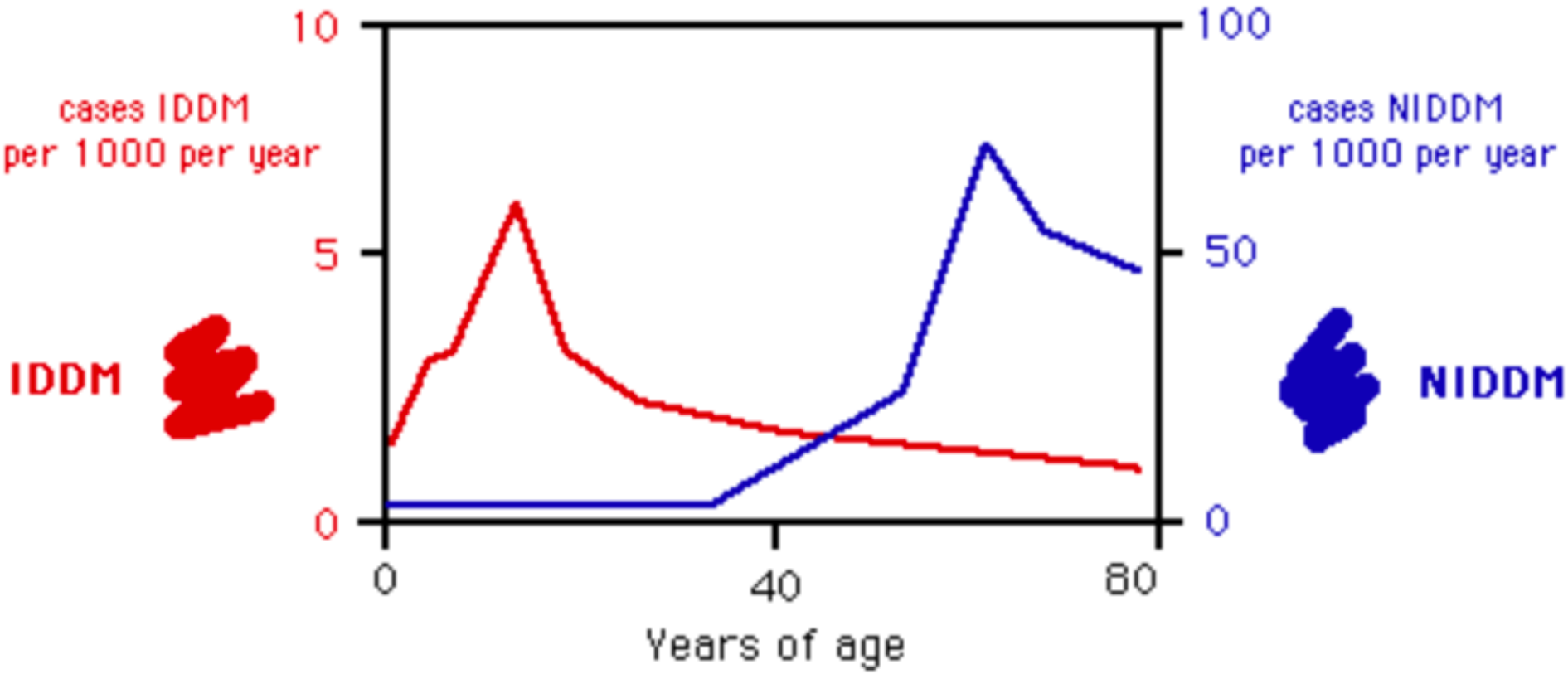
https://www.ncbi.nlm.nih.gov/books/NBK278943/

Diabetes and Obesity

Incidence of IDDM and NIDDM with age



Type I Diabetes (Juvenile diabetes)

Autoimmune destruction of the insulin producing β-cells

The body cells fail to take up glucose.
Plasma glucose rises, overflows into the urine taking with it water, and increasing the urine volume.
The liver then produces ketones, which eventually acidify the blood.
The brain cannot function in an acid medium.

Therapy:

1920 Insulin

Pathogenesis

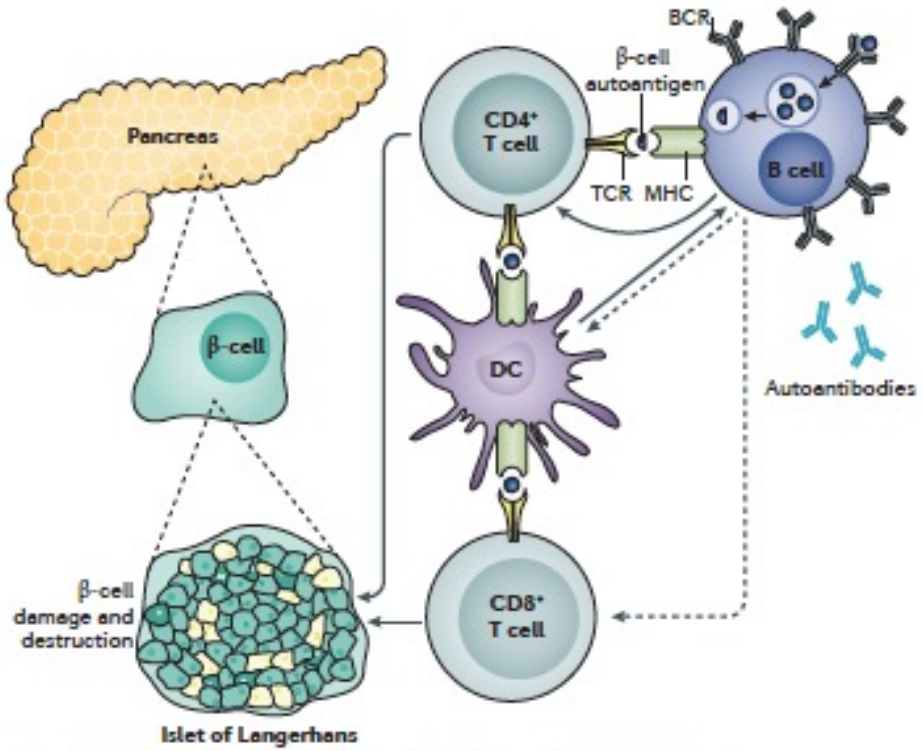


Figure 4 | **Pathogenesis of T1DM.** Type 1 diabetes mellitus (T1DM) is an immune-mediated disease. Activated B cells interact with CD4+ and CD8+ T cells, as well as dendritic cells (DCs). Antigen presentation by B cells and DCs drives the activation of β-cell-specific T cells. In addition, the exposure of B cells to β-cell autoantigens leads to the production of islet-targeting autoantibodies, which serve as biomarkers of asymptomatic disease. Dashed arrows indicate the potential interactions between B cells and CD8+ T cells and between B cells and DCs. BCR, B cell receptor; TCR, T cell receptor.

