglycerides are efficient storage molecules:
  - TAG oxidation releases about twice as much energy as the oxidation of glycogen on a per molecule basis.
  - Glycogen storage requires water, whereas fat can be stored in a relatively aqueous-free lipid droplet.
  - Compared to glycogen, a much smaller amount of fat is needed to produce a given amount of energy
- Hormone sensitive lipase and adipose triglyceride lipase are:
  - Increased by epinephrine and glucagon
  - Inhibited by insulin.

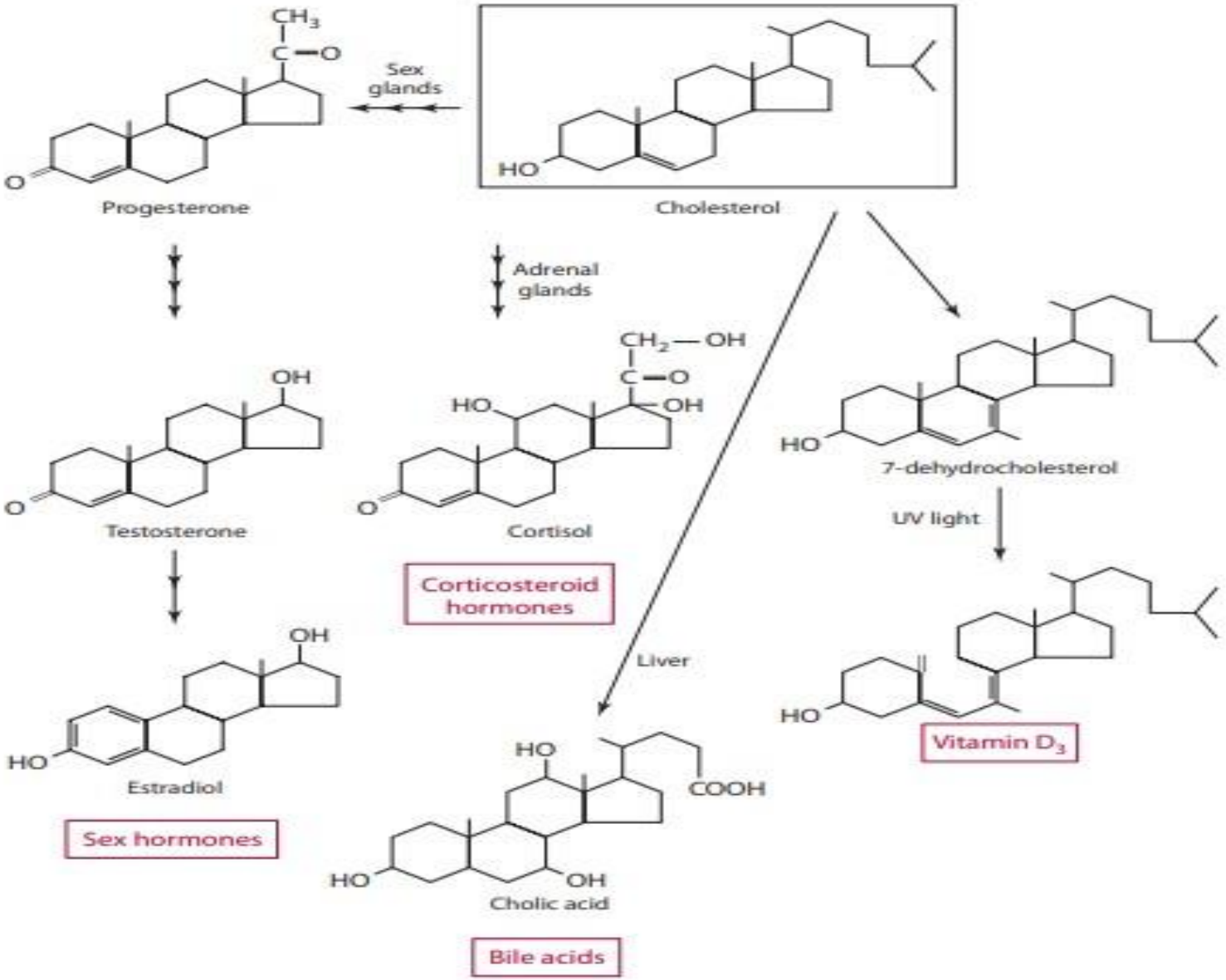


Thermal/Mechanical Insulation

- Adipose tissue’s ability to transmit heat (thermal conductivity) is lower than that of other tissues.
- During periods of cold exposure, subcutaneous fat depots can provide resistance to excessive heat loss.
- Adipose tissue also provides mechanical protection by surrounding internal organs, such as the reproductive organs.

Metabolism of Steroid Hormones

- Steroid hormones include:
  - Sex steroids: Androgens, estrogens, and progestogens
  - Glucocorticoids: Including cortisol. Cortisol and its derivatives regulate many aspects of metabolic function including insulin action, blood pressure, and fat deposition.
- Steroid hormones are derived *de novo* from cholesterol.
- Adipocytes express enzymes required for activation, interconversion, and inactivation of steroid hormones.

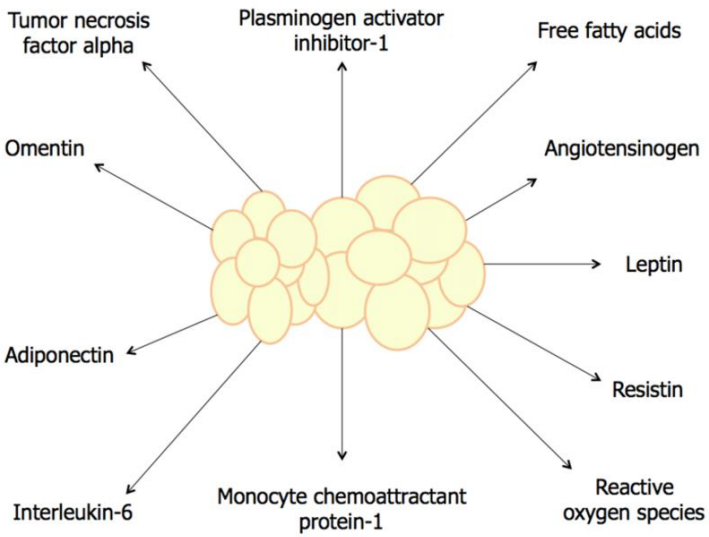


Metabolism of Steroid Hormones

- The effect of adipose tissue on systemic steroid metabolism is modest for young and lean people.
  - Example: When adipose tissue mass increases (e.g., in morbid obesity): estrogen levels are two-fold higher in morbidly obese compared to lean men.

Endocrine Functions

- Adipose tissue is now known to express and secrete a variety of bioactive peptides that act both locally and systemically .
- **Adipokines**: signaling molecules that are released from adipose tissue.
  - These provide an extensive network of communication both within adipose tissue and with other organs.



Endocrine Functions

Leptin

- Leptin is secreted into the circulation from adipocytes in direct proportion to adipose tissue mass and plays a significant role in the regulation of appetite and energy balance.
- In obesity, leptin levels are elevated in proportion to adiposity.
- **Leptin appears to have little potential for use as an anti-obesity**: treatment of obese individuals with large doses of leptin does not reduce body weight significantly. Some have interpreted this observation to mean that obese individuals are leptin-resistant

