

Nutritional disorders, Obesity, and Metabolic syndrome

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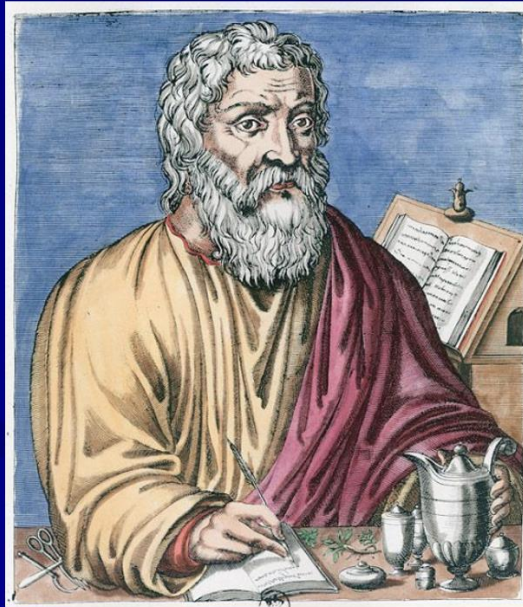
"Nature has given us all the pieces required to achieve exceptional wellness and health. But has left it to us to put these pieces together."



~ Diane McLaren

*"Let food be thy medicine, and
let thy medicine be food"*

~ Hippokrates



Pathophysiology of nutritional disorders

malnutrition · micronutrients · refeeding · obesity · gut–brain–immune axis

Three levels: cellular energetics, organ axes and systemic response.

Diagnosis is only the name; pathophysiology asks what mechanism drives the phenotype.

The lecture follows energy, protein, inflammation, hormones and organ consequences.

Objectives

- 1 Recognise the spectrum: malnutrition means deficit, excess, imbalance or impaired nutrient utilisation.
- 2 Explain the mechanism: energy, hormones and inflammation act on muscle, fat, liver, gut and immunity.
- 3 Predict risk: especially refeeding syndrome, immunodeficiency, sarcopenia and cardiometabolic complications.
- 4 Think mechanistically: insulin, glucagon, phosphate, muscle protein synthesis, hepcidin, leptin and adipokines.

01 · Definitions and systemic framework

Connecting biochemical mechanisms with clinical interpretation.

Malnutrition: one concept, three mechanisms

Deficiency

insufficient intake of energy, protein, or micronutrients

Excess

excess energy or nutrient intake with a maladaptive tissue response

Impaired utilization

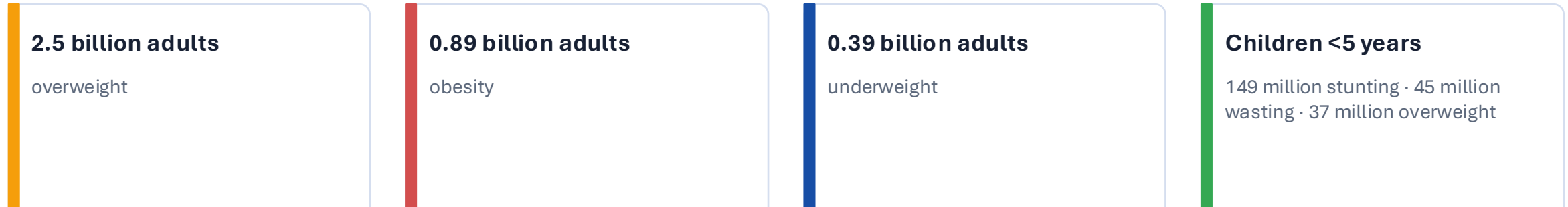
inflammation, malabsorption, organ failure, or endocrine dysregulation

Outcome: altered body composition + organ function

not only body weight, but especially muscle mass, visceral fat, metabolic flexibility, and immune function

WHO defines malnutrition broadly: it includes undernutrition, vitamin and mineral deficiencies, overweight, obesity, and diet-related noncommunicable diseases. Therefore, a malnourished patient does not necessarily have to be underweight. From a pathophysiological perspective, the key point is that the body responds to nutritional stress by altering energy and substrate fluxes. This results in functional changes: impaired immunity, wound healing, muscle strength, fertility, and cognition, or, conversely, insulin resistance and organ lipotoxicity.

Global burden: the double face of nutritional disorders



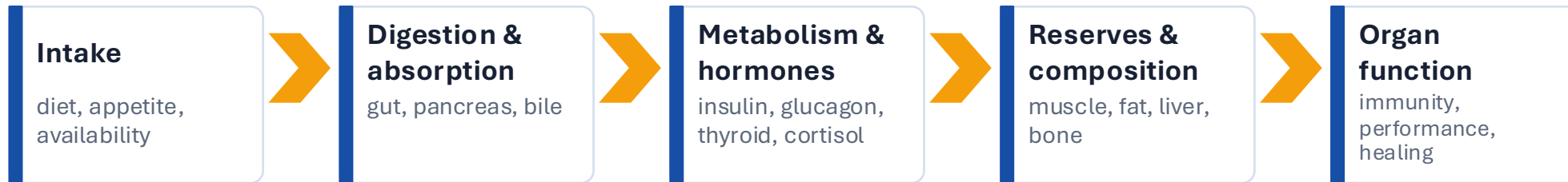
Modern pathophysiology describes a double burden of malnutrition: undernutrition and obesity share common determinants – poverty, infections, stress, an unhealthy food environment, sedentary lifestyle, and chronic inflammation.

Stunting (chronic undernutrition) – a child has a markedly lower height for age (**according to WHO, height-for-age more than 2 SD below the median of the international growth standards for the given age and sex**). It is an **indicator of long-term deprivation, poor nutrition, and recurrent infections**, especially during the critical period of the **first 1,000 days of life**.

Wasting in children (acute undernutrition) – a child has an excessively low weight in relation to height. It reflects an **acute nutrient deficiency** or may result from severe illness.

WHO data for 2022: nutritional disorders coexist within the same population, often even within the same household.

From intake to phenotype: nutritional state = balance + adaptation + reserves



The same nutrient intake may result in a different nutritional status depending on inflammation, insulin sensitivity, age, disease, and the microbiota.

A patient's nutritional status is not determined solely by what they eat. We need to distinguish between intake, absorption, metabolic adaptation, and functional reserves. For example, an oncology patient may have a relatively adequate energy intake, yet the inflammatory response increases proteolysis and energy expenditure. Conversely, a patient with obesity may have excess energy stores but still have iron deficiency, vitamin D deficiency, or sarcopenia.

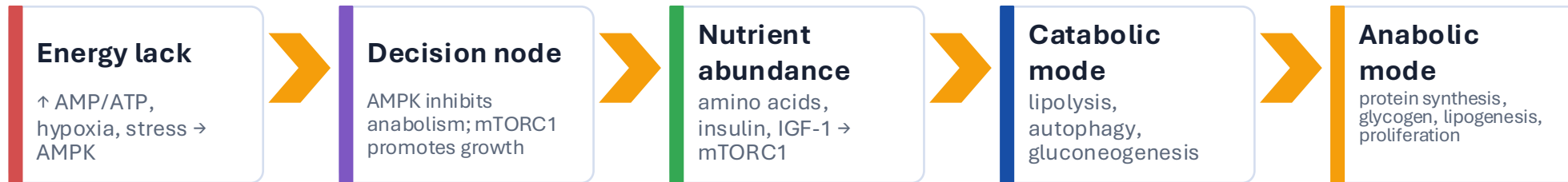
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Energy homeostasis

The cell first solves ATP.

Cellular nutrient sensors: AMPK versus mTOR

AMPK (*AMP-activated protein kinase*)
mTOR (*mechanistic target of rapamycin*)



AMPK is a sensor of low cellular energy. It activates catabolic processes that restore ATP levels and suppresses energy-consuming anabolic pathways. mTORC1 is sensitive to amino acids, insulin, and growth signals. When nutrients are abundant, it promotes protein synthesis and growth. During starvation, mTOR activity is suppressed and autophagy is activated. Clinically, this helps explain the loss of muscle mass in undernutrition and impaired wound healing.

Endocrine response to nutritional stress

Insulin

glucose transport,
lipogenesis, protein
synthesis

Glucagon

glycogenolysis,
gluconeogenesis,
ketogenesis

Cortisol / catecholamines

proteolysis, lipolysis,
insulin resistance

Leptin / ghrelin

satiety, hunger,
reproductive and immune
axes

IGF-1 / thyroid

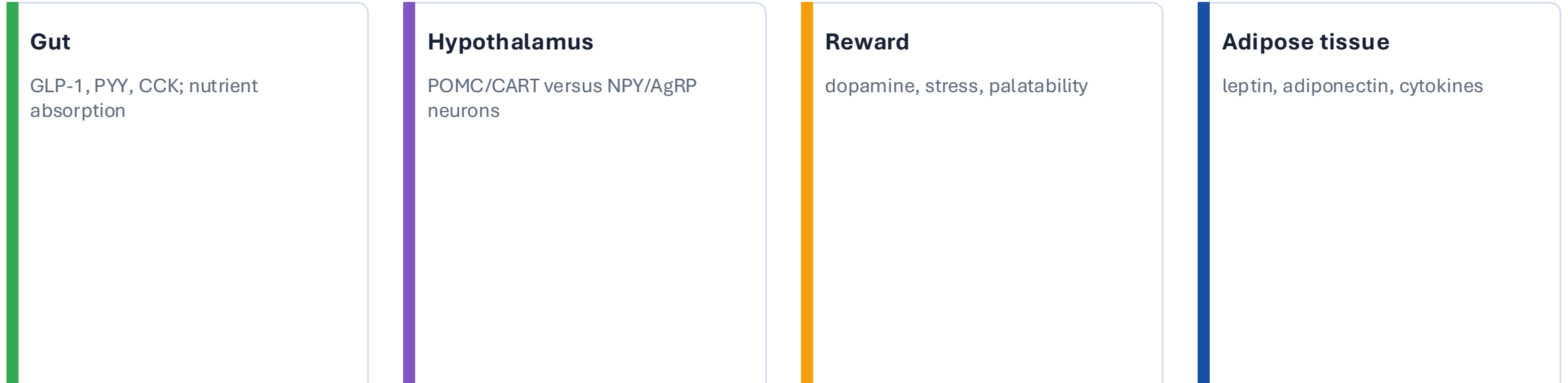
growth, basal metabolism,
thermogenesis

With prolonged deficiency, adaptation progresses to dysfunction: hypogonadism, low T3 levels, immunosuppression, and sarcopenia.

During starvation, insulin levels decrease while glucagon levels rise. The body mobilizes metabolic substrates. During illness-related stress, cortisol and catecholamines are also released, shifting metabolism toward insulin resistance and proteolysis. Leptin signals the status of energy stores. When body fat is low, leptin levels fall, suppressing the reproductive axis, thermogenesis, and some immune functions. Ghrelin increases hunger, but in anorexia nervosa its levels may be elevated without an appropriate increase in food intake.

SIGNALS OF SATIETY, HUNGER, AND REWARD

Gut-brain axis: food intake is not simply a matter of willpower



Current view: body-weight regulation is a neuroendocrine system with a biological defence of energy stores.

Food intake is regulated by homeostatic signals from the gut and adipose tissue, but also by the hedonic reward circuitry. GLP-1, PYY, and CCK signal satiety; ghrelin signals hunger; leptin informs the hypothalamus about fat stores. In obesity, leptin resistance develops together with altered responses to food-related stimuli. Therefore, reducing obesity to a lack of willpower is medically inaccurate and contributes to stigmatization.

*GLP-1, PYY, CCK, POMC, CART (Cocaine- and amphetamine-regulated transcript) = anorexigenic system
NPY, AgRP (Agouti-related peptide) = orexigenic system*

03 · Undernutrition and disease-related malnutrition

Energy/protein deficiency is a systemic disease of tissues.