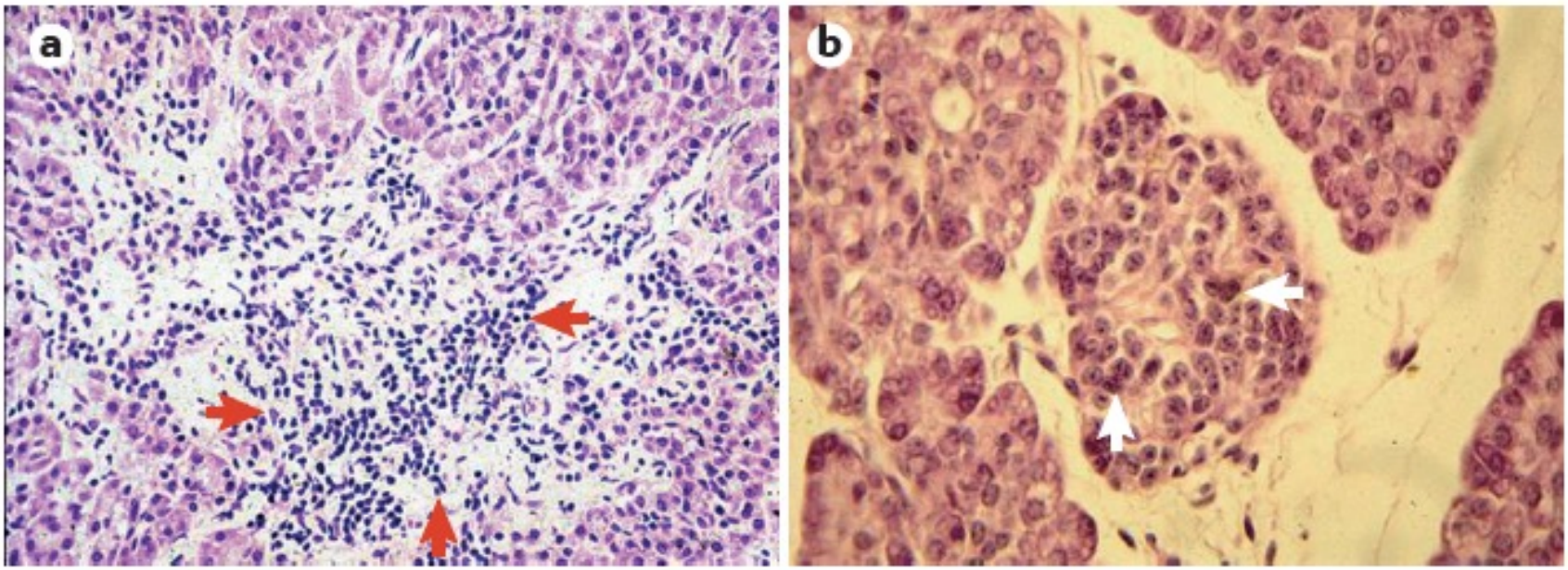
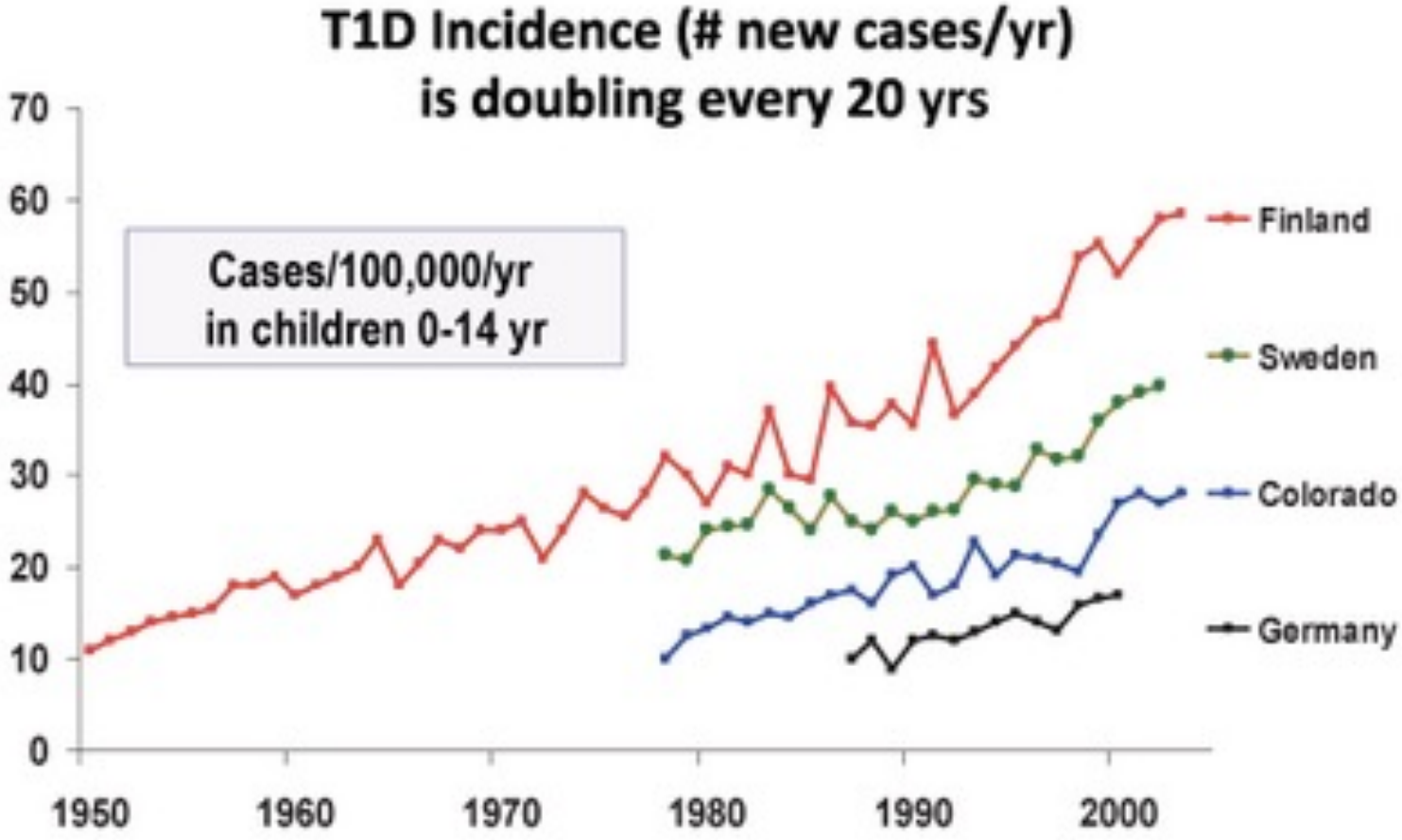