Endocrine Functions

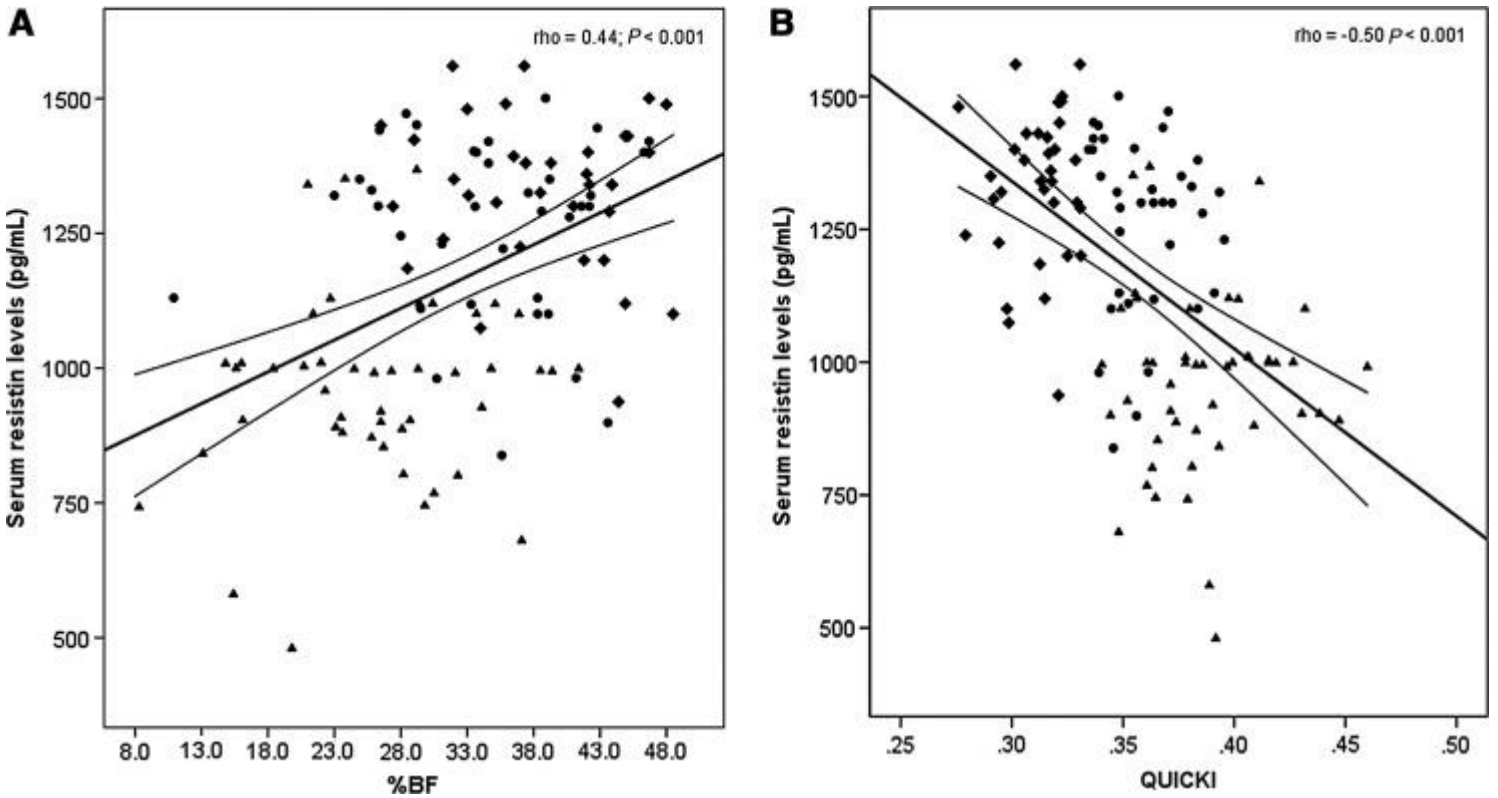
Adiponectin

- Adiponectin levels are high in normal lean subjects but low in the obese.
- Reduced circulating adiponectin concentrations are associated with reduced insulin sensitivity, increased rates of atherosclerosis, and impairment of immune function. In contrast to leptin, adiponectin levels increase after weight loss.

Resistin

- Resistin is an inflammatory protein
- Resistin has been linked to the onset of insulin resistance and obesity-associated diabetes

Nieva-Vazquez A, Pérez-Fuentes R, Torres-Rasgado E, López-López JG, Romero JR. Serum resistin levels are associated with adiposity and insulin sensitivity in obese Hispanic subjects. Metab Syndr Relat Disord. 2014 Mar;12(2):143-8. doi: 10.1089/met.2013.0118. Epub 2013 Nov 22. PMID: 24266722; PMCID: PMC3997139.



There are significant correlations between serum resistin levels with percentage body fat (%BF) **(A)** and quantitative insulin-sensitivity check index (QUICKI) **(B)**.

Endocrine Functions

Tumor Necrosis Factor-α (TNF-α)

- TNF-α is a cytokine that can be produced by most cell types, including adipocytes. Its expression is low in adipose tissue from lean animals but increases in obesity.
- In the liver, TNF-α suppresses expression of genes involved in glucose uptake, metabolism, and fatty acid oxidation, and increases expression of genes involved in cholesterol and fatty acid synthesis.
- High TNF-α → insulin resistance by impairing insulin signaling and increasing serum FFAs

Endocrine Functions

Interleukin 6 (IL-6)

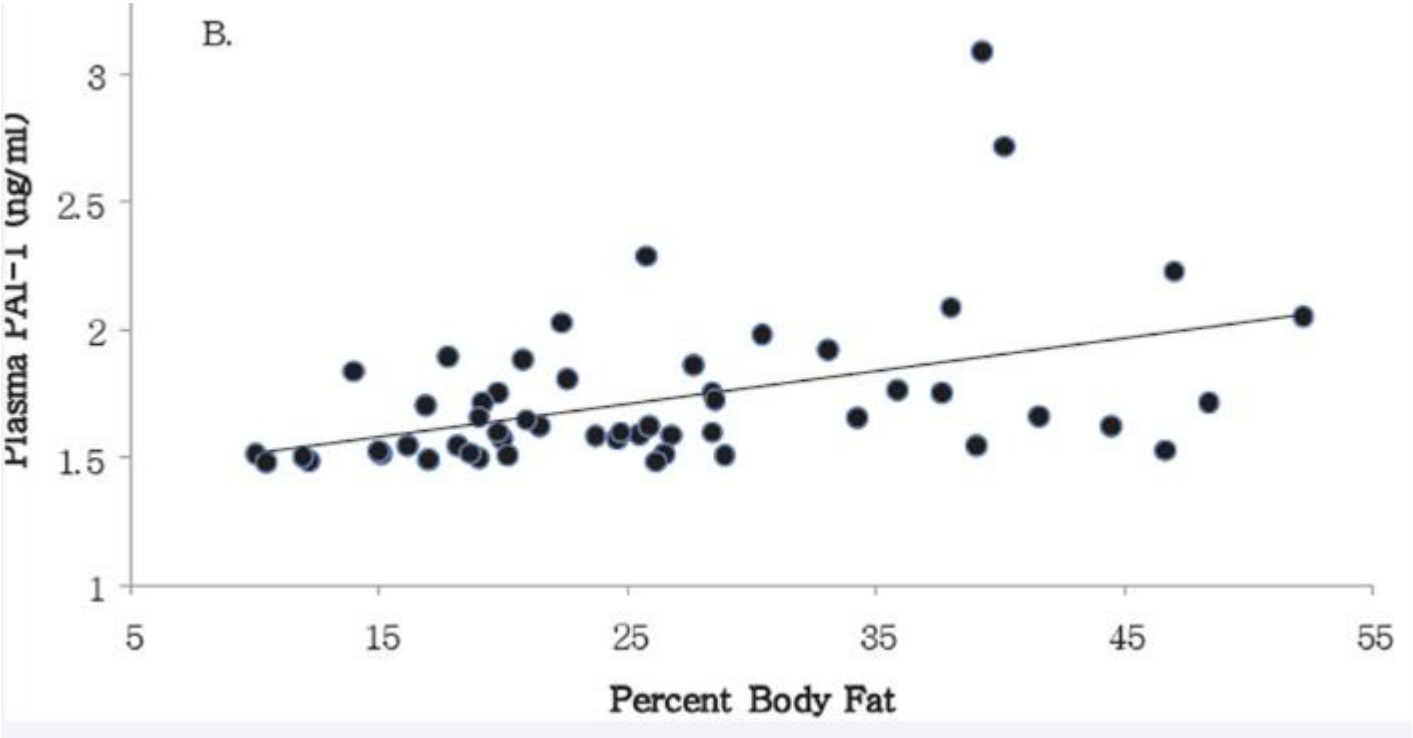
- IL-6 is a cytokine produced by many cell types including adipocytes.
- IL-6 concentration raises with obesity and insulin resistance.
- IL-6 is believed to decrease insulin-signaling, inhibit adipogenesis, and decrease adiponectin secretion.

Endocrine Functions

Plasminogen Activator Inhibitor (PAI-1)

- PAI-1 is an important inhibitor of fibrinolysis, which is the normal process of dissolving blood clots.
- Plasma PAI-1 levels are elevated in obesity and insulin resistance
- High PAI-1 levels are a risk factor for the development of type 2 diabetes and cardiovascular disease

McMillin S, Ryan AS. Plasminogen Activator Inhibitor-1, Body Fat and Insulin Action in Aging Women. Ann Gerontol Geriatr Res. 2014;1(2):1006. PMID: 26295064; PMCID: PMC4539000.