Undernutrition: acute, chronic and functional phenotypes

Wasting

acute/subacute deficit;
low weight for height; high
child mortality risk

Stunting

chronic or recurrent
undernutrition during
critical development;
growth and cognition

Sarcopenia

loss of muscle mass and
function; can coexist with
obesity

Clinical question

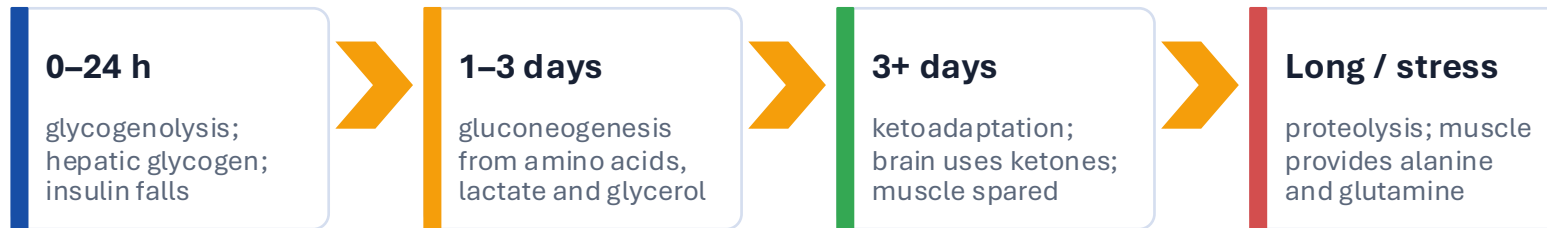
Is the problem intake,
absorption, inflammation
or endocrine/metabolic
response?

Laboratory question

Is low albumin caused by
protein deficit,
inflammation, loss or
haemodilution?

Wasting, stunting, and sarcopenia are phenotypic manifestations of different temporal and mechanistic processes. In adult patients, the main concern is the loss of muscle mass and function, not BMI alone. Albumin is not a specific marker of nutritional status. It is a negative acute-phase reactant and decreases in inflammation, sepsis, liver disease, nephrotic syndrome, and hemodilution.

Starvation occurs in phases: substrate utilization shifts



During inflammation, “muscle sparing” is disrupted: cytokines and stress hormones maintain proteolysis despite metabolic adaptation.

In disease-related malnutrition, inflammatory cytokines, cortisol, and catecholamines increase proteolysis, insulin resistance, and energy expenditure. The patient continues to lose muscle even during refeeding if inflammation and mobilization are not addressed.

Protein–energy malnutrition: marasmus versus kwashiorkor

Marasmus

Dominant energy deficit; marked loss of fat and muscle; adaptive metabolic slowing; usually no marked oedema.

Kwashiorkor

Relative protein deficit plus infection, inflammation and oxidative stress; altered barrier; oedema, fatty liver, skin and hair changes.

Key point

Oedema does not exclude malnutrition: inflammation changes albumin, capillary permeability and hepatic synthesis.

Disease-related malnutrition: inflammation rewrites metabolism



GLIM (Global Leadership Initiative on Malnutrition) refers to internationally recognized medical diagnostic criteria for identifying malnutrition in adults.

It combines **phenotypic criteria**, such as weight loss, low BMI, and reduced muscle mass, with **etiologic criteria**: reduced food intake or nutrient absorption, and inflammation or disease burden. Inflammation is not merely an accompanying phenomenon. It directly alters protein metabolism, enhances the hepatic acute-phase response, suppresses albumin synthesis, and impairs the anabolic response of skeletal muscle to amino acids and insulin.

Muscle as the central organ of malnutrition

Anabolic resistance

weaker response to protein, insulin and exercise

Ubiquitin–proteasome

accelerated breakdown of myofibrillar proteins

Autophagy

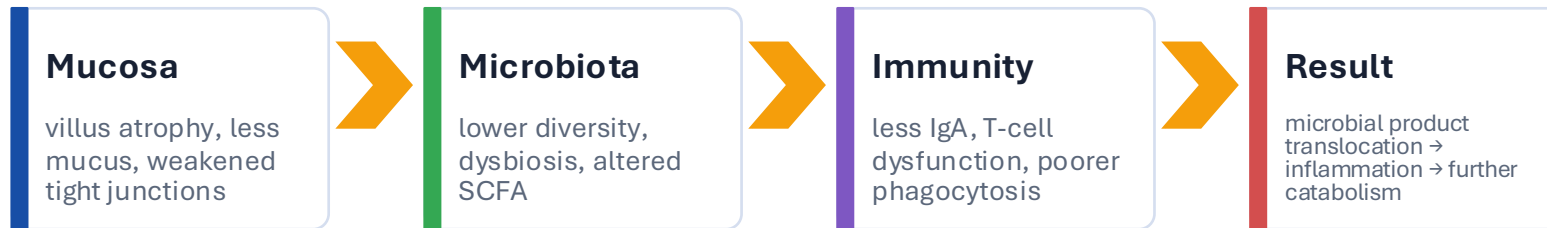
organelle recycling; adaptive acutely, harmful when chronic

Functional consequence

weak respiratory muscles, falls, immobility, longer hospital stay, poorer treatment tolerance

Skeletal muscle is the body's largest reservoir of amino acids. During starvation and inflammation, it serves as a source of substrates for gluconeogenesis, the acute-phase response, and immune cells. **Anabolic resistance** means that the same amount of protein fails to elicit a normal muscle protein synthesis response. It is aggravated by aging, immobility, insulin resistance, and inflammation.

Gut in undernutrition: barrier, microbiota, immunity



In malnutrition, the gut is both a victim and an active contributor. Nutrient deficiency reduces enterocyte turnover, mucus production, and the integrity of tight junctions. Dysbiosis alters microbial metabolites, particularly short-chain fatty acids. The resulting increase in intestinal permeability promotes translocation of bacterial products and inflammation, which in turn further drives catabolism. This is important in both childhood malnutrition and critically ill adults.

04 · Micronutrients and refeeding

Small molecules, large system failures.

Micronutrients: enzymes, hormones, membranes, immunity

Iron Hb, myoglobin, cytochromes → tissue hypoxia	Iodine T3/T4 → growth, neurodevelopment, basal metabolism	Vitamin D Ca/P homeostasis, muscle, immunomodulation	B12 / folate DNA synthesis, erythropoiesis, myelin	Zinc enzymes, skin, taste, immunity, wound healing	Vitamin A epithelium, vision, innate and mucosal immunity
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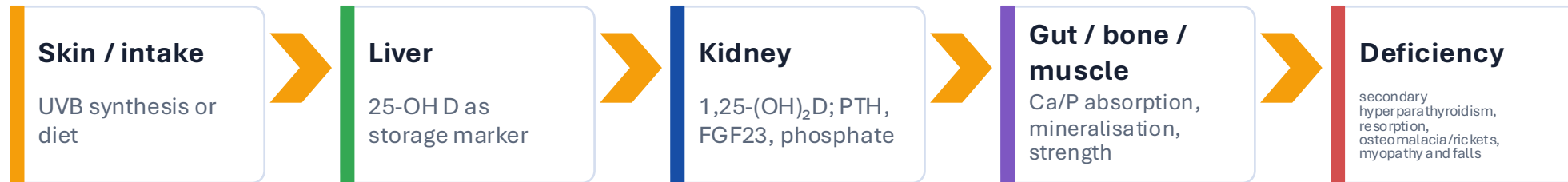
Micronutrients are not energy substrates, but enzymes, hormones, membranes, and immune functions cannot operate properly without them. The characteristic clinical presentation reflects the specific function of the deficient micronutrient. Deficiency may result from inadequate intake, malabsorption, increased losses, medications, or inflammation-related alterations in distribution. In chronic disease, assessment of body stores is complicated by the acute-phase response.

Iron: between deficiency and inflammation, hepcidin decides



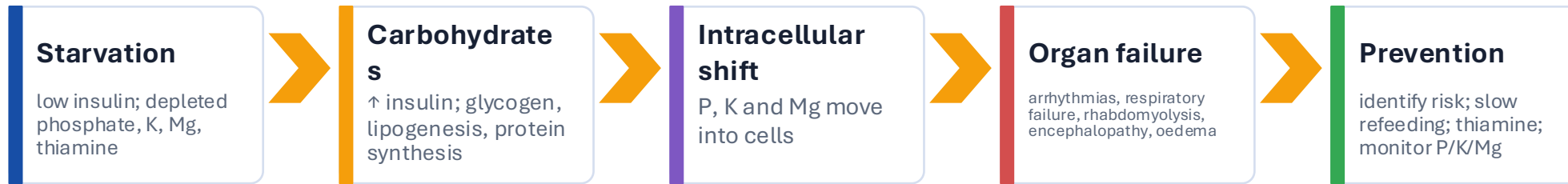
Hepcidin is the central regulator of iron homeostasis. Its levels increase during inflammation, particularly through IL-6 signaling. It binds to ferroportin, causing its internalization and degradation. As a result, iron cannot be released from enterocytes and macrophages into the plasma. Therefore, in anemia of chronic disease, ferritin levels may be normal or elevated, while iron remains functionally unavailable for erythropoiesis.

Vitamin D – Ca/P axis: bone is only the beginning



Vitamin D is a prohormone. Hepatic 25-hydroxylation produces the main marker of vitamin D stores, while the active form is generated primarily in the kidneys. Vitamin D regulates calcium and phosphate absorption and also influences muscle function. In deficiency, intestinal calcium absorption decreases, PTH levels rise, and bone resorption increases; severe deficiency may lead to osteomalacia or rickets. In clinical practice, the muscle phenotype is also important, particularly proximal muscle weakness and an increased risk of falls.

Refeeding syndrome: the dangerous error is to “fix hunger” too fast



Refeeding syndrome occurs when nutrition is reintroduced after a period of starvation. Carbohydrate intake increases insulin secretion. Cells begin to synthesize ATP, glycogen, and proteins, which requires phosphate, potassium, magnesium, and thiamine. Plasma phosphate levels may fall rapidly. Consequences include arrhythmias, respiratory failure due to respiratory muscle weakness, neurological symptoms, and edema. Therefore, a malnourished patient should not be refeed aggressively. Risk should first be assessed, with thiamine supplementation, electrolyte correction, and close monitoring.