Figure 5 | **Pancreatic inflammation and insulitis in T1DM.** Histological examination of pancreas tissue after symptom onset (diabetic ketoacidosis) shows very severe insulitis with massive mononuclear cell infiltration in and around the pancreatic islets in one patient (part **a**; red arrows; magnification ×125) and less-severe insulitis only involving dendritic cells in another patient (part **b**; white arrows; magnification ×250). Biopsies were obtained from individuals who carried the *HLA-DR3/4* genotype and succumbed to brain oedema <1 week after symptom onset. Adapted with permission from REF. 108, Springer.


T1D Incidence (# new cases/yr)
is doubling every 20 yrs
Cases/100,000/yr
in children 0-14 yr
70
60
50
40
30
20
10
0
1950
1960
1970
1980
1990
2000
Finland
Sweden
Colorado
Germany

Aetiology of Type I diabetes

- An environmental factor triggers a selective autoimmune destruction of the β-cells of the pancreas in a genetically predisposed individual

- Genetic risk
  - HLA region allele combinations important to T cell tolerance
  - Class II HLA region in MHC: HLA-DR, HLA-DQ
  - Other loci: modify the vulnerability of b-cell to inflammatory mediators

- Putative environmental triggers:
  - Chemicals: N-nitro compounds
  - Viruses: mumps, rubella, cytomegalovirus, enteroviruses
  - Increased hygiene
  - Vaccination
  - Stress
  - Perinatal factors: maternal rubella, blood group incompatibility, maternal age, birth weight, gestational age, birth order
  - Food components: milk and wheat protein, Vitamin D deficiency

The 'Hygiene hypothesis' and the sharp gradient in the incidence of autoimmune and allergic diseases between Russian Karelia and Finland

ANITA KONDRASHOVA,[1] TAPIO SEISKARI,[1,2] JORMA ILONEN,[3,4] MIKAEL KNIP,[5,6,7,8] and HEIKKI HYÖTY[1,2]

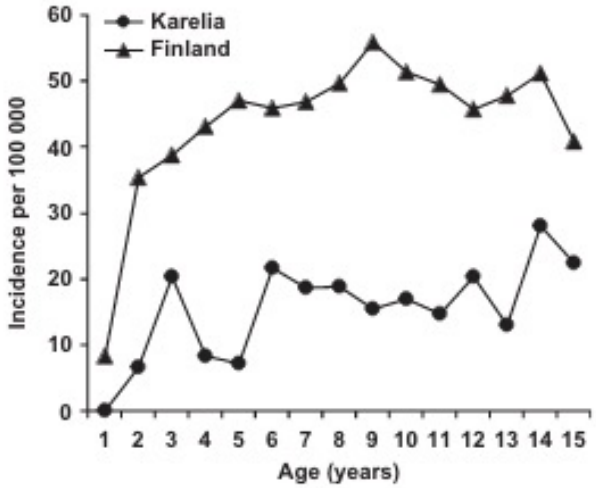
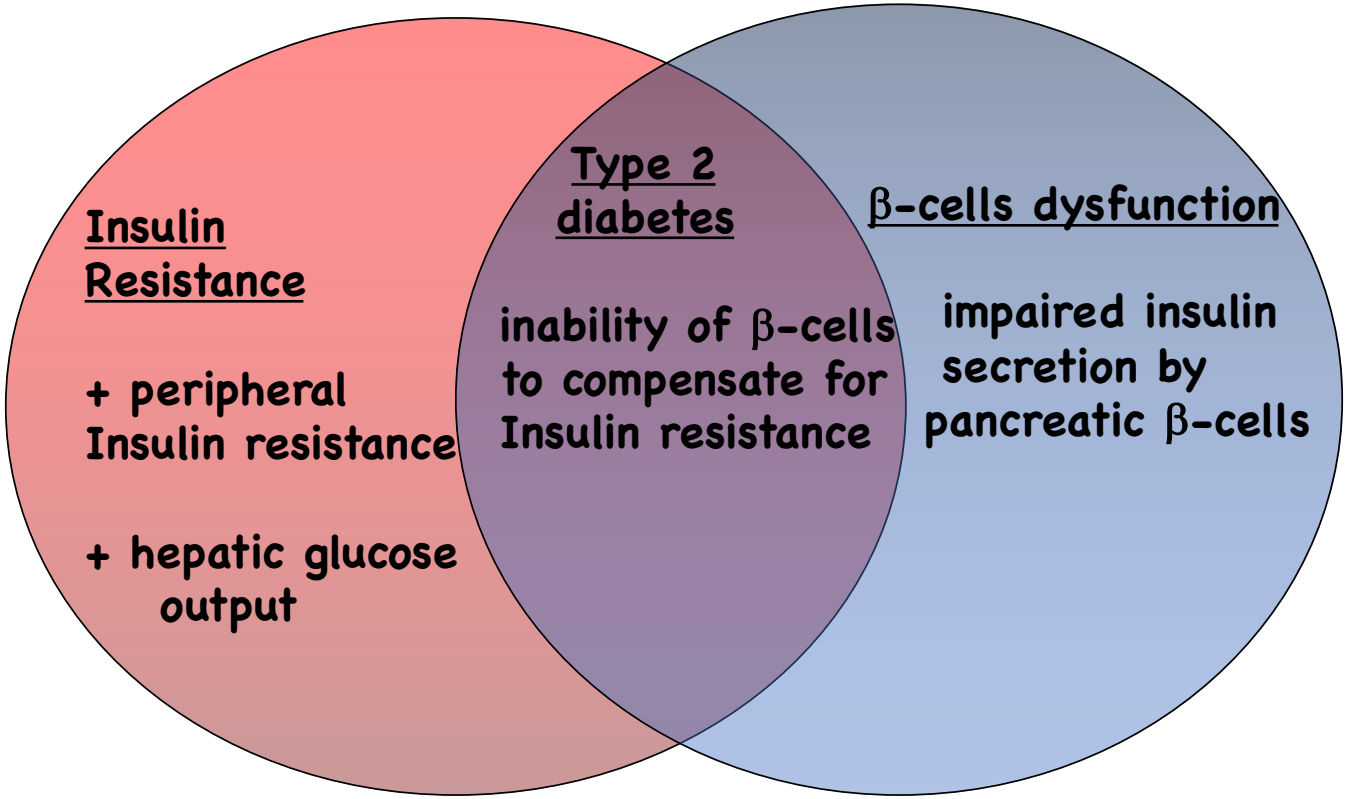