Relationship of percent body fat to plasma PAI-1 activity levels ($r = 0.66$, $P<0.001$).

Summary

Table 7-1 Level of different adipokines in lean and obese individuals, and their effect on insulin sensitivity

	Obese State	Lean State	Effect on insulin sensitivity
	Levels		
Adipokines			
Leptin	↑	↓	Deficiency of leptin or its receptor leads to obesity and insulin resistance
Adiponectin	↓	↑	Low adiponectin concentrations are associated with reduced insulin sensitivity
Resistin	↑	↓	Possible link between high resistin levels and insulin resistance
TNF-alpha	↑	↓	TNF-alpha decreases insulin signaling and increases serum-free fatty acids
IL-6	↑	↓	IL-6 decreases insulin signaling and adiponectin secretion
PAI-1	↑	↓	Possible link between high PAI-1 levels and insulin resistance

Adipose Tissue in Obesity

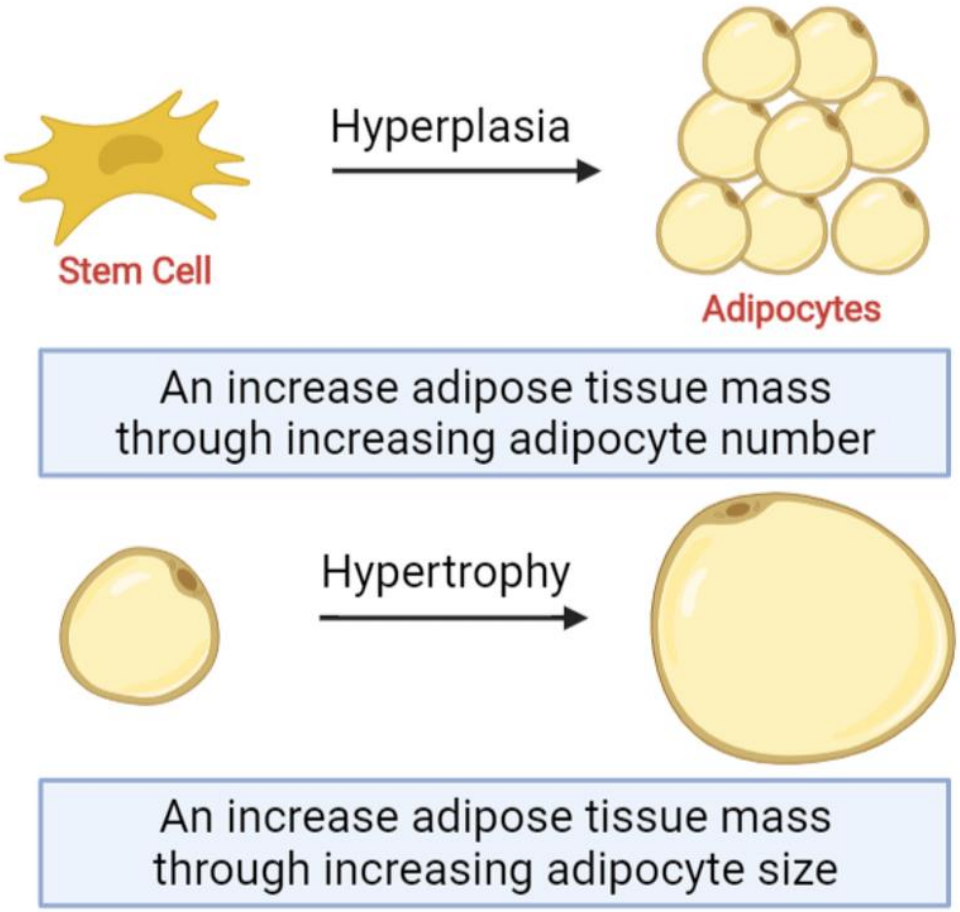
- Obesity is a state of excessive total adipose tissue, or adiposity.
- The relationship between body weight and disease risk is continuous, with the disease risk increasing as weight increases across all classifications: lean, overweight, and obese.

Classification*	BMI (kg/m^2)	Risk of comorbidity	
		WC <90 cm in men <85 cm in women	WC ≥90 cm in men ≥85 cm in women
Underweight	<18.5	Low	Moderate
Normal	18.5–22.9	Moderate	Slightly high
Pre-obese	23–24.9	Slightly high	High
Class I obesity	25–29.9	High	Very high
Class II obesity	30–34.9	Very high	Highest
Class III obesity	≥35	Highest	Highest

*Pre-obese can be referred to as overweight and class III obesity as severe obesity.
BMI, body mass index; WC, waist circumference.

Adipose Tissue in Obesity

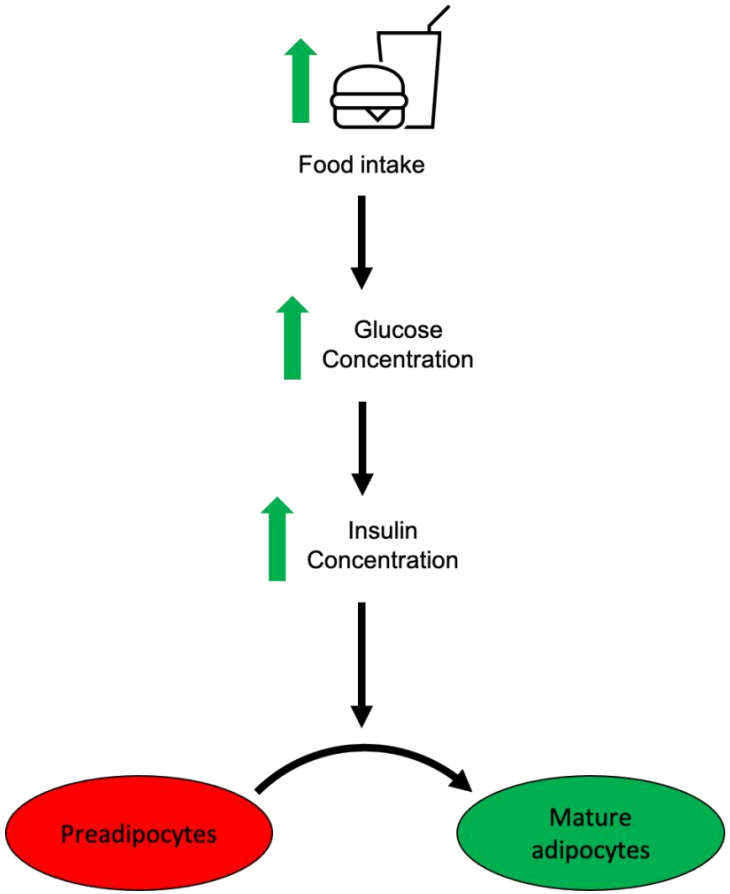
- In obesity, adipose tissue mass increases through **hyperplasia** (increased adipocyte number) and **hypertrophy** (increased adipocyte size).