Eating disorders: brain, starvation and somatic consequences

Starvation brain

changes in reward, anxiety,
cognitive rigidity and interoception

Endocrine adaptation

↓ leptin, ↓ T3, hypogonadotropic
hypogonadism, ↑ cortisol

Somatic risk

bradycardia, QT changes,
osteopenia, amenorrhoea,
hypothermia, refeeding

Clinical point

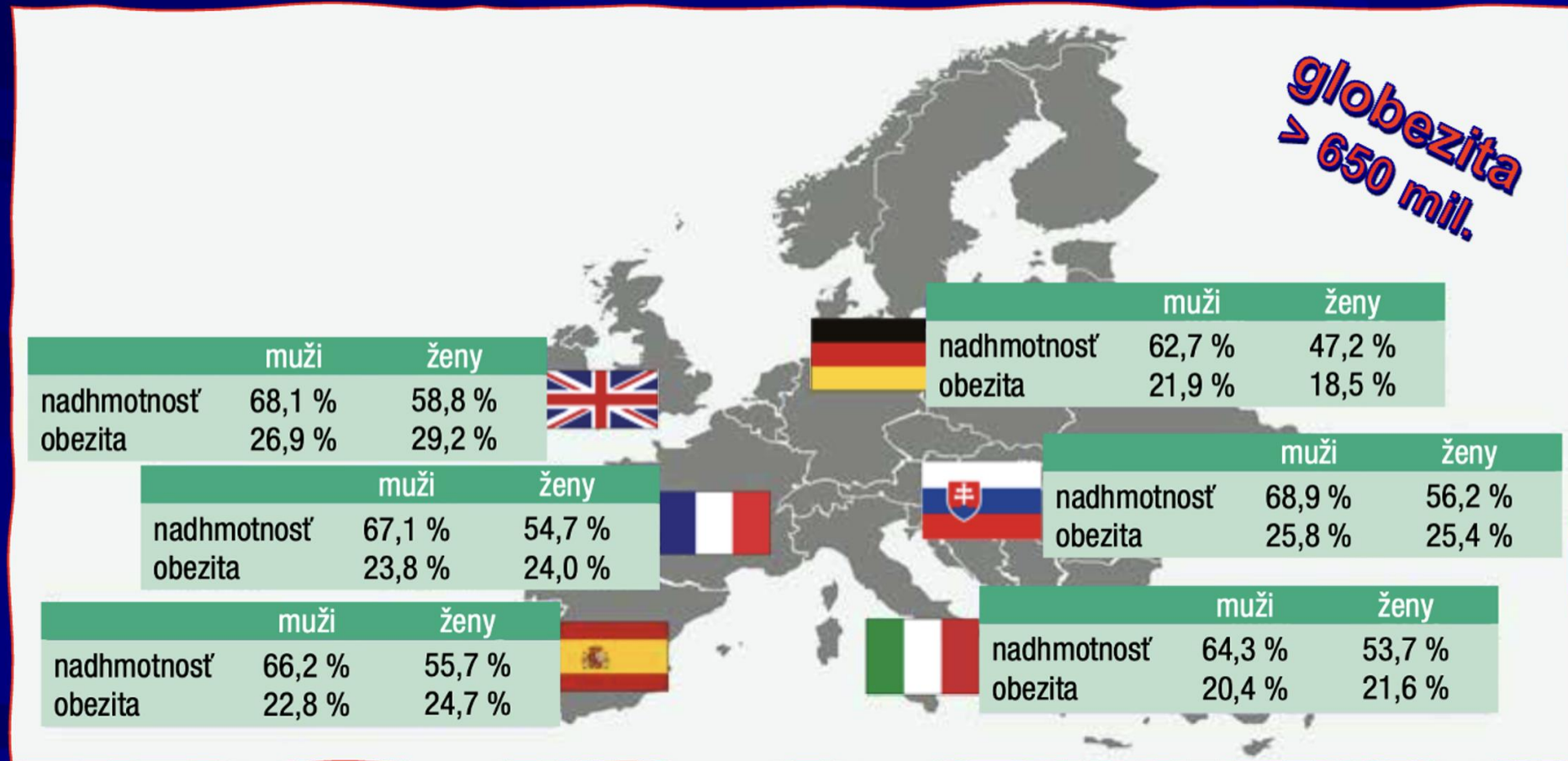
Even a psychiatric disorder requires
somatic thinking: electrolytes,
ECG, bone mass and
thermoregulation.

In anorexia nervosa, starvation itself becomes a biological maintaining factor. Alterations in the reward system, anxiety, interoception, and cognitive rigidity reinforce one another. Somatic pathophysiology is crucial: low leptin levels and hypogonadism lead to amenorrhea and bone loss; low T3 levels and bradycardia are energy-conserving adaptations; and refeeding syndrome may occur during treatment.

05 · Obesity and metabolic dysfunction

Adipose tissue is an endocrine and immune organ.

Obesity prevalence



➤ a global epidemic with widespread health and socio-economic consequences

Diseases and psychosocial problems related to (pre)obesity

metabolické	IR, hyperinzulinémia, PGT, DM2T poruchy metabolizmu lipidov: aDLP (najčastejšie), hTG, hypercholesterolémia hyperurikémia MAFLD zvýšenie koncentrácie Fbg a PAI-1	gynekologické	PCOS poruchy cyklu oligomenorea, amenorea, infertilita metrorágia komplikácie v gravidite a pri pôrode prolaps uteru zápaly rodidiel
kardiovaskulárne	AH hypertrofia a dilatácia ľavej komory ICHS znížená kontraktilita myokardu – systolicko-diastolická dysfunkcia – SZ arytmie náhla smrť CMP varixy TECH (zvýšenie koncentrácie Fbg a PAI-1 pri viscerálnej obezite)	onkologické	karcinóm endometria, krčka maternice, vaječníka, postmenopauzálna rakovina prsníka kolorektálny karcinóm, karcinóm žľazy, žľazových ciest, pankreasu a pečene adenokarcinóm obličiek karcinóm prostaty
endokrínne	hyperestrogenémia hyperandrogenizmus u žien mužský periférny hypogonadizmus funkčný hyperkortizolizmus (porucha plasticity a supresibility kortizolu) hyposekrécia rastového hormónu zmena aktivity sympatoadrenálneho systému	ortopedické	degeneratívne ochorenia kĺbov a chrbtice (najčastejšie gonartróza a koxartróza) epifyzeolýza v detskom veku
respiračné	hypoventilačné syndrómy až Pickwickov syndróm OSAS AB	kožné	ekzémy a mykózy strie celulitída hypertrichóza, hirsutizmus benígna papilomatóza
gastro-intestinálne a hepatobiliárne	gastroezofageálny reflux hiátová hernia cholecystitída, cholelitiáza pankreatitída MAFLD, NASH	neurodegeneratívne	Alzheimerova choroba, Parkinsonova choroba
nefrologické	nefropatia CKD nephrolitiáza karcinóm obličiek oneskorený nástup funkcie štepu po Tx obličky, resp. vyššie riziko akútnej reekcie	psychosociálne	spoločenská diskriminácia, sebaopodceňovanie, motivačné poruchy, depresie, úzkosť, únava, poruchy príjmu potravy, izolácia, nezamestnanosť, matrimoniálne problémy, diskriminácia
urologické/sexuologické	erektilná dysfunkcia BHP noktúria inkontinencia moču urolitiáza	chirurgické a anesteziologické	kardiorespiračné komplikácie TECH horšie hojenie a dehiscencia rán, hernie v pooperačných jazvách vyššie riziko úrazov
		iatrogénne	inadekvátne diéty nevhodná farmakologická liečba nesprávne indikovaná BMO
		infekčné	vyššia náchylnosť k infekciám, závažnejší priebeh infekčných ochorení (COVID-19, chrípka a podobne)

Obesity

- a chronic complex disease defined by excessive fat storage that can impair health
- BMI 30 or more kg/m²

Preobesity / Overweight

- state of excessive fat storage
- BMI 25-29.9 kg/m²

Children under 5 years old

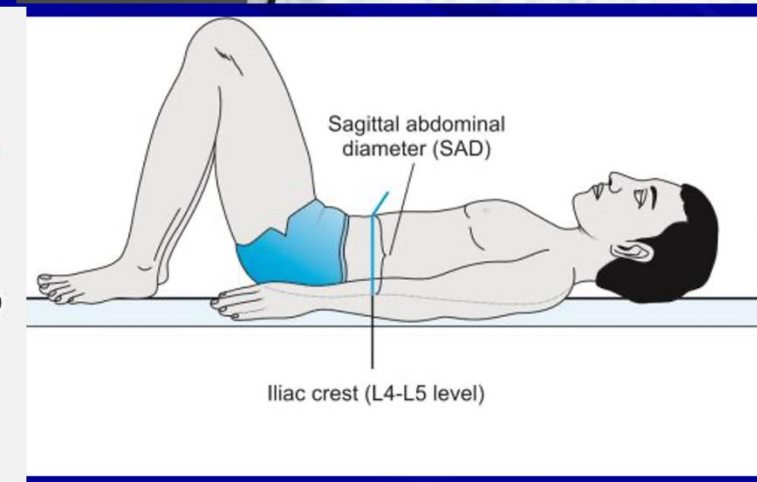
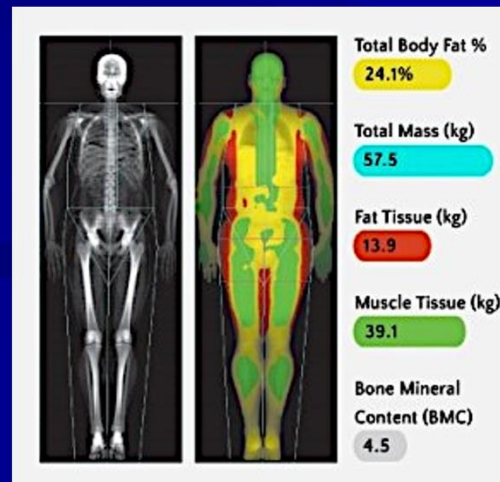
- overweight is a weight-for-height ratio greater than 2 standard deviations above the median of the WHO child growth standards;
- obesity is a weight-for-height ratio greater than 3 standard deviations above the median of the WHO child growth standards

Children from 5 yrs to 19 years

- overweight is a BMI for age greater than 1 SD above the median of the WHO reference height;
- obesity is greater than 2 standard deviations above the median of the WHO reference height.

Assessment of the amount of adipose tissue

- BMI (Quetelet index)
- SAD (sagito-abdominal diameter)
- air-displacement plethysmography
- bioelectrical impedance measurement
- Dual-energy X-ray absorptiometry (DEXA scan)
- CT, MR, 3D scan
- callipometry
- hydrometry
- underwater weighing





<https://www.cosmed.com/en/products/body-composition/bod-pod-gs-x>

Classification of (pre)obesity

WHO CLASSIFICATION OF WEIGHT STATUS

WEIGHT STATUS	BODY MASS INDEX (BMI), kg/m ²
Underweight	<18.5
Normal range	18.5 – 24.9
Overweight	25.0 – 29.9
Obese	≥ 30
Obese class I	30.0 – 34.9
Obese class II	35.0 – 39.9
Obese class III	≥ 40

Phenotypic classification of obesity

- metabolically unhealthy normal weight (MUNW)
- metabolically healthy (pre)obesity (MHO)
- metabolically unhealthy (pre)obesity (MUO)
- sarcopenic obesity (SO)

Phenotypic classification of obesity

- **Metabolically Healthy Normal Weight (MHNW):** Normal weight with good metabolic health.
- **Metabolically Unhealthy Normal Weight (MUNW):** Normal weight but with metabolic dysfunction, also known as Normal Weight Obesity (NWO) or Metabolically Obese Normal Weight (MONW).
- **Metabolically Healthy Obesity (MHO):** Obese but with preserved metabolic health.
- **Metabolically Unhealthy Obesity (MUO):** Obesity accompanied by metabolic complications like metabolic syndrome.
- **Sarcopenic Obesity (SO):** Low muscle mass in addition to excess fat.
- **Lipodystrophic Phenotype (LP):** Abnormal fat distribution