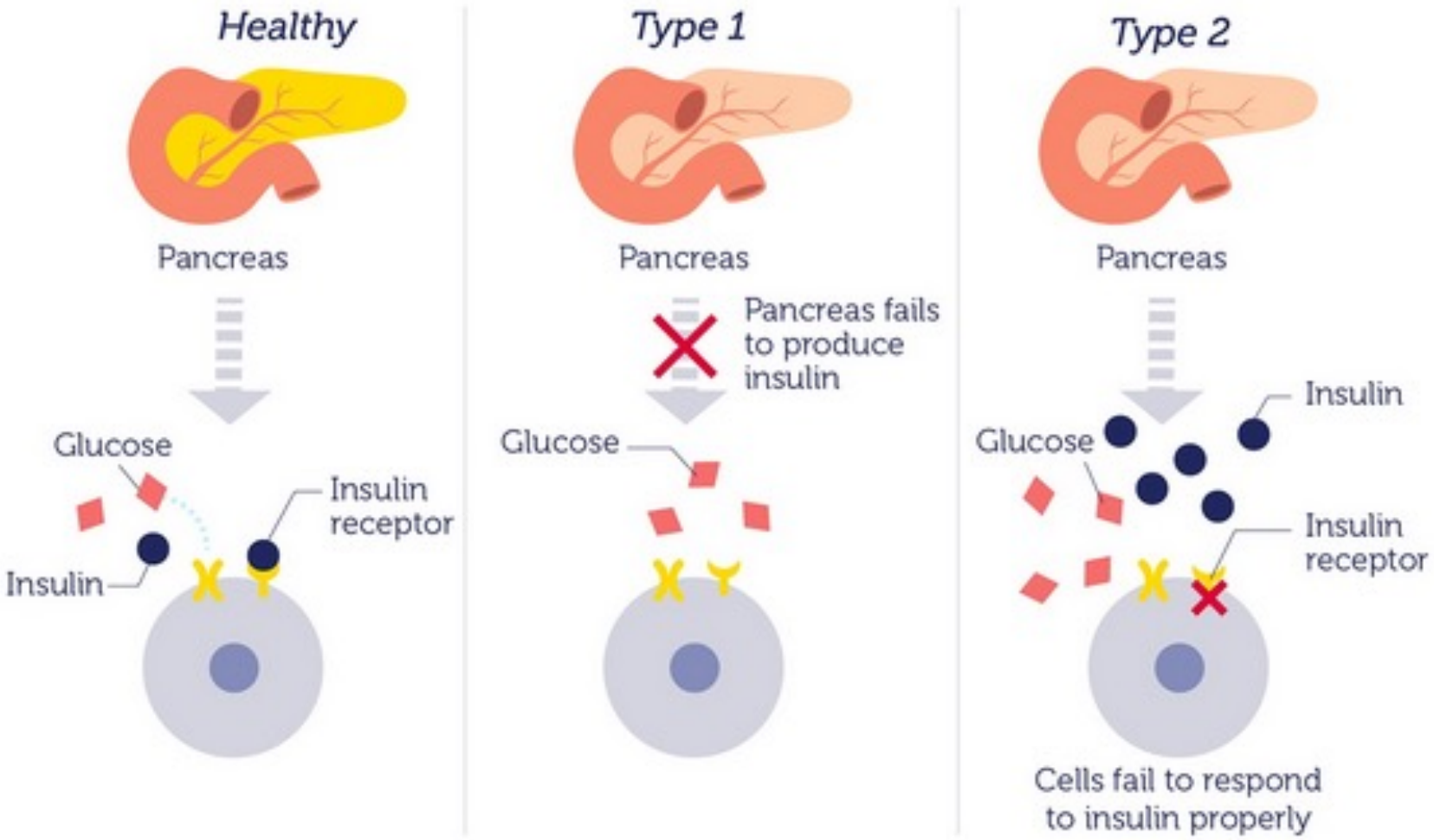
Fig. 2. Annual incidence of type 1 diabetes by age in 0–14-year-old children in Russian Karelia (circles) and Finland (triangles) during the years 1990–99.