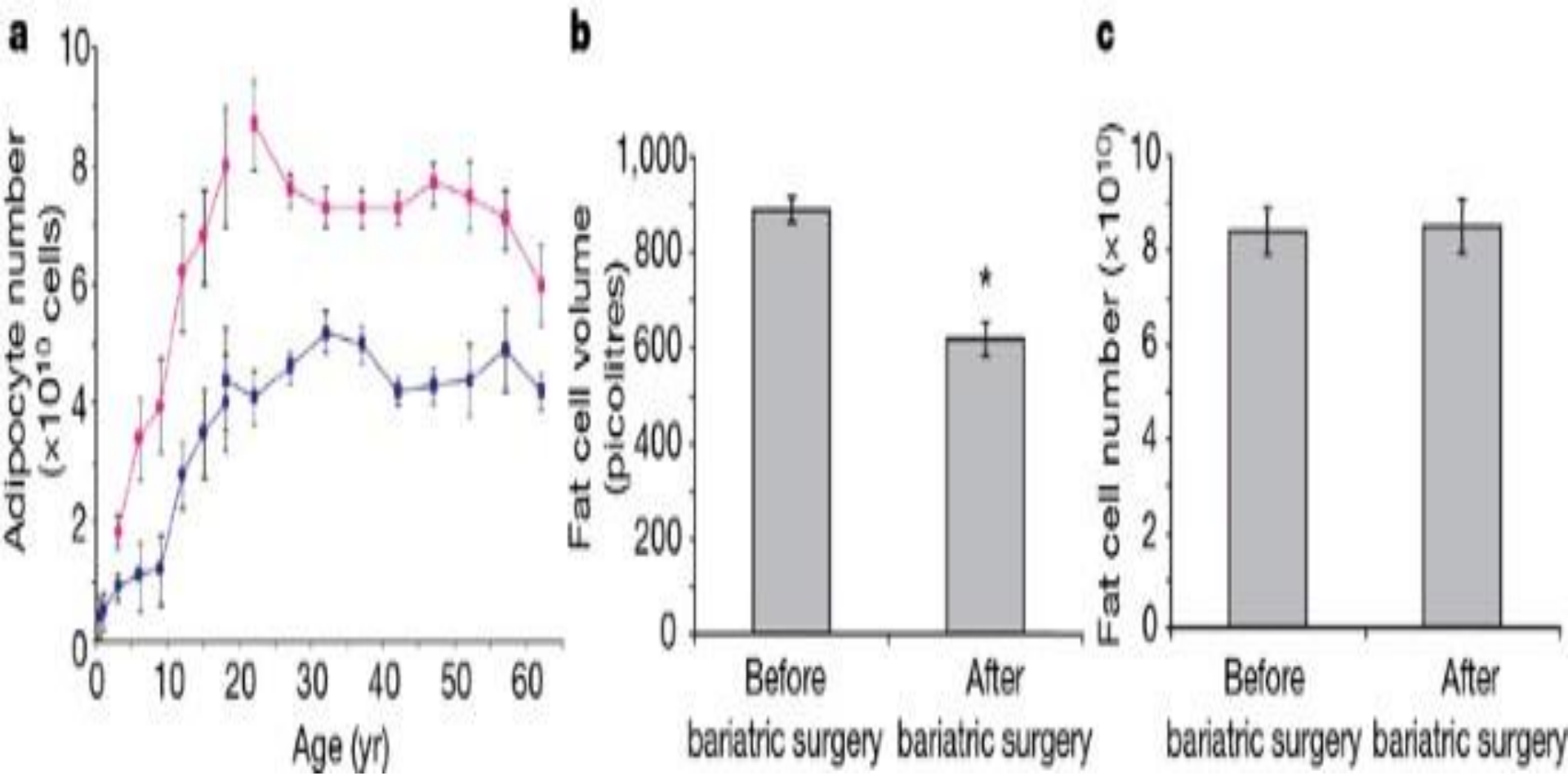


Adipose Tissue in Obesity

- It has been suggested that increased presence of **insulin** circulating in the blood stimulates the differentiation of preadipocytes into mature adipocytes → hyperplasia

- **Overconsumption** & **under-expenditure** → continuous adipose hypertrophy and hyperplasia → Increase fat mass.





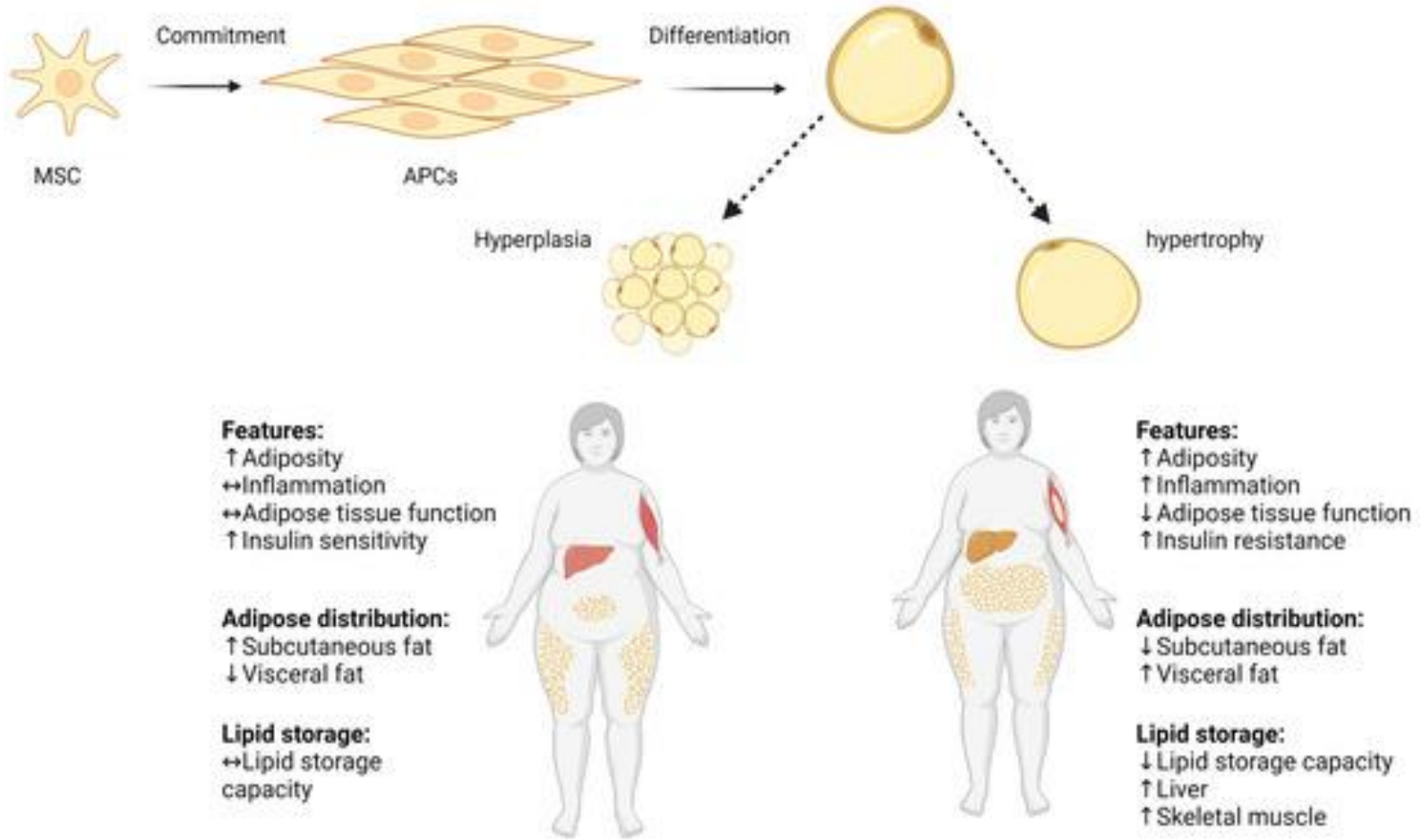
Total adipocyte number from 595 (*n* lean = 253; *n* obese = 342) adult individuals (squares) was combined with previous results for children and adolescents[8] (circles; *n* lean = 178; *n* obese = 120). **a**, The adipocyte number increases in childhood and adolescence, with the number levelling off and remaining constant in adulthood in both lean (blue) and obese (pink) individuals. **b**, **c**, Major weight loss by bariatric surgery results in a significant decrease in cell volume (**b**), however fails to reduce adipocyte cell number (**c**), 1–2 yr post surgery (*n* = 20). All error bars represent s.e.m.; asterisk, $P < 0.0001$.

Adipose Tissue in Obesity

- The number of adipocytes in a specific fat depot is primarily established early in life and tends to remain stable throughout adulthood
- Adipose tissue hyperplasia and hypertrophy depend on and vary with age:
  - Rapid hyperplasia and hypertrophy during early childhood (0–2 years) and adolescence (12–18 years)
  - Relative hyperplasia stabilization at adulthood
- During adulthood, there is a gradual decline in adipose tissue hyperplasia potential with **hypertrophy becoming predominant** especially in visceral depots

https://encyclopedia.pub/entry/48267#:~:text=At%20normal%20weight%20states%2C%20the,Scheme%201.