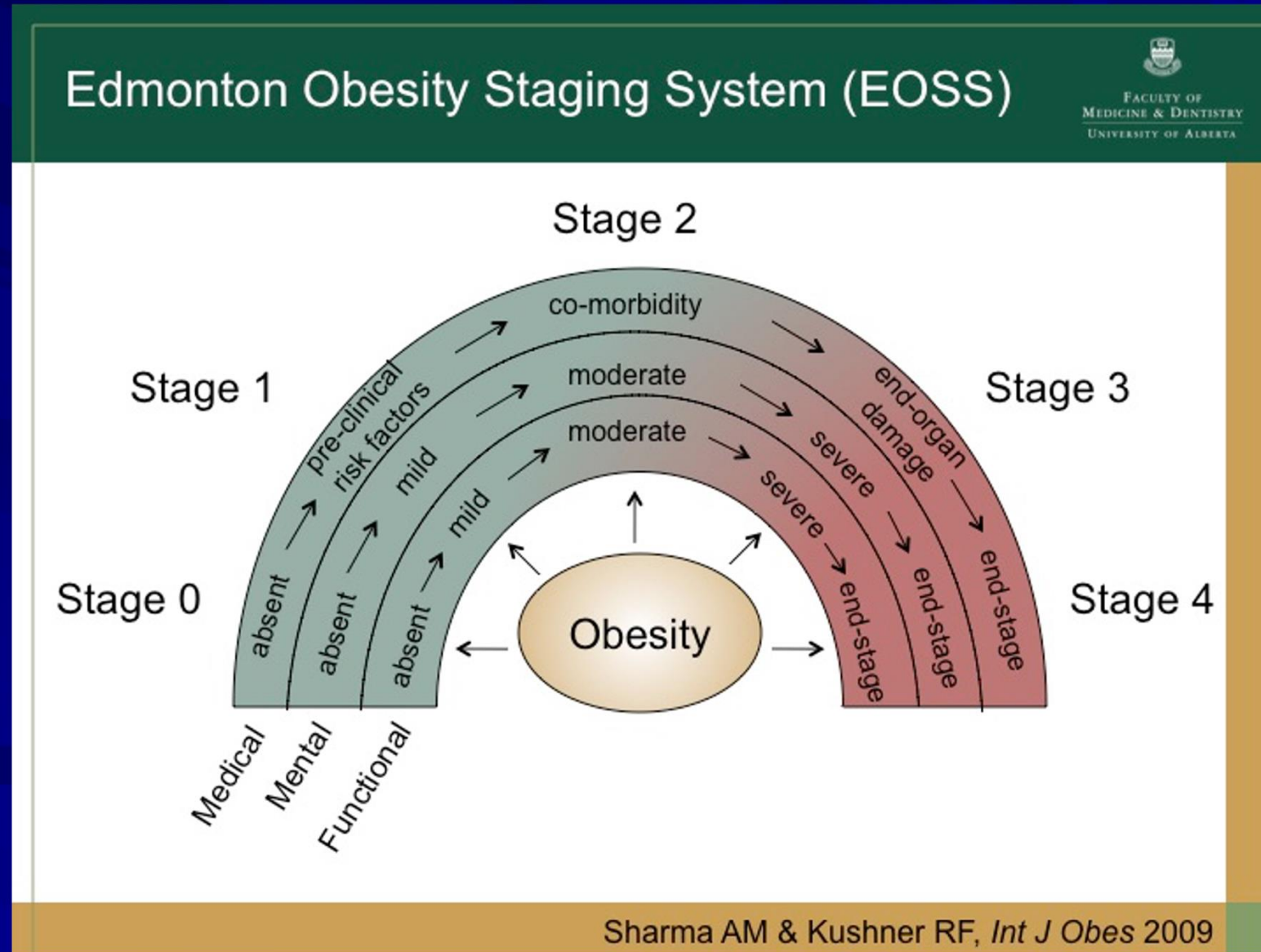
Adiposity-Based Chronic Disease (ABCD)

- a new diagnostic term for obesity, refers to the precise pathophysiological basis and avoids the stigma associated with the different uses of the multiple meanings of the term "obesity"
- based on 3 dimensions: etiology, degree of adiposity and health risks related to (pre)obesity

Edmonton Obesity Staging System

- stratifies the presence and severity of obesity-related health impairments
- a five-stage system of obesity classification that considers the metabolic, physical, and psychological parameters in order to determine the optimal obesity treatment
- EOSS has been reported to be a better predictor of mortality than BMI or metabolic syndrome.

Edmonton Obesity Staging System



Etiopathogenesis of (pre)obesity

- in up to 90% of cases, (pre)obesity is a complex multifactorial disease
- only in a very low percentage of individuals with obesity are we able to identify the exact cause of the development of (pre)obesity (monogene-related obesity, obesity caused by endocrinopathy, pharmacotherapy associated with weight gain, etc.)

Etiopathogenesis of (pre)obesity

- **genetically determined factors:**

- body weight, resting and postprandial energy expenditure, spontaneous physical activity, postprandial thermogenesis, taste preference for fats and carbohydrates, appetite regulation, ability to metabolize nutrients, body composition and fat distribution, behavior, eating and exercise habits of the individual

- **non-genetic factors:**

- "obesitogenic" environment - excessive energy intake and insufficient energy expenditure, increased consumption of ultra-processed foods, composition of the gut microbiome - decrease in phylogenetic diversity of the gut microbiome, psychological and emotional factors, chronic stress and inadequate sleep, social, economic, educational and cultural factors, environmental factors (persistent organic pollutants)

Etiology of obesity

- Monogenic causes of obesity
- Polygenic causes of obesity
- Causes responsible for excessive food intake

Polygenic obesity

- there are changes in several genes (currently more than 1000 loci are known), which in interaction with the obesogenic environment help develop the resulting phenotype of (pre)obesity
- the gene for melanocortin receptor 4 (MC4R) is associated with increased hunger, reduced satiety and increased total protein and fat intake
- the genes for adipokine and adipokine receptor, the gene encoding dopamine, serotonin and cannabinoid receptors

Polygenic obesity

- FTO gene (fat mass and obesity associated) is associated with obesity, IR, DM2, lipids and blood pressure
- FTO gene variants lead to increased total food intake as well as higher intake of fatty foods and reduced satiety and increased hunger
- SH2B1, KCTD15, MTCH2, BDNF, Mrap2 genes

Syndromic obesity

- diseases with Mendelian inheritance
- often mental retardation, dysmorphic features, and organ-specific developmental abnormalities
- more than 20 syndromes associated with obesity
- Prader-Willi syndrome, Bardet-Biedl syndrome, Albright hereditary osteodystrophy

Obesity syndromes

Zo zdrojov na internete

Bardet–Biedl syndrome	▼	Prader–Willi syndrome	▼	Albright's hereditary osteodystrophy
Alström syndrome	▼	Cohen syndrome	▼	WAGR syndrome
Down syndrome	▼	Fragile X syndrome	▼	Kallmann syndrome
Leptin	▼	Smith–Magenis syndrome	▼	Börjeson–Forssman–Lehmann syndrome
PCSK1 deficiency	▼	MC4R deficiency	▼	Melanocortin 4 receptor
Myt1l-variants Syndrome	▼	POMC deficiency	▼	Pseudohypoparathyroidism
SH2B1 deficiency	▼			

Monogenic obesity

- caused by a mutation in a single gene
- 5% of all patients with obesity
- severe obesity in childhood, may/may not be associated with endocrinological abnormalities or behavioral disorders
- there is no mental retardation, dysmorphic features or developmental anomalies
- the pathophysiology of monogenic obesity lies in the disruption of the so-called leptin-melanocortin axis, which plays an important role in the neuronal control of satiety and hunger, i.e. in maintaining the energy homeostasis of the organism

Monogenic obesity

Clinical features:

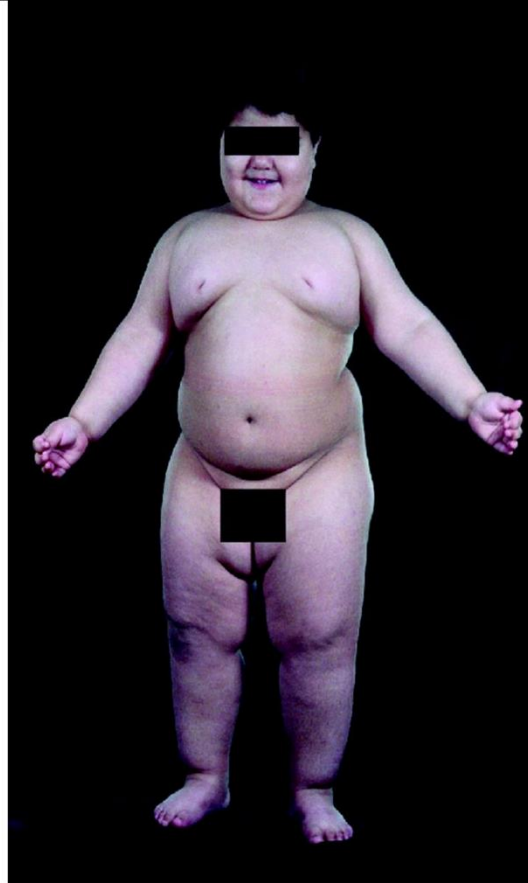
- obesity with hyperphagia starting in childhood (0-5 years), severe obesity in adults
- BMI > 30, in children > 97th percentile, or BMI > 2.5 SDS for a given age
- positive family history of obesity starting in childhood
- frequent association with endocrinopathies
- accessory features (short stature, red hair, hypogonadism, hypopituitarism)

Monogenic causes of obesity

- mutation of the LEP gene for leptin
- mutation of the LEPR gene for leptin receptor
- mutation of the SH2B1 gene for SH2B1 adaptor protein
- mutation of the POMC gene for proopiomelanocortin
- mutation of the PCSK1 gene for prohormone convertase 1 (PC1)
- mutation of the CPE gene for carboxypeptidase E
- mutation of the MC4R gene for melanocortin receptor 4
- mutation of the SIM1 gene for single-minded homolog 1 (SIM1)
- mutation of the GNAS gene for guanine nucleotide binding protein
- mutation of the BDNF gene for hypothalamic neurotrophic factor (BDNF)
- mutation of the MC3R gene for melanocortin 3 receptor
- mutation of the GPR24 gene for G-protein coupled receptor 24
- mutation of other genes



ob/ob mouse



3yr old weighing 42 kg



7yr old weighing 32 kg

A 3-year-old boy with **congenital leptin deficiency**, weighing 42kg before (left) and 32kg after (right) 4 years of treatment with recombinant leptin therapy.



Obesity: from BMI to functional tissue damage

BMI is screening

simple, cheap and useful at population level; misses fat distribution and muscle

Adiposity is pathogenic

visceral and ectopic fat carry higher metabolic risk

Clinical obesity

newer frameworks emphasise organ dysfunction, not BMI alone

Pathophysiology question

Where is fat stored, is adipose tissue inflamed, and what does it do to insulin, liver, muscle and vessels?

In 2025, a *Lancet Diabetes & Endocrinology* Commission published a framework emphasizing that BMI alone should not be used as the sole diagnostic criterion for obesity. It recommends confirming excess adiposity using additional measures and distinguishing between clinical and preclinical obesity. The key pathophysiological point is that risk depends on fat distribution, adipocyte function, inflammation, ectopic lipid deposition, and associated complications.

Adipose tissue: reservoir, endocrine organ, immune tissue

Leptin energy stores, satiety, reproduction	Adiponectin insulin sensitivity, anti-inflammatory signal	IL-6 / TNF-α low-grade inflammation, insulin resistance	FFA lipotoxicity in liver, muscle and pancreas	Angiotensinogen RAAS, blood pressure, vascular risk	PAI-1 prothrombotic state
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Adipocytes produce adipokines, cytokines, coagulation factors, and metabolic substrates. Healthy adipose tissue expands safely and stores lipids predominantly in subcutaneous depots. Dysfunctional adipose tissue becomes hypoxic, fibrotic, and inflamed. Adiponectin levels generally decrease in visceral obesity, accompanied by reduced insulin sensitivity. Leptin levels are elevated, but the satiety signal is impaired — a state known as leptin resistance.

Adipocyte expansion: hyperplasia is safer than hypertrophy

Metabolically flexible expansion

more small adipocytes, better vascularisation,
less hypoxia and inflammation

Metabolically unhealthy expansion

large adipocytes, hypoxia, fibrosis, macrophages
and free fatty-acid spillover

The boundary

when adipose tissue can no longer safely store
energy, lipids are deposited ectopically in liver,
muscle and pancreas

Insulin resistance: common node of obesity, inflammation and lipotoxicity

Muscle

less GLUT4 translocation, less glucose oxidation, lipid intermediates

Liver

gluconeogenesis persists while lipogenesis continues → dyslipidaemia

Adipose tissue

insulin fails to suppress lipolysis →
↑ FFA → further resistance

Molecular mechanisms

DAG/ceramides, PKC, ER stress, mitochondrial dysfunction, JNK/IKK β and inflammatory serine phosphorylation of IRS

Insulin resistance is not a single defect. In skeletal muscle, glucose uptake is reduced; in the liver, gluconeogenesis paradoxically persists while lipogenesis remains active; and in adipose tissue, insulin fails to adequately suppress lipolysis. At the molecular level, important mechanisms include lipid intermediates, endoplasmic reticulum stress, mitochondrial dysfunction, and inflammatory kinases that disrupt insulin signaling.

Ectopic fat: when the reservoir overflows

Liver

steatosis, insulin resistance, VLDL, inflammation/fibrosis

Muscle

intramyocellular lipids, lower metabolic flexibility

Pancreas

β -cell lipotoxicity, failure of insulin secretion

Heart / vessels

diastolic dysfunction, atherogenic environment

Key idea

Lipotoxicity explains why the same BMI does not imply the same risk.