Type II Diabetes

85% of all diabetes worldwide



DIABETES MELLITUS



Type II Diabetes Therapy

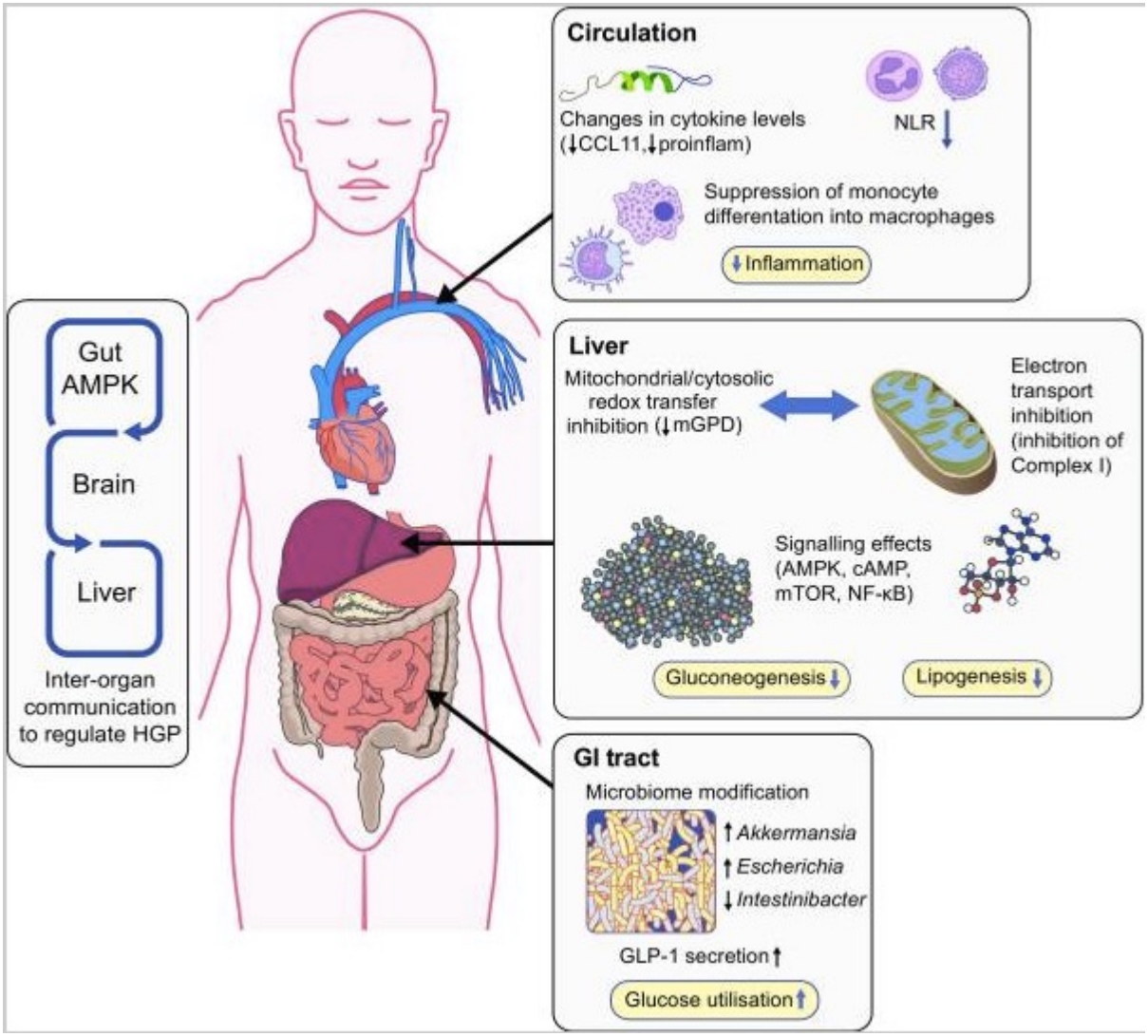
- 1. Healthy eating!
- 2. Exercise!
- blood sugar monitoring

- Medication
  - Metformin: -reduces hepatic gluconeogensis
    -increases insulin uptake (sensitivity)
  - Sulfonylureas: 1942 increase insulin secretion
  - Thiazolidinediones: decrease blood glc levels
    - 1990 PPARgamma inhibitor
  - DPP-4 inhibitors: inhibit glucagon degradation
  - SGLT2 inhibitors: block glc reabsorption in the kidney
    - Sodium dependent glucose trasnporter
    - 2012: Canaglifozin