Adipose Tissue in Obesity



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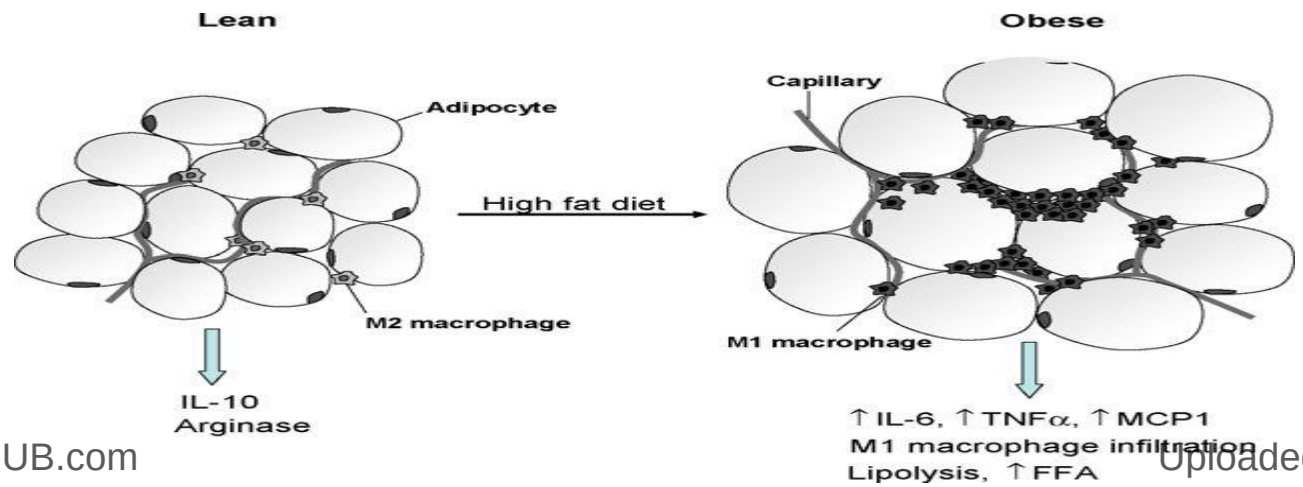
Adipose Tissue in Obesity

- Adipose tissue of obese humans and mice is characterized by increased **macrophage** infiltration

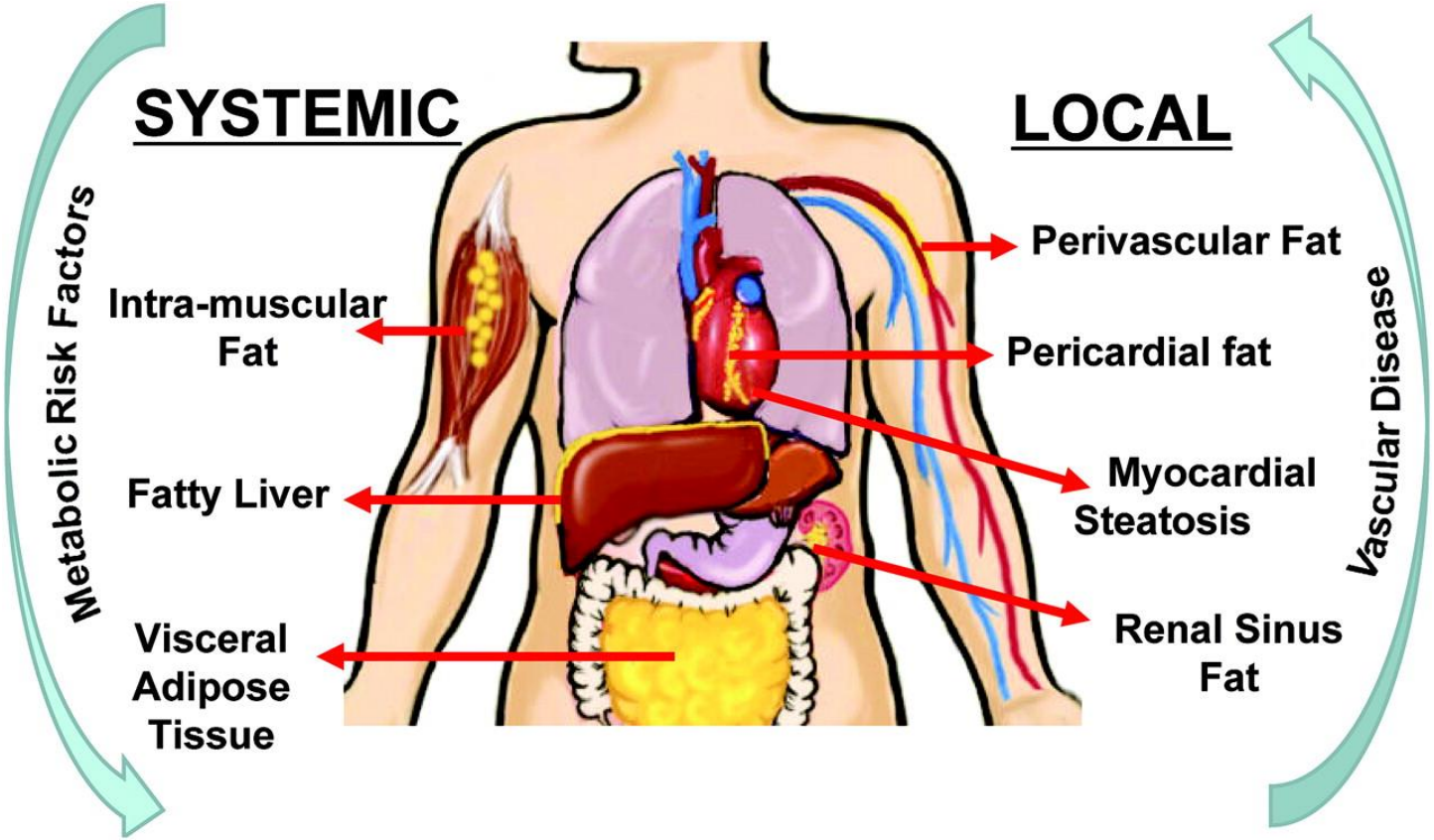
A type of white blood cell of the innate immune system that engulf and digest pathogens

  - Responsible for increased inflammation (↑ TNF-α, Il-6 and PAI-1) → obesity-induced inflammation.
  - Macrophages recruited during diet-induced obesity differ from resident macrophages (↑ inflammatory properties)



Ectopic Fat

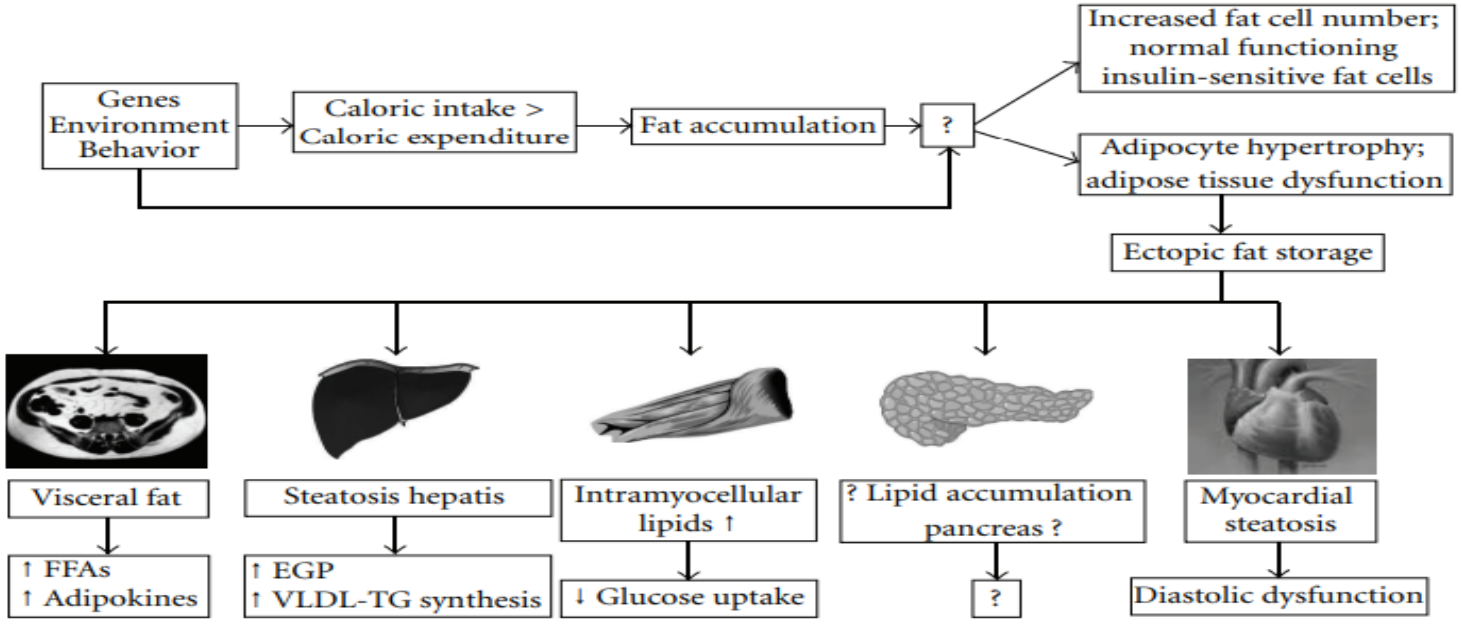
- Excess adipose tissue in locations not classically associated with adipose tissue storage