Liver in energy excess: MASLD as a metabolic mirror



Microbiota and metabolism: mediator, not magic cause

SCFA

acetate, propionate, butyrate;
energy, epithelium, GLP-1/PYY
signals

Bile acids

FXR/TGR5 signalling, glucose,
lipids, thermogenesis

Endotoxaemia

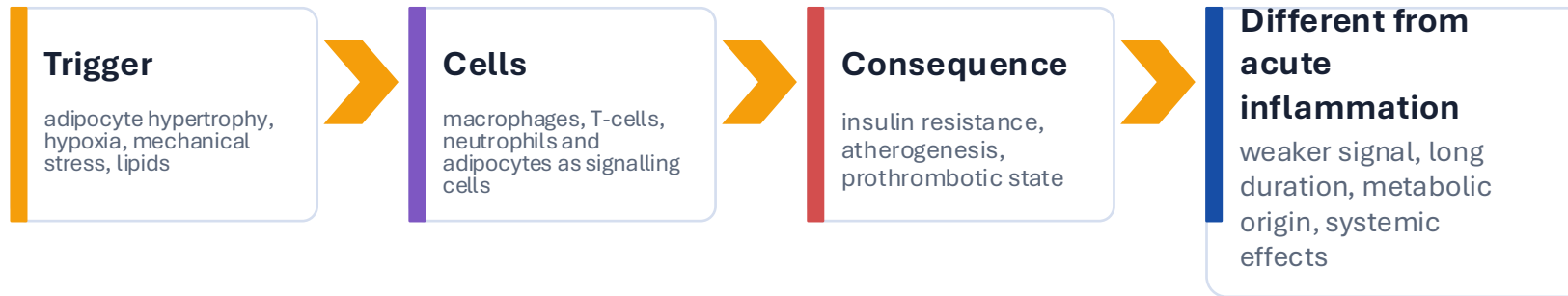
LPS, permeability, innate immunity,
low-grade inflammation

Interpretation

Microbiota is part of the diet–gut–
immune–metabolic network;
correlation alone is not causality.

The microbiota influences metabolism through short-chain fatty acids, bile acids, the intestinal barrier, and immune signaling. Many findings are associative rather than causal. The microbiota is not a simple switch that turns obesity on or off. Rather, it acts as a modulator within a complex network involving diet, genetics, physical activity, medications, sleep, stress, and immune tone.

Metaflammation: chronic, silent and metabolic



Metaflammation is a chronic, low-grade inflammatory state driven by metabolic overload. Adipose tissue undergoes changes in immune-cell composition, with an increased presence of pro-inflammatory macrophages and enhanced cytokine signaling. The result is not fever, but insulin resistance, endothelial dysfunction, a prothrombotic state, and long-term organ damage.

Incretins and twincretins: therapy has revealed physiology

Pancreas

glucose-dependent insulin secretion; lower glucagon

Brain

satiety, lower food intake, changes in reward circuits

Stomach / gut

slower gastric emptying, enteroendocrine signals

Pathophysiological message

Obesity can be treated through biological regulatory circuits, but a drug does not replace diagnosis of cause and complications.

GLP-1 and GIP are incretin signals. Modern anti-obesity medications have confirmed that energy balance is strongly regulated by biological mechanisms. Their effect is not simply due to mechanical appetite suppression; it involves gut–brain–pancreas signaling pathways.

→ **Body-weight regulation involves hormonal, neural, and metabolic feedback mechanisms.**

06 · Integrated view and clinical interpretation

One mechanism affects many organs.

Double burden of malnutrition: deficit and excess together

Obesity + sarcopenia

high body weight can hide low muscle reserve

Obesity + micronutrient deficit

vitamin D, iron, B12 and folate depending on intake, inflammation and malabsorption

Poverty + ultra-processed foods

energy accessible, but protein and micronutrient quality poor

Clinical lesson

assess body composition, function, inflammation and risky nutrients — not only BMI

The double burden of malnutrition means that deficiency and excess are not mutually exclusive. They may coexist within the same country, household, or even the same patient. Sarcopenic obesity is a good clinical example: the patient has a high BMI but low muscle strength and reduced functional reserve, a poorer prognosis during hospitalization, and a higher risk of complications.

How a pathophysiologist evaluates a patient

Phenotype

weight, BMI, waist circumference, muscle, oedema, weight loss

Aetiology

intake, absorption, inflammation, disease, drugs, alcohol, social factors

Function

grip strength, gait, fatigue, wound healing, immunity, organ complications

Laboratory: carefully

albumin, CRP, ferritin, electrolytes, glucose, lipids, liver enzymes

Body composition

BIA/DEXA/CT if available; muscle is a prognostic organ

A practical framework consists of **phenotype, etiology, and function**. The phenotype tells us **what we see**; the etiology explains **why it is present**; and function tells us **whether and how it is harming the patient**. Laboratory values must be interpreted in the context of inflammation. CRP can help determine whether a low albumin level is more likely related to inflammation. Ferritin is an iron-storage protein, but it is also a **positive acute-phase reactant**.

Typical laboratory traps

Low albumin

often inflammation, loss or dilution; not automatically protein deficit

High ferritin

may mean iron stores or inflammation; check transferrin saturation and CRP

Normal BMI

does not exclude sarcopenia, visceral fat or micronutrient deficit

Phosphate after feeding

a sudden drop warns of refeeding syndrome

HbA1c in deficiency

erythrocyte turnover, anaemia and transfusion can distort interpretation

A laboratory parameter does not translate directly into a diagnosis. Albumin is often a marker of inflammation and prognosis rather than a specific marker of protein intake. During refeeding, phosphate is a dynamic parameter—it may be normal before feeding but can fall sharply after the insulin surge.

Clinical case 1: risk of refeeding

Patient

BMI 16.5; 12% weight loss in two months; minimal intake for ten days; alcohol history; CRP high; Mg low-normal; wants to eat normally

Mechanism to look for

depleted intracellular phosphate/K/Mg; thiamine as carbohydrate-metabolism cofactor; insulin shift after refeeding

Predictable risk

arrhythmia and respiratory muscle weakness; oedema; neurologic complications

Correct response

cautious realimentation, thiamine, electrolyte monitoring and correction

What happens if we immediately give the patient a full caloric intake?

The answer: the insulin surge drives phosphate, potassium, and magnesium into the cells, thiamine requirements increase, and clinically there is a risk of arrhythmias, respiratory failure, and edema.

The appropriate pathophysiological response is cautious refeeding with close monitoring.

Clinical case 2: same BMI, different risk

Person A

BMI 31; high muscle mass; low waist circumference; normal glycaemia and triglycerides; good cardiorespiratory fitness

Person B

BMI 31; high visceral fat; low muscle strength; high triglycerides; elevated ALT; prediabetes and hypertension

Pathophysiological conclusion

Risk is determined by fat distribution, muscle reserve, inflammation and organ consequences.

Limitations of BMI. The same BMI may reflect different body compositions and different levels of metabolic risk. Person B is likely to have visceral adiposity, insulin resistance, hepatic steatosis, and a sarcopenic component. Person A may fall within the obesity range according to BMI, but their pathophysiological risk is different. This is why modern frameworks require assessment beyond BMI alone.

Integrated map of nutritional disorders



Nutritional stress may originate from inadequate intake, impaired absorption, inflammation, or excess energy supply. Its consequences then extend to hormonal axes, skeletal muscle, the liver, adipose tissue, the brain, and the immune system.

For example: **low intake → low insulin → lipolysis and gluconeogenesis → muscle proteolysis**; or **excess energy → adipocyte hypertrophy → inflammation → insulin resistance → ectopic fat deposition**.

Take-home messages

- 1 Malnutrition is a spectrum: deficit, excess and impaired utilisation of nutrients.
- 2 Muscle is a prognostic organ; loss of function is more clinically important than BMI alone.
- 3 Inflammation changes nutrition through hepcidin, albumin, proteolysis and insulin resistance.
- 4 Refeeding risk is predictable: phosphate, potassium, magnesium and thiamine come before rapid realimentation.
- 5 Obesity is tissue dysfunction: adipokines, lipotoxicity, microbiota and brain circuits require a serious medical approach without moralising.

Selected sources

WHO. Malnutrition fact sheet / health topic, aktualizované údaje a rámec foriem malnutrície.

WHO. Obesity and overweight; globálne údaje a definície BMI, nadváhy a obezity.

Global Leadership Initiative on Malnutrition (GLIM). Criteria for diagnosis of malnutrition, Clin Nutr. 2019.

ASPEN Consensus Recommendations for Refeeding Syndrome, Nutr Clin Pract. 2020.

Lancet Diabetes & Endocrinology Commission. Definition and diagnostic criteria of clinical obesity, 2025.

NIH Office of Dietary Supplements: Iron Health Professional Fact Sheet, aktualizácia 2025.

UNICEF / Child Nutrition Report 2025: posun v globálnej detskej malnutrícii smerom k obezite.

NICE NG246 Overweight and obesity management, 2025; súčasný klinický rámec hodnotenia.

Metabolic syndrome

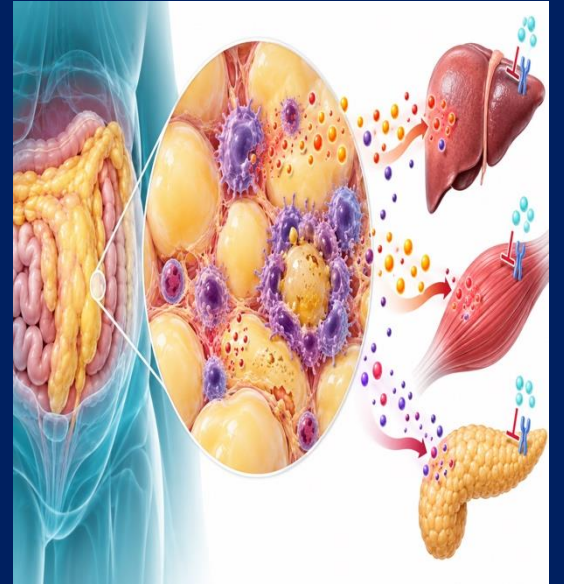
Pathophysiology of Metabolic Syndrome

current pathomechanisms and clinical implications

insulin resistance

ectopic fat

immunometabolism



- Metabolic syndrome is not merely the sum of risk factors; it is a systemic disorder of communication among adipose tissue, the liver, skeletal muscle, blood vessels, the pancreas, the kidney, and the CNS.
- **a dynamic pathophysiological network**
- **Diagnostic criteria are important, but they represent only a clinical cross-section of complex processes:** visceral adiposopathy, insulin resistance, atherogenic dyslipidemia, metabolically driven hypertension, MASLD/MASH, β -cell dysfunction, endothelial dysfunction, a procoagulant state, and cardiorenal injury.

- explain the role of visceral fat, ectopic fat, and insulin resistance
- link dyslipidemia, hypertension, MASLD/MASH, atherosclerosis, and type 2 diabetes
- recognize newer mechanisms: immunometabolism, mitochondria, ER stress, the microbiome, and circadian rhythm
- derive therapeutic mechanisms from pathophysiology

Main message of the lecture

Metabolic syndrome is a disorder of energy and signal flow between organs. This is why one patient may simultaneously have an increased waist circumference, elevated blood pressure, abnormal lipids, dysglycemia, and often hepatic steatosis.