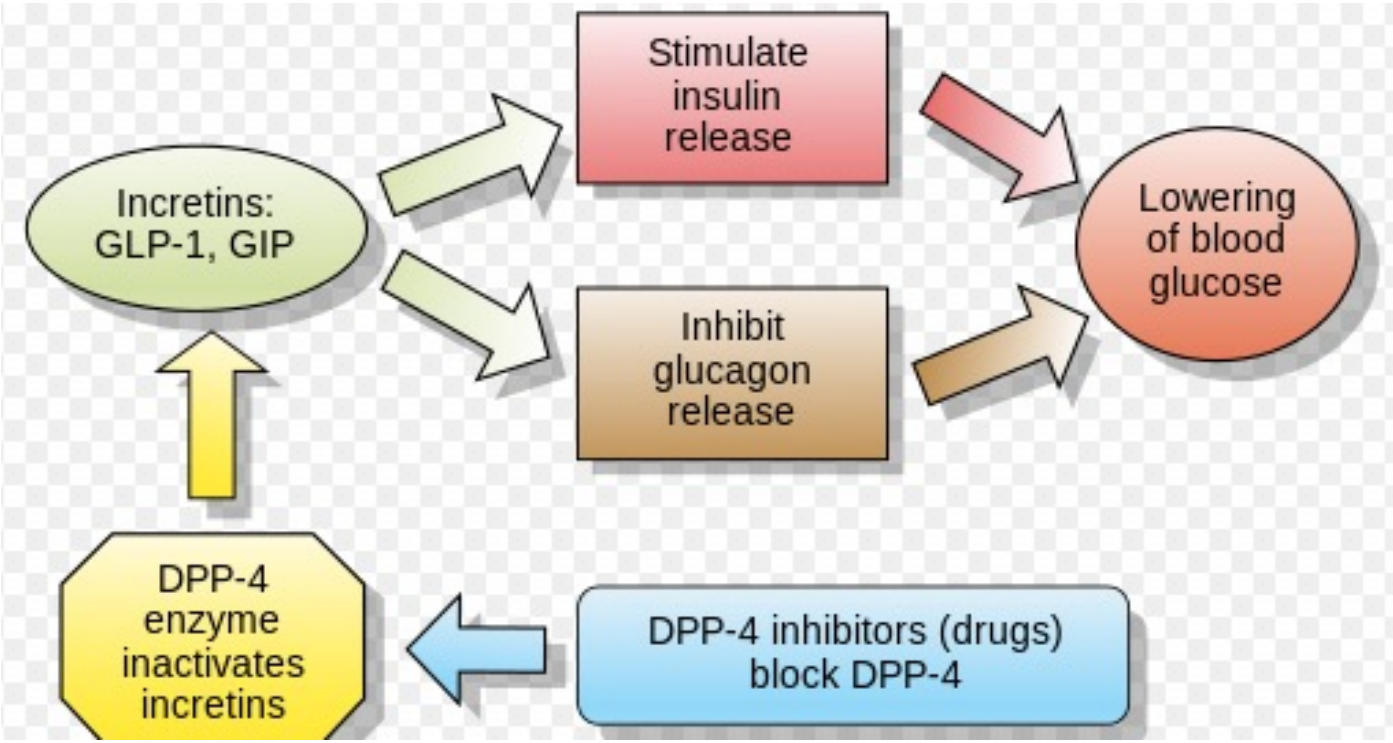
- Barometric surgery

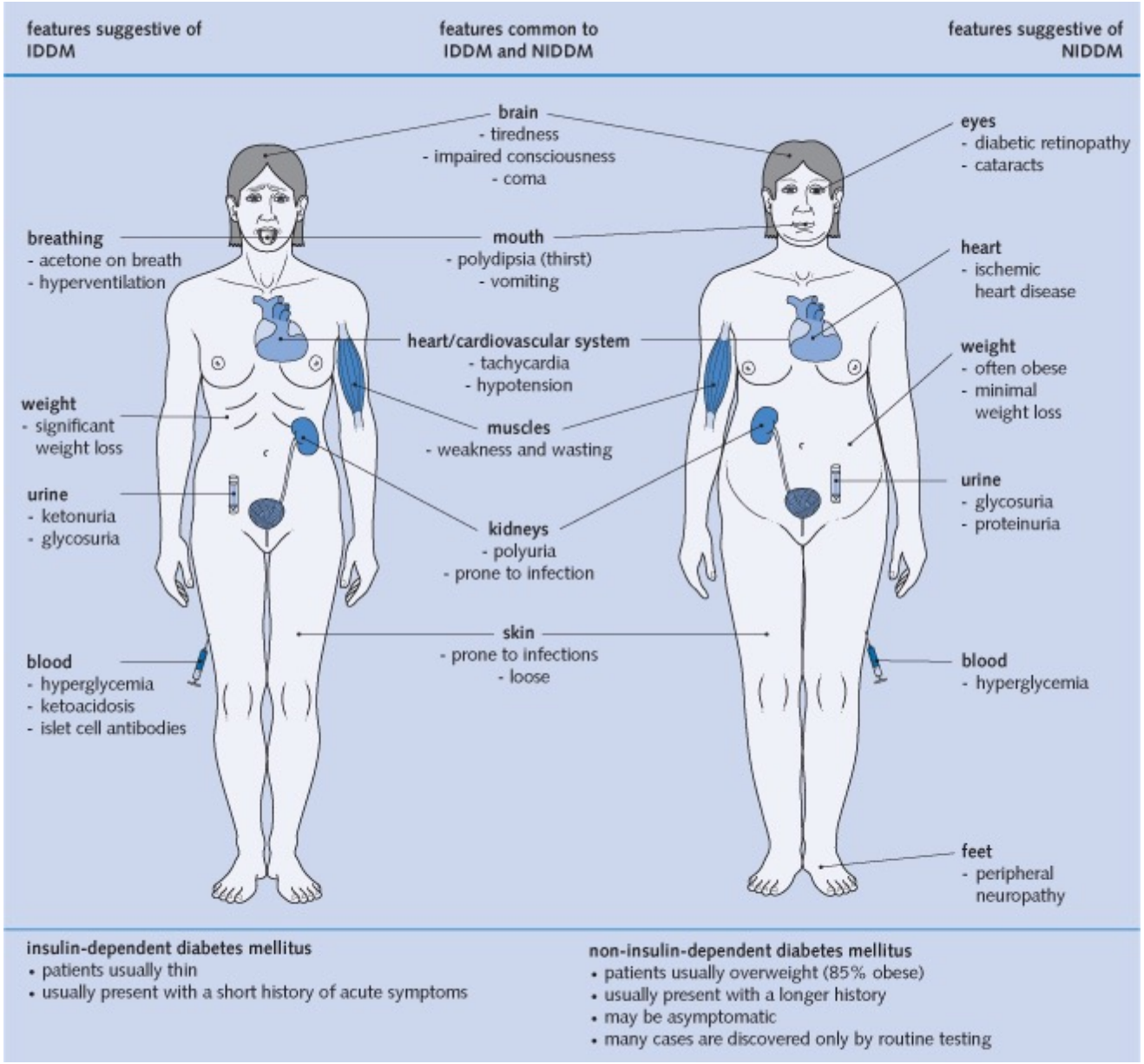
- Insulin

Metformin


Circulation
Changes in cytokine levels
(↓CCL11,↓proinflam)
NLR
Suppression of monocyte
differentation into macrophages
↓Inflammation
Liver
Mitochondrial/cytosolic
redox transfer
inhibition (↓mGPD)
Electron
transport
inhibition
(inhibition of
Complex I)
Signalling effects
(AMPK, cAMP,
mTOR, NF-κB)
Gluconeogenesis↓
Lipogenesis↓
GI tract
Microbiome modification
↑Akkermansia
↑Escherichia
↓Intestinibacter
GLP-1 secretion↑
Glucose utilisation↑
Gut
AMPK
Brain
Liver
Inter-organ
communication
to regulate HGP

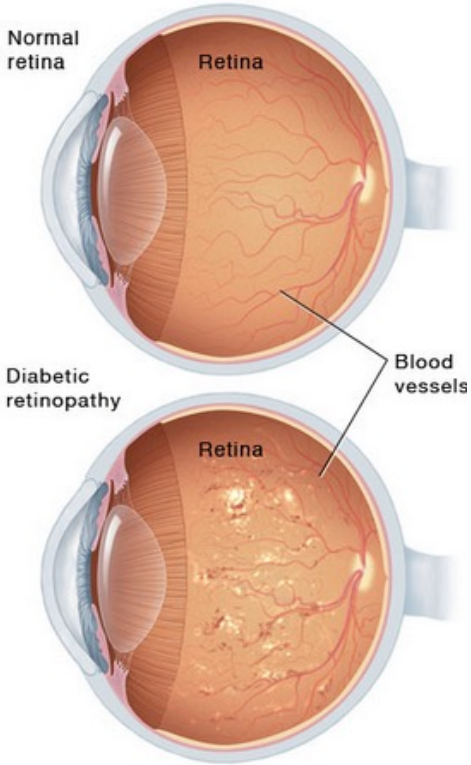
dipeptidyl peptidase 4 (DPP-4)




features suggestive of IDDM
features common to IDDM and NIDDM
features suggestive of NIDDM
brain
- tiredness
- impaired consciousness
- coma
eyes
- diabetic retinopathy
- cataracts
breathing
- acetone on breath
- hyperventilation
mouth
- polydipsia (thirst)
- vomiting
heart
- ischemic heart disease
heart/cardiovascular system
- tachycardia
- hypotension
weight
- often obese
- minimal weight loss
weight
- significant weight loss
muscles
- weakness and wasting
urine
- ketonuria
- glycosuria
urine
- glycosuria
- proteinuria
kidneys
- polyuria
- prone to infection
skin
- prone to infections
- loose
blood
- hyperglycemia
- ketoacidosis
- islet cell antibodies
blood
- hyperglycemia
feet
- peripheral neuropathy
insulin-dependent diabetes mellitus
• patients usually thin
• usually present with a short history of acute symptoms
non-insulin-dependent diabetes mellitus
• patients usually overweight (85% obese)
• usually present with a longer history
• may be asymptomatic
• many cases are discovered only by routine testing