https://www.ahajournals.org/doi/full/10.1161/circulationaha.111.077602

Ectopic Fat

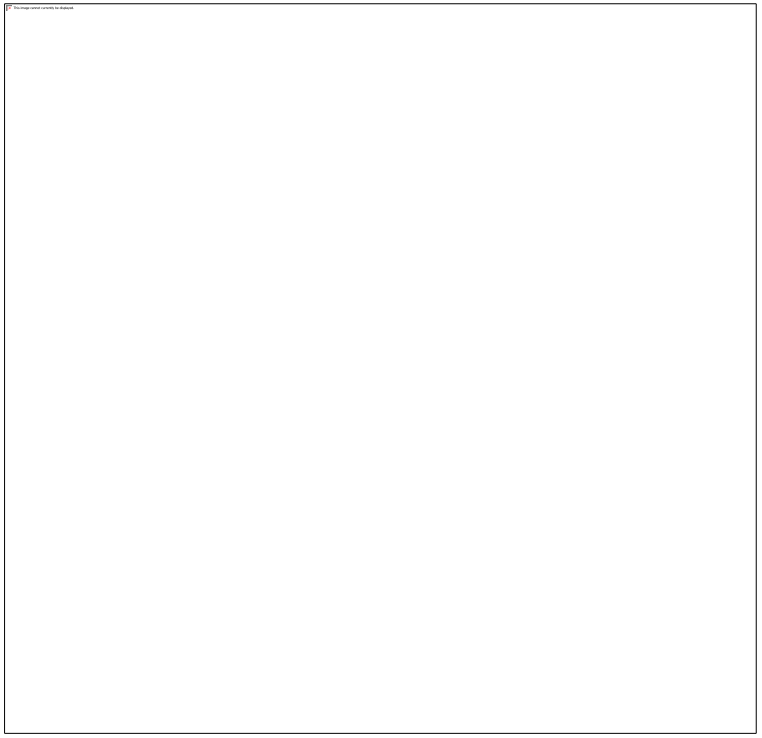
- Points of discussion
  - Dysfunctional adipose tissue
  - Insulin resistance



Snel M, Jonker JT, Schoones J, Lamb H, de Roos A, Pijl H, Smit JW, Meinders AE, Jazet IM. Ectopic fat and insulin resistance: pathophysiology and effect of diet and lifestyle interventions. Int J Endocrinol. 2012;2012:983814. doi: 10.1155/2012/983814. Epub 2012 May 24. PMID: 22675355; PMCID: PMC3366269

Diabetes Introduction

- Type 2 diabetes develops when the pancreatic β-cell no longer meets the demand for insulin secretion.



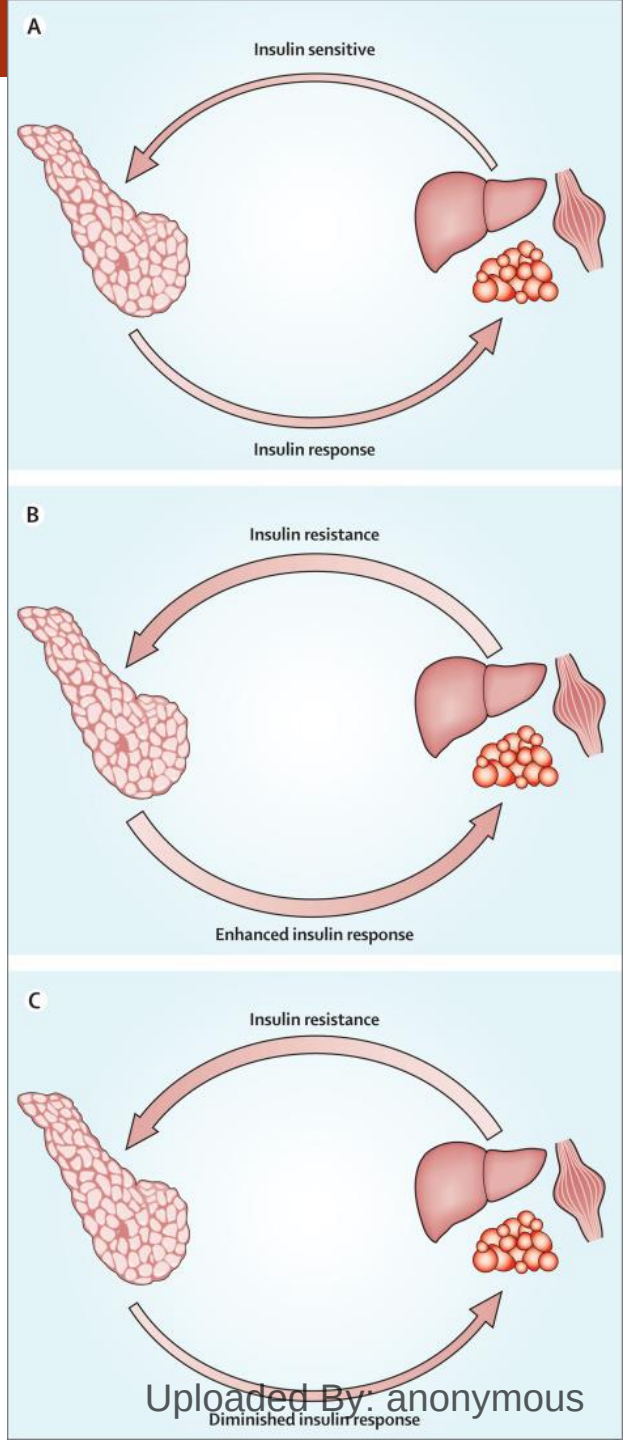
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2813%2962154-6/fulltext

(A) Insulin interacts with the liver, muscle, and adipose tissue to stimulate uptake of glucose. Insulin released → maintain normal glucose homoeostasis.

(B) Insulin resistance develops → feedback to β cells ensures that the cells increase insulin output to maintain normal glucose.

(C) β cells are incapable of increasing insulin output → increased glucose concentrations.

β-cell dysfunction progresses → elevations in glycaemia → diabetes.



Obesity and Diabetes

- There is a strong positive correlation between the average weight and the presence of T2D, and an inverse relationship between BMI and age of diabetes onset.
- Risk factors:
  - Duration of obesity
  - Degree of obesity
  - Central distribution of weight
- Insulin receptor and post-receptor abnormalities → decreased glucose transport, oxidation, and storage.
- Net effect → Decrease glucose entry into and use by insulin-sensitive cells