Teaching axis

1. adipose tissue → 2. insulin → 3. liver/skeletal muscle → 4. vessels/kidney → 5. pancreas → 6. therapeutic disruption of pathological loops



Criteria		MetS	WHO (1998)	EGIR (1999)	NCEP: ATP III (2001)	AACE (2003)	IDF (2005)	AHA/NHLBI (2009)
Central obesity	WC	-		≥94 cm (M) ≥80 cm (W)	>102 cm (M) >88 cm (W)	-	≥94 cm (M) ≥80 cm (W) *	≥94 cm (M) ≥80 cm (W) *
	BMI	>30 kg/m ²		-	-	-	>30 kg/m ²	-
	WTH	>0.90 (M) >0.85 (W)		-	-	-	-	-
Increased TG	TG	≥150 mg/dL #		>177 mg/dL or under Tx #	≥150 mg/dL	≥150 mg/dL	≥150 mg/dL or under Tx	≥150 mg/dL or under Tx
Reduced HDL	HDL	<35 mg/dL (M) <39 mg/dL (W) #		<39 mg/dL or under Tx #	<40 mg/dL (M) <50 mg/dL (W)	<40 mg/dL (M) <50 mg/dL (W)	<40 mg/dL (M), <50 mg/dL (W), or under Tx	<40 mg/dL (M), <50 mg/dL (W), or under Tx
Increased BP	BP	≥160/90 mmHg		≥140/90 mmHg or under Tx	≥130/85 mmHg	>130/85 mmHg	≥130/85 mmHg or under Tx	≥130/85 mmHg or under Tx
Increased glucose concentration	IFG	≥110 mg/dL		≥110 mg/dL (2 measures)	≥110 mg/dL	110–125 mg/dL	≥100 mg/dL or under Tx	≥100 mg/dL or under Tx
	IGT ¶	140–200 mg/dL		-	-	140–200 mg/dL	-	-
	IR	Yes †		Yes ‡	-	-	-	-
	DM	≥126 mg/dL		-	-	-	Yes	Yes
Other	MA	UAE ≥ 20 ug/min UACR ≥ 20 mg/g		-	-	-	-	-
Diagnosis		IGR §, DM, or IR + ≥2 other criteria		IGR § or IR + ≥2 other criteria	≥3 criteria	≥2 criteria	Central obesity + ≥2 other criteria	≥3 criteria

¶ Impaired glucose tolerance is defined as 2-h glucose levels of 140–200 mg/dL on the 75-g oral glucose tolerance test. † Insulin resistance refers to glucose uptake below lowest quartile for background population under investigation in euglycemic hyperinsulinemia conditions. ‡ Insulin resistance refers to top 25% of fasting insulin concentrations from non-diabetic population. § Impaired glucose regulation refers to impaired fasting glucose or impaired glucose tolerance. * Central obesity is defined as ethnicity-specific values of waist circumference: United States ≥ 102 cm (men) or ≥88 cm (women); Europids ≥ 94 cm (men) or ≥80 cm (women); and Asians ≥ 90 cm (men) or ≥80 cm (women). # Increased triglyceride and decreased high-density lipoprotein cholesterol are considered one criterion in WHO (1998) and EGIR (1999) definitions. Abbreviations: M = men; W = women; BMI = body mass index; BP = blood pressure; DM = diabetes mellitus; HDL = high-density lipoprotein cholesterol; TG = triglyceride; IGR = impaired glucose regulation; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; IR = insulin resistance; MA = microalbuminuria; Tx = treatment; UAE = urinary albumin excretion rate; UACR = urinary albumin-to-creatinine ratio; WC = waist circumference; WTH = waist-to-hip ratio; WHO = World Health Organization; EGIR = European Group for the Study of Insulin Resistance; NCEP: ATP III = National Cholesterol Education Program Adult Treatment Panel III; AACE = American Association of Clinical Endocrinology; IDF = International Diabetes Federation; AHA/NHLBI = American Heart Association/National Heart, Lung, and Blood Institute.

Harmonized definition

Metabolic syndrome is diagnosed when at least 3 of 5 components are present. Increased waist circumference is important, but it is not absolutely required in all definitions.

Five components

central obesity • ↑ triglycerides • ↓ HDL-C • ↑ blood pressure • ↑ fasting glucose or treatment of the corresponding disorder

Pathophysiological message

The criteria capture the phenotype. Two patients with the same three components may have different dominant causes.

Waist / visceral fat

failure of safe energy storage

TG ↑

increased FFA flux to the liver, VLDL ↑

HDL-C ↓

atherogenic dyslipidemia

BP ↑

sympathetic nervous system, RAAS, sodium, endothelium

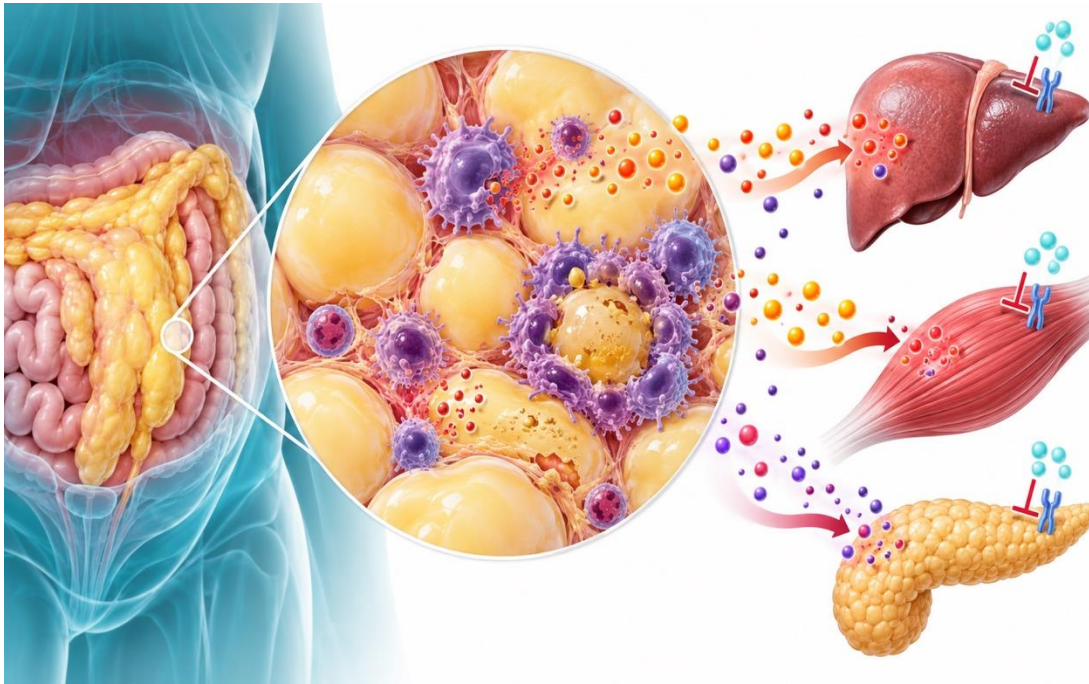
Glucose ↑

hepatic/muscle IR + β -cell reserve

Insulin resistance is mechanistically central, although fasting insulin and HOMA-IR are not routinely included in diagnosis.

The harmonized criteria proposed by Alberti et al. in 2009 unified several earlier definitions. In clinical practice, metabolic syndrome is defined by the presence of three or more of five components.

The definition is a tool, not an explanation. The criteria identify the visible consequences of an underlying disorder: dysfunctional adipose tissue, insulin resistance, ectopic fat deposition, inflammation, endothelial dysfunction, and impaired renal regulation of blood pressure.



1. Energy excess

genetic susceptibility + sedentary lifestyle + hypercaloric diet + sleep/stress

2. Breaking point in adipose tissue

adipocytes hypertrophy; hypoxia, fibrosis, inflammation, and adipokine dysfunction develop

3. Systemic response

FFAs, cytokines, adipokines, and lipid mediators alter the liver, skeletal muscle, blood vessels, pancreas, kidney, and CNS

Adiposopathy = adipose tissue as a diseased endocrine and immune organ.

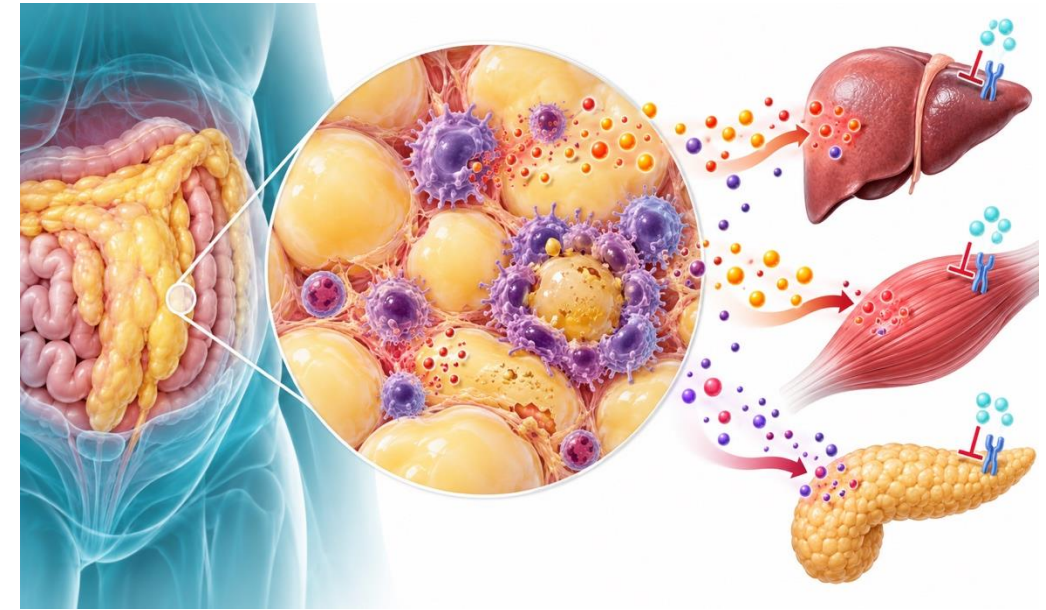
The problem is not merely the amount of fat, but the biological quality of adipose tissue. Relatively safe adipose tissue expansion is characterized by adequate angiogenesis, the formation of smaller adipocytes, and preserved insulin sensitivity. High-risk expansion is characterized by adipocyte hypertrophy, hypoxia, fibrosis, immune-cell infiltration, and ectopic fat deposition.

Visceral fat is particularly important for the liver because its metabolites and free fatty acids reach the liver through the portal circulation. More recent concepts view adipose tissue as an organ that communicates through adipokines, cytokines, lipid mediators, and extracellular vesicles.

adipocyte hypertrophy → hypoxia → HIF-1 α , fibrosis, ER stress
chemokines recruit monocytes; macrophages form crown-like structures
↑ TNF- α , IL-6, MCP-1; ↓ adiponectin
insulin no longer suppresses lipolysis → high free-fatty-acid flux
sterile low-grade inflammation becomes systemic

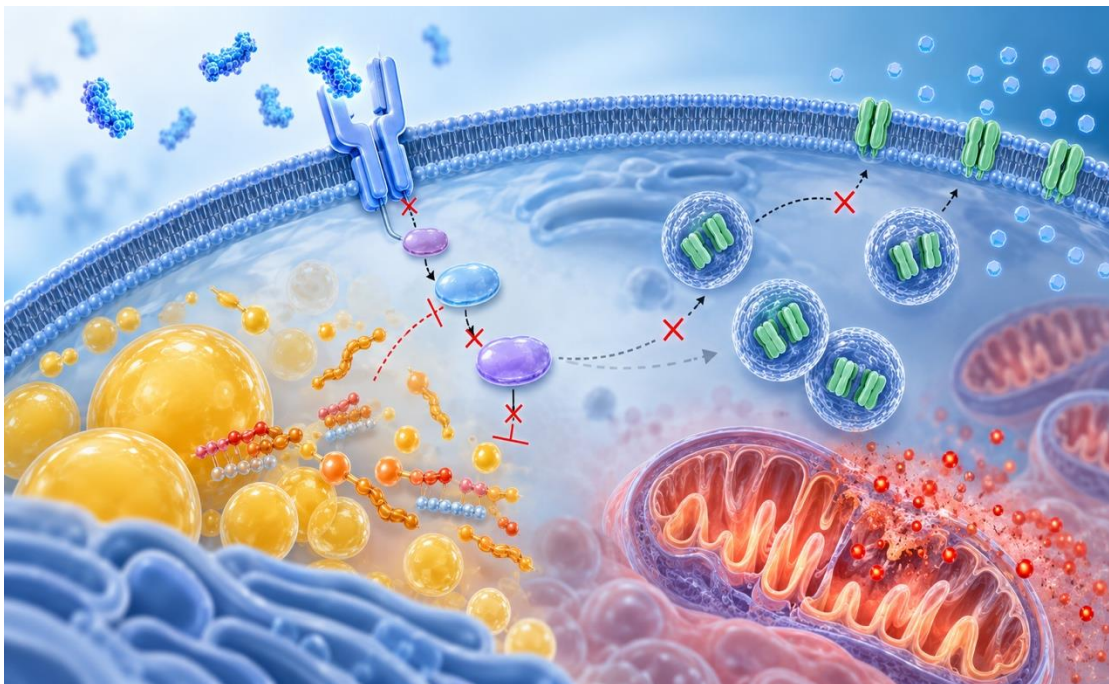
*Insulin normally inhibits lipolysis in adipocytes. In adipocyte insulin resistance, this inhibitory effect is lost. The flux of free fatty acids increases, particularly toward the liver. Enlarged adipocytes have poorer oxygen supply, activate HIF-1 α , and promote fibrosis. Macrophages surround damaged adipocytes, forming **crown-like structures**.*

*Adiponectin levels decrease, impairing fatty acid oxidation and insulin sensitivity. Leptin levels increase, but leptin resistance develops. This represents **sterile metabolic inflammation**, not infection.*



Key mechanism

When insulin no longer inhibits hormone-sensitive lipase, adipose tissue “spills” fatty acids into the liver and skeletal muscle.