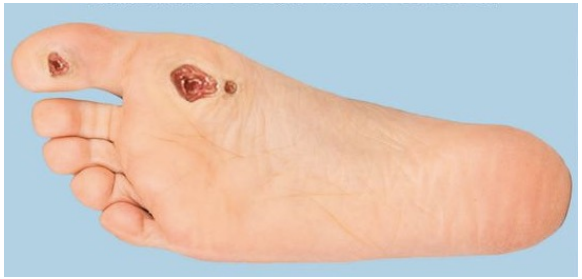
Complications of Diabetes

- Chronic microvascular complications
  - Eyes: retinopathy
  - Kidney
  - Nerves
- Macrovascular complications
  - Myocardial infarction
  - Stroke
  - Peripheral vascular disease



Chronic complications of Diabetes

- Retinopathy: most common cause of blindness in people of working age
- Nephropathy: 16% of all patients needing renal replacement therapy have diabetes
- Erectile dysfunction: may affect up to 50% of men with long-standing diabetes
- Macrovascular disease: 2-3 fold increased risk of coronary heart disease and stroke
- Foot problems: 15% of people with diabetes develop foot ulcers; 5-15% of people with diabetic foot ulcers need amputations



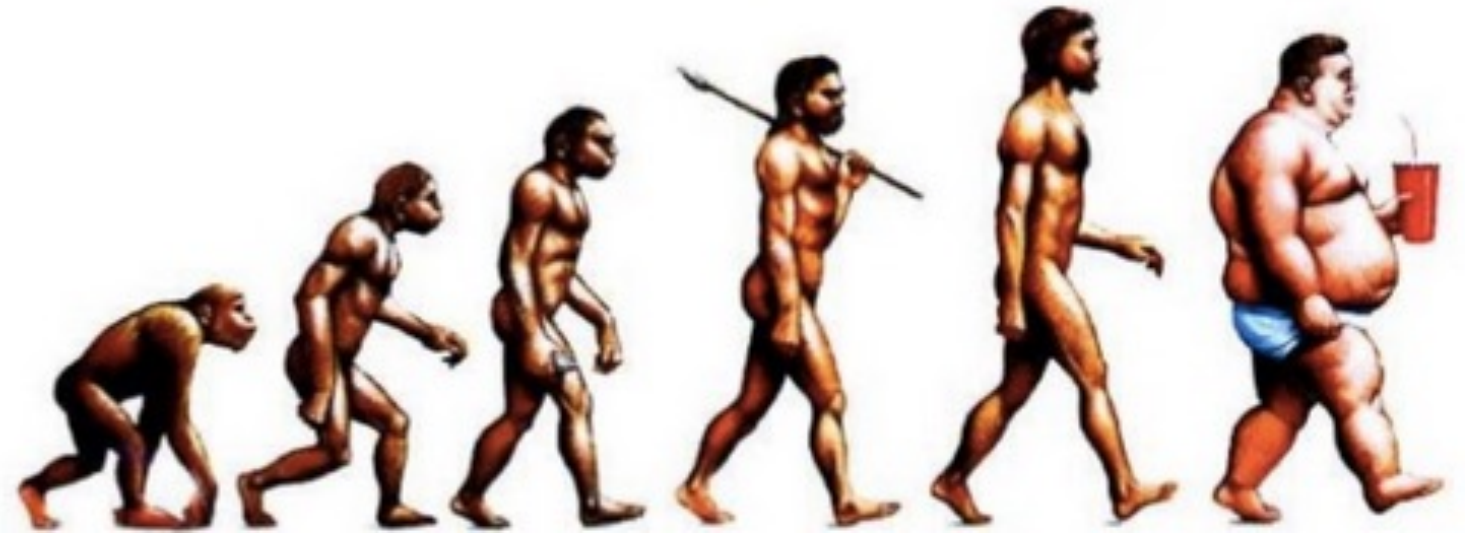
Risk Factors for Type II diabetes

Unmodifiable Risk Factors	Environmental Risk Factors
family history	obesity
prenatal malnourishment	physical inactivity
ethnicity	diet
age	
past history of in pregnancy diabetes	
severe mental illness	

Obesity

Evolution – Costs - Origins – Remedies

By Valerie Orsoni (Founder of LeBootCamp.com)



Obesity

- recognized as one of the most important public health problems
- has increased dramatically throughout the world over the past 2 decades
- associated with a range of medical and psychological complications
- current public health measures to prevent obesity fail

Body Mass Index

- Weight in kilograms/(height in meters)^2

- WHO definitions:
  - Underweight BMI <18.5 kg/m^2
  - Normal weight BMI 18.5-25 kg/m^2
  - Overweight BMI > 25 kg/m^2 (Asians >23 kg/m^2)
  - Obesity >30 kg/m^2 (Asians >25 kg/m^2)
  - Morbid obesity BMI > 40 kg/m^2