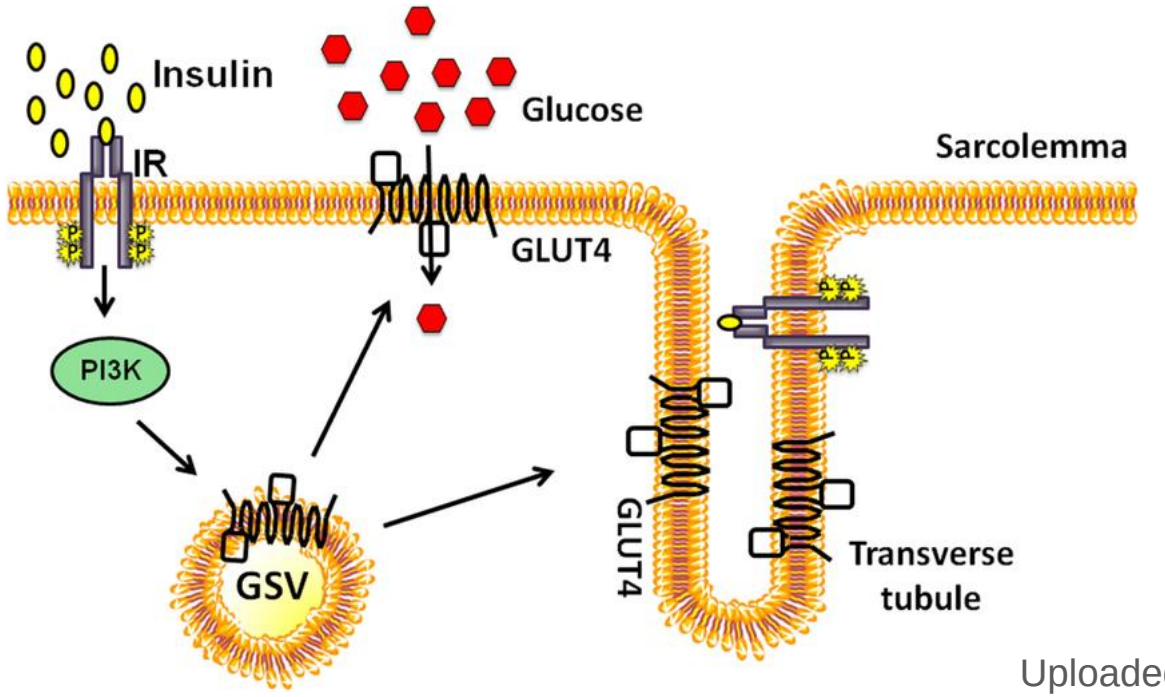
Insulin Resistance in Obesity

- Insulin resistance is a state in which higher than normal concentrations of insulin are required for a normal response.
- The point at which insulin resistance develops varies from individual to individual. Increases in adiposity increase insulin resistance.
  1. Accumulation of lipid in sites other than the adipocyte
  2. Production of hormonal and paracrine factors by adipose tissue.

Insulin Resistance in Obesity

Lipid deposition in non-adipocytes is believed to be a key factor in the development of insulin resistance.

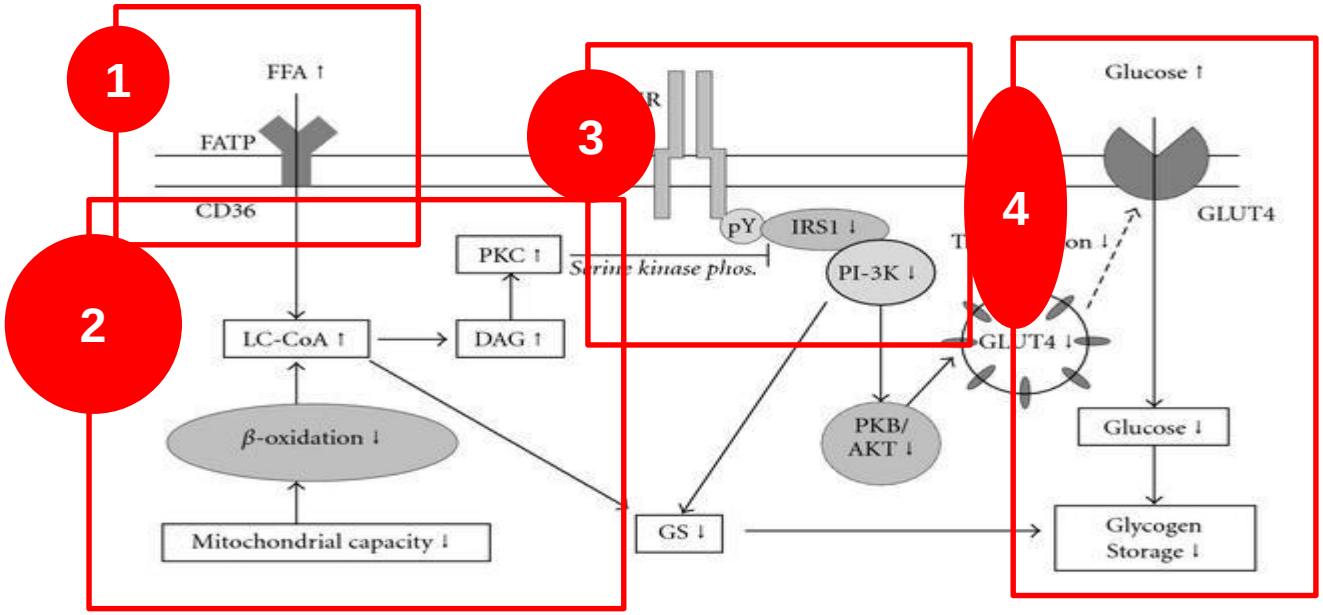
- FA accumulation in muscle and liver leads to insulin resistance by directly interfering with insulin signaling.



Insulin Resistance in Obesity

Lipid deposition in non-adipocytes is believed to be a key factor in the development of insulin resistance.

- FA accumulation in muscle causes decreased phosphorylation of insulin receptor substrates, resulting in decreased activation of PI-3 kinase.

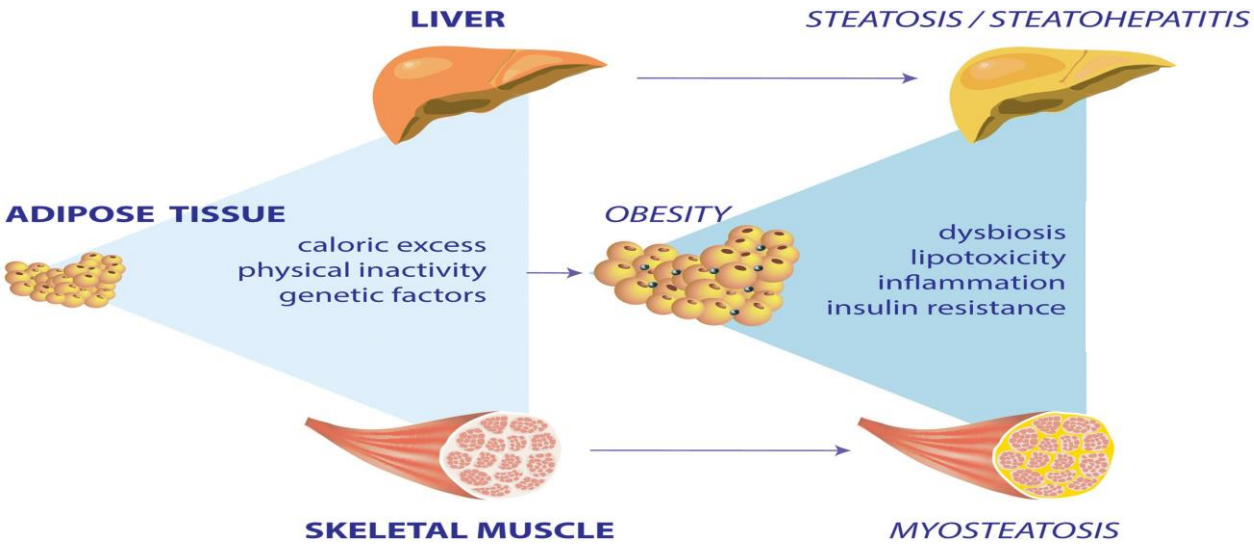


Insulin Resistance in Obesity

- Muscle insulin resistance is the earliest detectable feature indicating increased T2D risk.
- Increased FFA fluxes → intramyocellular accumulation of TAG and long-chain Acyl CoA → accumulation of intracellular signaling molecules (ceramides and diacylglycerol)
- → Activates cellular pathways that lead to decreased insulin sensitivity → down-regulate GLUT-4 → ↓ glucose-transport activity → ↓ glycogen synthesis and glucose oxidation
- Instead of being stored as glycogen → Carbohydrates are used for hepatic de novo lipogenesis and VLDL production → dyslipidemia.

Insulin Resistance in Obesity

- Also, reduced activation of PI-3 kinase upon lipid accumulation in the **liver**, similar to the muscle.
- The observed reduction in insulin signaling is associated with increased gluconeogenesis.