Normal

insulin receptor $\rightarrow$ IRS-1/2 $\rightarrow$ PI3K $\rightarrow$ Akt $\rightarrow$ GLUT4; inhibition of gluconeogenesis and lipolysis

In MetS

serine phosphorylation of IRS, JNK/IKK β /PKC, ROS, and lipid intermediates weaken the signal

Selective IR

the liver may continue to produce glucose while also carrying out lipogenesis; both hyperglycemia and $\uparrow$ TG/VLDL develop

DAG and ceramides activate PKC
mitochondrial ROS and ER stress amplify inflammation
hyperinsulinemia is both a compensatory and a pathogenic signal

In skeletal muscle, insulin promotes GLUT4 translocation and glucose uptake. In the liver, it suppresses gluconeogenesis. In adipose tissue, it inhibits lipolysis. In metabolic syndrome, inflammatory kinases, PKC, and lipid intermediates disrupt IRS signaling.

Skeletal muscle

↓ GLUT4, ↓ glycogen synthesis, ↓ metabolic flexibility

Liver

↑ gluconeogenesis, ↑ de novo lipogenesis, ↑ VLDL, MASLD

Adipose tissue

↑ lipolysis despite insulin, ↓ adiponectin, ↑ FFAs/cytokines

A single laboratory phenotype arises from simultaneous impairment of multiple organ loops.

CNS

leptin/insulin resistance, appetite, sympathetic drive

Blood vessels

↓ NO, ↑ endothelin-1, oxidative stress, intimal inflammation

Kidney

sodium retention, hyperfiltration, albuminuria, CKD

Insulin resistance is not uniform across all tissues. Skeletal muscle has impaired glucose uptake and loses metabolic flexibility. The liver continues to produce both glucose and fat. Adipose tissue undergoes uncontrolled lipolysis. The CNS maintains appetite and sympathetic activation. Blood vessels lose their nitric oxide-mediated response, while the kidneys retain sodium.

The patient does not have five random problems; rather, these abnormalities represent a single network of organ dysregulation.

**FFAs to the liver
flux from visceral fat**

**VLDL ↑
hepatic TG export**

**TG-rich HDL/LDL
CETP-mediated lipid
exchange**

**HDL-C ↓
faster catabolism**

**small dense LDL
oxidizes more easily and
penetrates the intima**

LDL-C may appear unremarkable, but the number of atherogenic particles is higher
apoB and non-HDL-C often reflect the atherogenic burden better than LDL-C alone
hypertriglyceridemia, low HDL, and small dense LDL form the typical MetS profile

Hyperinsulinemia
sympathetic drive, Na⁺ retention, vascular reactivity

RAAS in adipose tissue
angiotensinogen, aldosterone, inflammation, and fibrosis

Endothelium
↓ NO, ↑ endothelin-1, oxidative stress

Hypertension is not an incidental passenger; it arises from the same energy-inflammatory environment.

Kidney
sodium, hyperfiltration, albuminuria, CKD

Vascular wall
stiffness, remodeling, adventitial and intimal inflammation

Metabolic hypertension has multiple mechanisms. Hyperinsulinemia activates the sympathetic nervous system and promotes sodium retention. Adipose tissue produces components of the RAAS. The endothelium loses its ability to generate nitric oxide, while endothelin-1 production and oxidative stress increase. The kidneys retain sodium, and with prolonged exposure, hyperfiltration and albuminuria may develop.

→ **Therapeutic implications:** reduction of visceral fat, physical activity, lower sodium intake, adequate sleep, and pharmacotherapy can act simultaneously on several pathophysiological nodes.

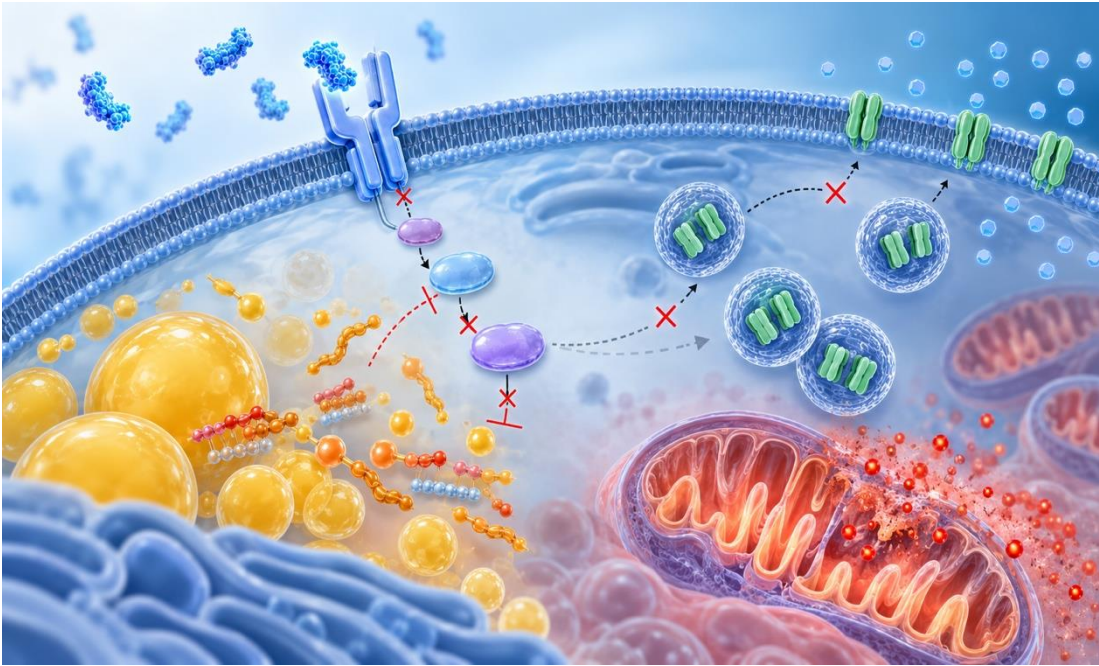
- metabolic inflammation is sterile, low-grade, and chronic
- macrophages, T cells, and neutrophils alter insulin signaling
- the NLRP3 inflammasome responds to lipids, ROS, and DAMP signals
- TNF- α , IL-1 β , and IL-6 link adipose tissue, the liver, and the vessel wall
- inflammation is both a cause and a consequence of insulin resistance

Three triggers of inflammation

1. **lipotoxicity:** DAG, ceramides, oxidized LDL
2. **organelle stress:** mitochondria, ER stress, ROS
3. **microbiome/barrier:** LPS, metabolites, TLR signals

Core mechanism

Inflammatory kinases alter phosphorylation of IRS proteins and inhibit the insulin pathway.



Lipotoxic intermediates

DAG, ceramides, and acylcarnitines are not inert fat; they are signaling molecules that disrupt the insulin pathway.

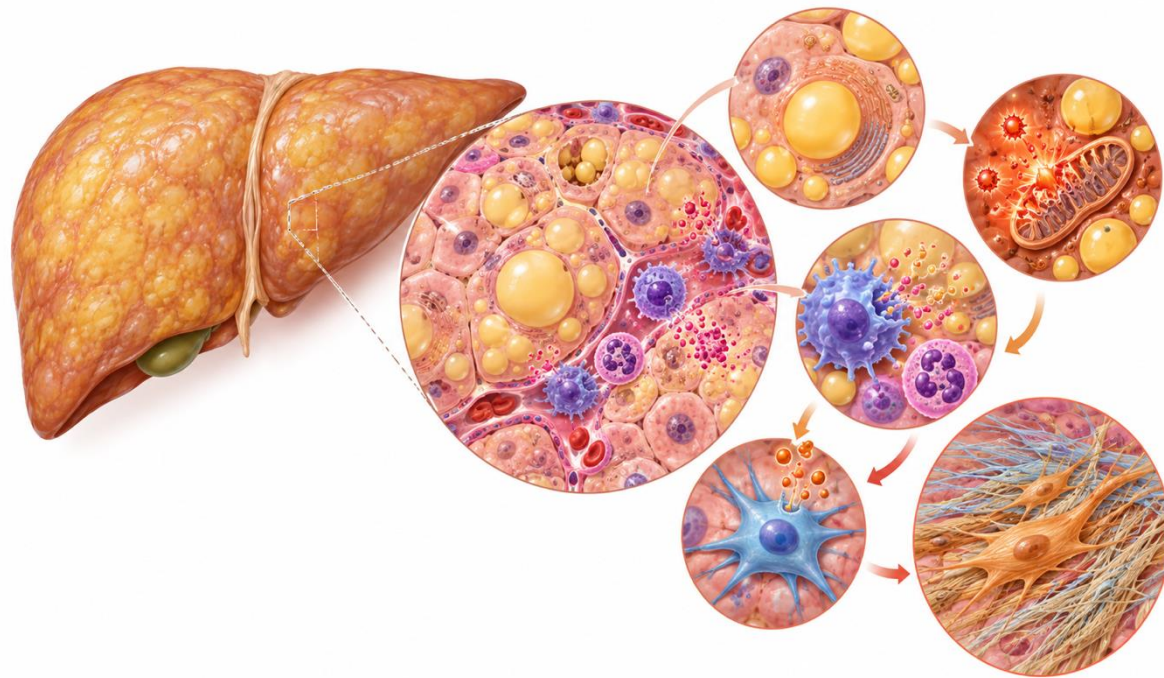
Mitochondria

substrate overload → incomplete oxidation, ROS, impaired fusion/fission and mitophagy.

Endoplasmic reticulum

chronic unfolded protein response links nutrient excess with inflammation, apoptosis, and insulin resistance.