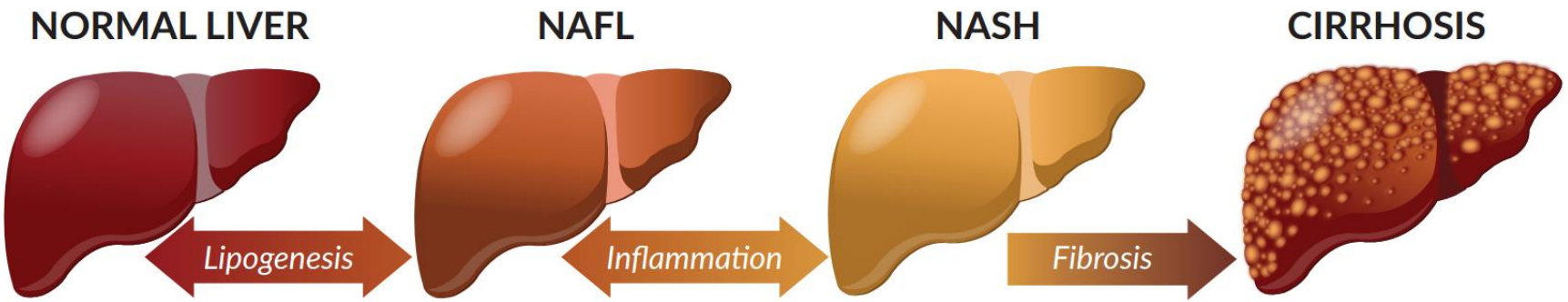


https://www.xiahepublishing.com/2310-8819/JCTH-2020-00065

Non-Alcoholic Fatty Liver Disease

- NAFLD is defined as the presence of ≥5% of HS in the absence of other causes of liver disease

- NAFLD is associated with obesity, T2DM, and hyperlipidemia
- Diabetes in individuals with NAFLD is a risk factor for progression to NASH, cirrhosis, and mortality.



Non-Alcoholic Fatty Liver Disease

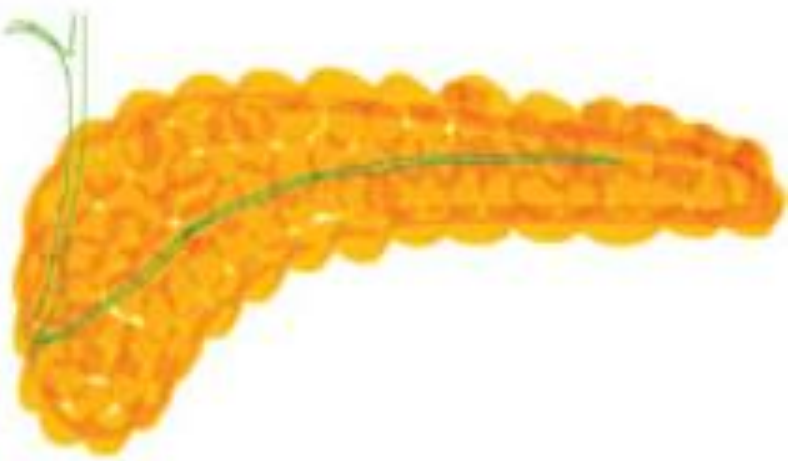
- The liver is particularly prone to the accumulation of ectopic lipids
- ↑ dietary fat intake, adipose tissue-derived FFA's, and the novo lipogenesis in the liver → Excess liver fat storage.
- In an insulin-resistant state, the liver ↑ its glucose production, leading to modest hyperglycemia → increases insulin secretion by the pancreas.
- ↑ insulin levels enhance liver lipogenesis from carbohydrates → ↑ fat accumulation → a vicious cycle
- Dietary carbohydrates (including fructose) further stimulate de novo lipogenesis → ↑ liver steatosis and it's metabolic consequences
- Serum levels of adiponectin are reduced in patients with NAFLD: adiponectin activates β-oxidation and suppresses de novo lipogenesis → inhibiting liver fat accumulation.

Insulin Resistance in Obesity

- Chronic low-grade inflammation: the chronic production, but a low-grade state, of inflammatory factors
- Increased levels of TNF-α, IL-6, and resistin as well as reduced adiponectin are commonly associated with the development of insulin resistance.
- Adipokines and pro-inflammatory molecules may induce insulin resistance either by:
  - Affecting the insulin signaling directly
  - Altering lipid metabolism.

Pancreatic steatosis

- Fat accumulation within the cytoplasm of exocrine and endocrine cells results in **β cells dysfunction**.
- Long-term excess fat exposure links β-cell dysfunction and hepatic insulin resistance with the development of T2DM.



Surrogate Markers on IR

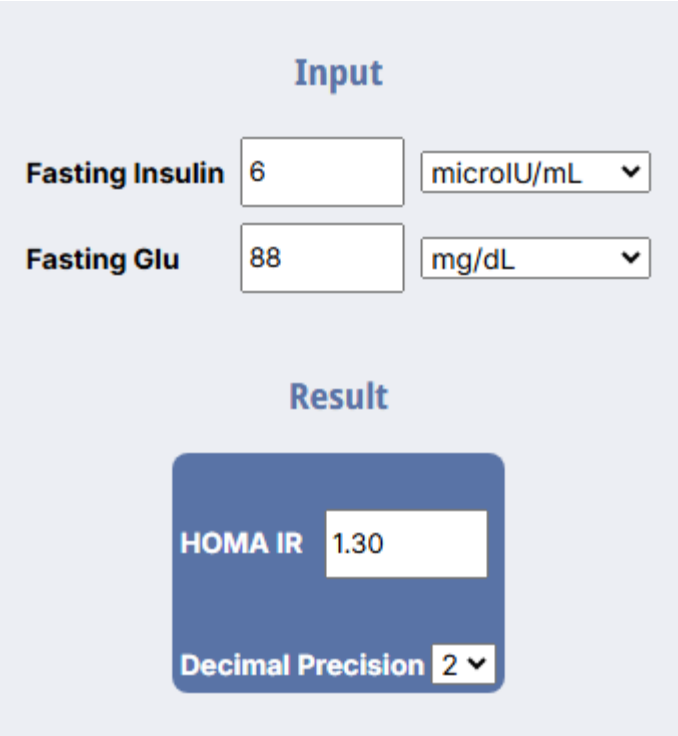
1. HOMA-IR: The homoeostasis model assessment for Insulin Resistance
2. QUICKI: The quantitative insulin sensitivity check index

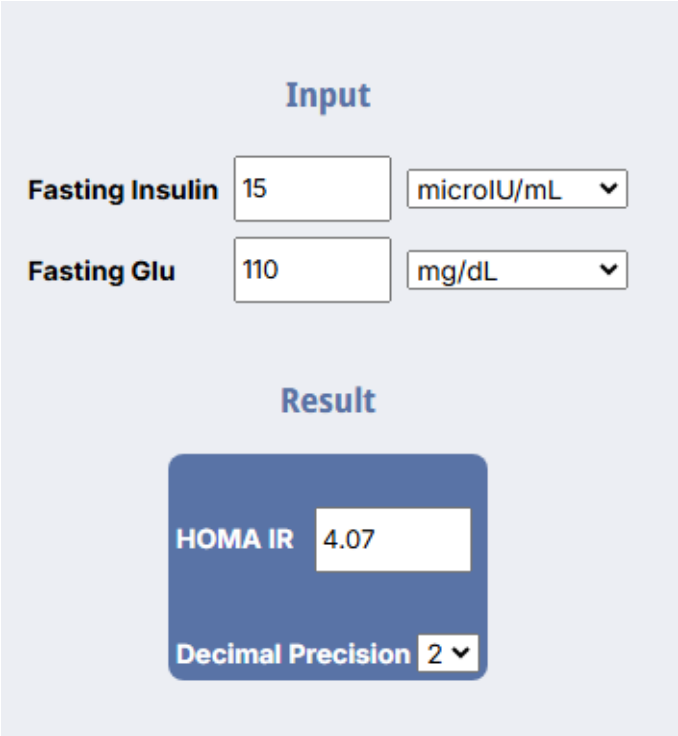
Both are widely used surrogate indices, and are based on fasting plasma glucose and insulin values.

$$\text{HOMA index} = \text{insulin (mU/L)} \times [\text{glucose (mmol/L)}/22.5]$$

$$\text{QUICKI} = \frac{1}{\log \text{insulin (mU/L)} + \log \text{glucose (mg/dL)}}$$

Example: HOMA-IR





- Normal: 0.5 - 1.4
- Early IR: ≥1.9
- IR: ≥2.9

Key points

By the end of this section you should know:

1. Differentiate between white and brown adipocytes
2. Functions of adipose tissues
3. Relating the endocrine function of adipose tissue with the co-morbidities of obesity
4. Differentiate between the processes of hyperplasia and hypertrophy
5. Define ectopic fat
6. Describe how IR develops in diabetes: Due to ectopic fat and the endocrine effects
7. Describe NAFLD and its association with IR
8. Understand surrogate markers of IR