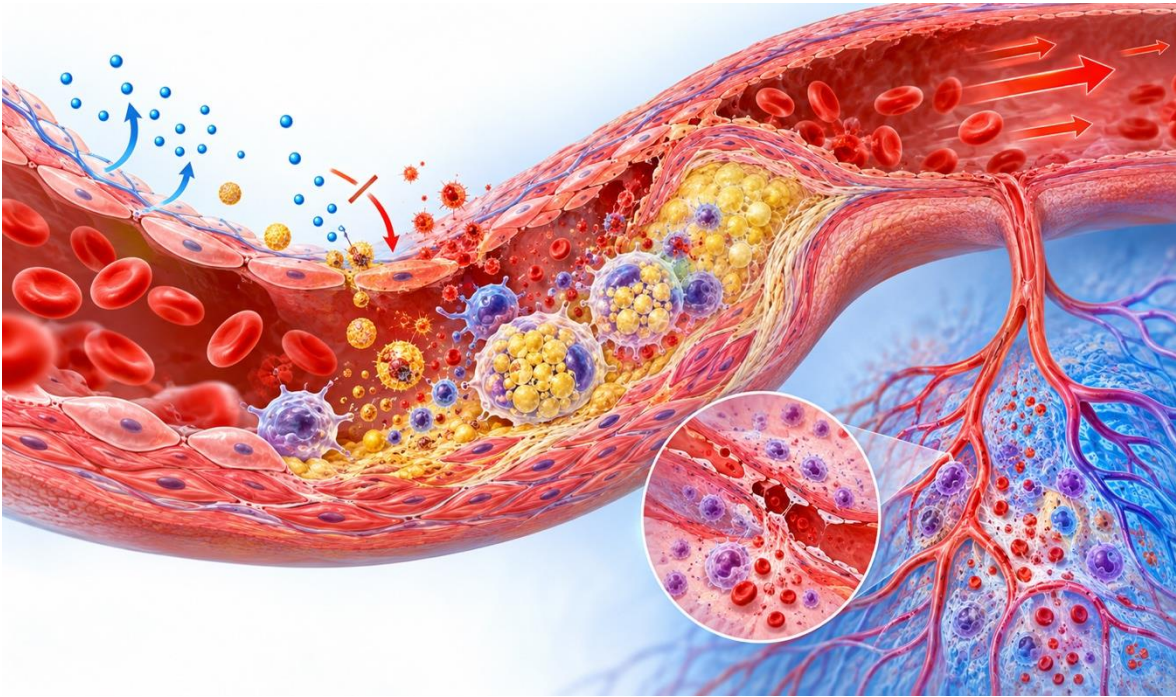
Cellular stress converts energy excess into signaling dysfunction.



↑ FFA supply from adipose tissue + ↑ de novo lipogenesis
hepatic insulin resistance: glucose production escapes,
lipogenesis persists
steatosis → lipotoxicity → inflammation → hepatocyte
ballooning → fibrosis
2023: NAFLD is replaced by MASLD; NASH by MASH
MASLD: steatosis + at least one cardiometabolic risk
factor

The liver is a metabolic amplifier of the syndrome.

*Since 2023, an international consensus has recommended the terminology **MASLD** instead of NAFLD and **MASH** instead of NASH. The rationale is to more accurately reflect the metabolic basis of the disease and to use less stigmatizing terminology. **MASLD** refers to hepatic steatosis in the presence of at least one cardiometabolic risk factor. The liver receives fatty acids from visceral adipose tissue, synthesizes fat de novo, and exports VLDL. When its adaptive capacity is exceeded, lipotoxicity develops, together with activation of Kupffer cells and hepatic stellate cells, inflammation, and fibrosis.*



Endothelium

insulin resistance $\downarrow$ eNOS/NO, $\uparrow$ endothelin-1 and vasoconstriction

Intima

small dense LDL + oxidation + monocyte infiltration $\rightarrow$ foam cells

Thrombosis

PAI-1, fibrinogen, platelets, and inflammation $\rightarrow$ procoagulant state

Microcirculation

impaired perfusion, capillary rarefaction, and glycation promote organ damage

In the vasculature, lipids, inflammation, blood pressure, and glycation converge. Under normal conditions, insulin promotes nitric oxide production through the PI3K–Akt–eNOS pathway. In insulin resistance, this vasodilatory pathway is impaired, while vasoconstrictive and proliferative signaling may persist.

Small dense LDL particles more readily penetrate the intima, undergo oxidation, and promote foam-cell formation. Adipose tissue and the endothelium increase PAI-1, fibrinogen, and platelet activation. Therefore, metabolic syndrome promotes both atherosclerosis and atherothrombosis.

- insulin resistance induces compensatory hyperinsulinemia
- the β -cell expands functionally and in mass — but only up to a limited reserve
- gluco- and lipotoxicity activate ER stress, ROS, and apoptosis
- islet amyloid, inflammation, and genetic susceptibility accelerate failure
- prediabetes is a phase of declining β -cell reserve

Initially, insulin resistance may not yet increase blood glucose levels because pancreatic β -cells compensate by increasing insulin secretion. Therefore, normal glycemia does not exclude metabolic stress. Over time, however, glucotoxicity, lipotoxicity, endoplasmic reticulum stress, oxidative stress, islet amyloid deposition, and inflammation progressively contribute to β -cell dysfunction.

Clinical message: prediabetes is not a “minor problem,” but a stage in which β -cell reserve is already declining.

Step 1

IR + normoglycemia

Step 2

hyperinsulinemia

Step 3

prediabetes

Step 4

β -cell failure

Step 5

T2D

Metabolites

SCFAs, secondary bile acids, TMAO, and indoles modulate energetics, inflammation, and endocrine signals.

Barrier

increased intestinal permeability → metabolic endotoxemia; LPS activates TLR4 and inflammatory kinases.

Gut–liver axis

portal flow carries microbiome-derived signals to the liver, where they modify steatosis and inflammation.

the microbiome is a modulator, not a single simple cause
effects depend on diet, medications, host genetics, and barrier function
clinically relevant mechanisms mainly involve fiber, bile acids, incretins, and inflammation

The gut is a metabolic organ; dietary change alters signals, not only calories.

- sleep deprivation worsens insulin sensitivity and appetite signals
- circadian desynchronization alters glucose tolerance and lipid metabolism
- chronic stress activates the HPA axis and sympathetic nervous system
- cortisol and catecholamines promote visceral adiposity, lipolysis, and blood pressure
- meal timing, light exposure, and regularity of routine are metabolic signals

Neuroendocrine loop

The CNS integrates sleep, stress, leptin, insulin, ghrelin, sympathetic tone, and cortisol. Therefore, the same diet may not have the same metabolic effect under a different daily regimen.

Practical message

MetS cannot be explained by food alone; daily routine, sleep, physical activity, and stress alter the hormonal background.

Stage 0
no risk factors

Stage 1
excess/dysfunctional
adiposity, prediabetes

Stage 2
metabolic risk factors or
CKD

Stage 3
subclinical CVD in the
CKM context

Stage 4
clinical CVD with CKM
risk factors

AHA 2023

Cardiovascular–kidney–metabolic health emphasizes the continuum between adipose/metabolic dysfunction, CKD, and CVD.

Stage 0
no risk factors

Stage 1
excess/dysfunctional
adiposity, prediabetes

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subclinical CVD in the
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clinical CVD with CKM
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AHA 2023

Cardiovascular–kidney–metabolic health emphasizes the continuum between adipose/metabolic dysfunction, CKD, and CVD.

*In 2023, the AHA introduced the **CKM framework — cardiovascular-kidney-metabolic syndrome**. It represents a broader concept than the traditional metabolic syndrome. It emphasizes that metabolic dysfunction, kidney disease, and cardiovascular disease form a continuum.*

Explanation of the stages: from the absence of risk factors, through excess or dysfunctional adiposity, metabolic risk factors and/or CKD, subclinical cardiovascular disease, and finally to clinically manifest cardiovascular disease.

Metabolically healthier obesity

greater capacity of subcutaneous fat to expand, less ectopic fat, lower inflammation — often a transient state

Metabolically unhealthy normal weight

visceral/ectopic fat, low muscle mass, genetics, sleep, stress, medications, or endocrine causes

Clinical risk depends more on tissue distribution and function than on BMI alone.

Sarcopenic obesity

less muscle reserve means less capacity for glucose disposal; higher frailty and a more inflammatory profile

Life course

puberty, pregnancy, menopause, aging, and PCOS alter insulin sensitivity and fat distribution

BMI is a useful population-level indicator, but from a pathophysiological perspective, what matters is fat distribution, ectopic fat, inflammation, and muscle mass. Patients with the same BMI may have very different amounts of visceral fat and hepatic steatosis. Conversely, a person with normal body weight may still have significant metabolic risk.

CAVE: sarcopenic obesity and PCOS. Metabolically healthy obesity may not represent a permanently safe state.

Weight reduction

↓ visceral fat, ↓ FFAs, ↑ insulin sensitivity

Physical activity

AMPK, GLUT4, mitochondria, muscle as a glucose reservoir

Fiber-rich diet

microbiome, bile acids, satiety, postprandial glycemia

Sleep/stress

cortisol, sympathetic drive, appetite, blood pressure

GLP-1/GIP strategies

body weight, appetite, glycemia, liver fat — according to indication

SGLT2 inhibitors

glycosuria, natriuresis, cardiorenal protection — according to indication

Good treatment disrupts pathological loops, rather than merely “correcting numbers” in the laboratory.

Patient

42 years, sedentary job, 5 h sleep

waist 108 cm, BP 145/92

TG 2.4 mmol/L, low HDL

fasting glucose 6.0 mmol/L

ALT mildly ↑, ultrasound steatosis

Question 1

Which pathological loop is likely dominant?

Question 2

How would you connect adipose tissue, liver, blood pressure, and lipids into one causal map?

Question 3

Which three mechanistic interventions could disrupt the loop?

The correct answer should not be merely “lose weight”; it should be: reduce visceral/ectopic fat, restore insulin sensitivity, and reduce inflammatory–cardiorenal risk.

Causal map: central obesity and physical inactivity → dysfunctional adipose tissue → increased FFA flux to the liver → ↑ VLDL/TG → ↓ HDL → atherogenic lipid profile. Hyperinsulinemia and inflammation → sympathetic activation, RAAS activation, and sodium retention → ↑ blood pressure. Elevated ALT and ultrasonographic steatosis suggest MASLD. A fasting glucose level of 6.0 mmol/L indicates that β -cells are still compensating, but their functional reserve may already be unstable.

Mechanistic interventions: physical activity, reduction of visceral fat, a diet of higher nutritional quality with increased fiber intake, optimization of sleep and stress, and treatment of hypertension and dyslipidemia according to the patient’s risk profile and current guidelines.

- MetS is a network disorder of energy homeostasis.
- Visceral fat is an endocrine and immune organ.
- Insulin resistance is organ-specific and often selective.
- FFA flux to the liver explains TG, VLDL, and MASLD.
- Hypertension also arises metabolically: sympathetic drive, RAAS, sodium, endothelium.
- Inflammation, lipotoxicity, mitochondria, and ER stress are causal loops.
- An atherogenic profile may be present even with unremarkable LDL-C.
- The β -cell compensates for years and then fails.
- The microbiome and circadian rhythm modulate the metabolic network.
- Treatment should disrupt pathological loops, not only correct numbers.

→ Think causally: **adipose tissue** → **insulin** → **liver/muscle** → **vasculature/kidney** → **pancreas**.

→ For each patient, identify the **dominant pathophysiological node**: visceral fat, liver, blood pressure, lipids, glycemia, kidney, or sleep/stress.

Alberti KGMM et al. Harmonizing the Metabolic Syndrome. *Circulation*. 2009.

Grundy SM et al. Diagnosis and Management of the Metabolic Syndrome. *Circulation*. 2005.

Fahed G et al. Metabolic Syndrome: Updates on Pathophysiology and Management. *Int J Mol Sci*. 2022.

Hamooya BM et al. Metabolic syndrome: epidemiology, mechanisms, and management. *Frontiers in Nutrition*. 2025.

Ndumele CE et al. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the AHA. *Circulation*. 2023.

Rinella ME et al. Multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol/Hepatology*. 2023.

AASLD. New MASLD nomenclature. Online resource, 2023–2026.

Hou K et al. Microbiota in health and diseases. *Signal Transduct Target Ther*. 2022.

Valdes AM et al. Role of the gut microbiota in nutrition and health. *BMJ*. 2018.

Bonetti PO et al. Endothelial dysfunction: a marker of atherosclerotic risk. *ATVB*. 2003.

Note: This lecture is pathophysiological; clinical decision-making must always be linked to current professional guidelines, comorbidities, and local availability of diagnostics/treatment.

Thank you for your attention

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