  - Central obesity >80 cm for women, >90 cm for men

Homeostasis: energy balance

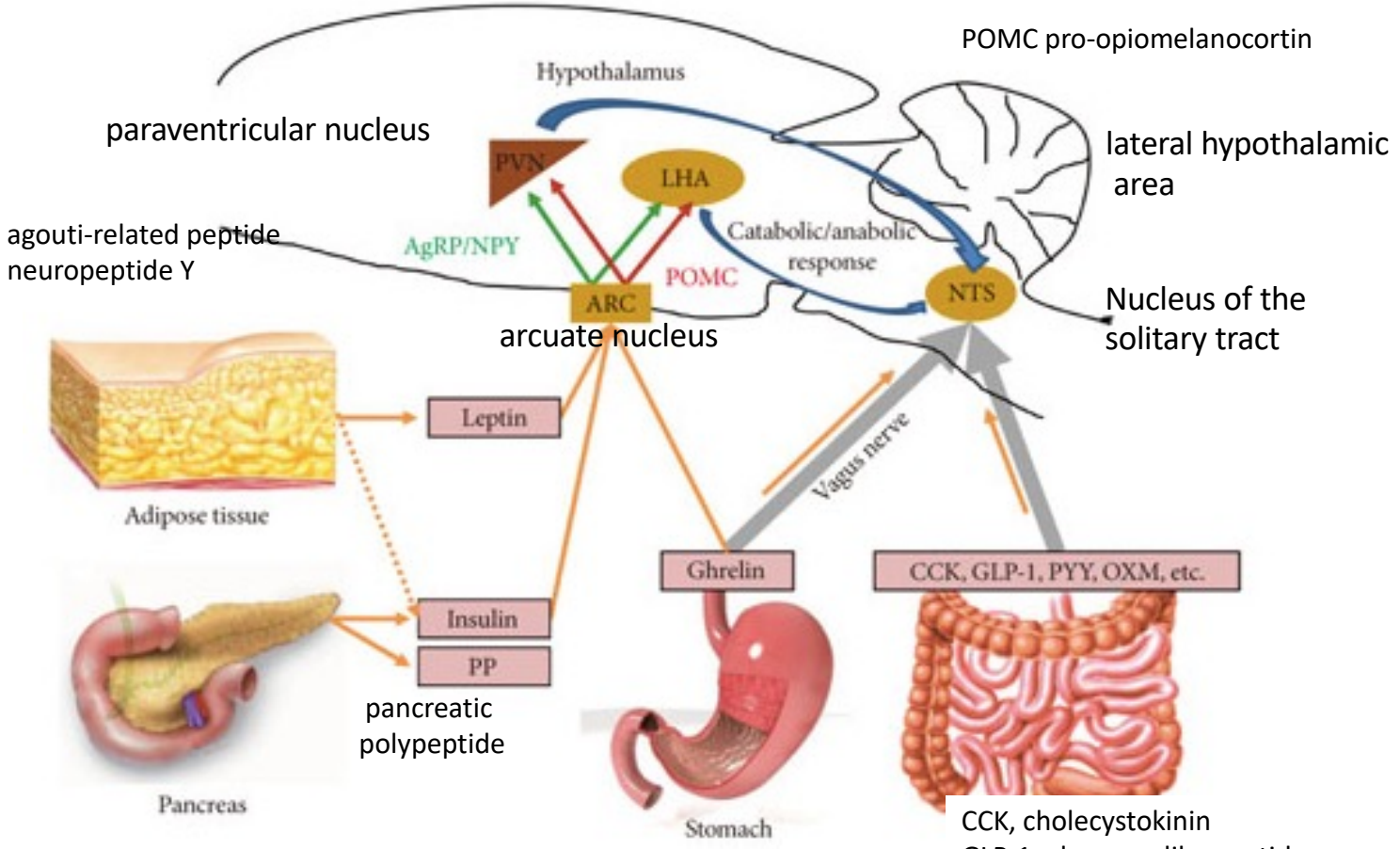
- Most adults are able to maintain their body weight within a few kilograms over 40 or more years in spite of having eaten in excess of 20 tonnes of food.

Daniel Lamberts

1770-1809

- 336 kg
  - 230 kg fat = 2 million kcal
- If there was progressive weight gain throughout his life, the excess consumption would have been only around 140kcal/day, equivalent to an apple a day

Multiple systems regulating appetite

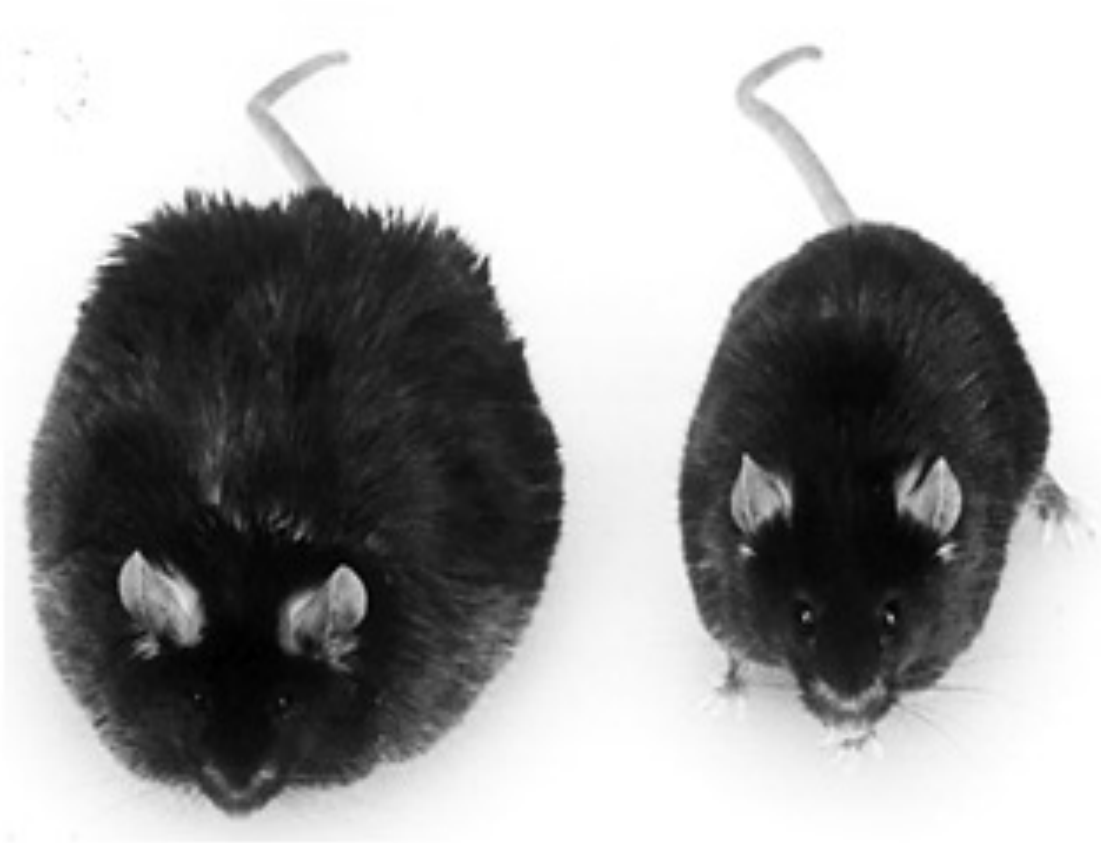


CCK, cholecystokinin
GLP-1, glucagon-like peptide
OXM oxyntomodulin
PYY peptide YY

Diabetes Metab J. 2012 Dec;36(6):391-398.

Leptin the “adipostat”

- 1994 leptin discovered at Rockefeller by the group of Jeffrey Friedman (Zhang et al., 1994)
- polypeptide hormone secreted by fat cells
- blood levels proportional to total fat mass
- plasma circadian rhythm: acrophase during the night (4 am), nadir during the afternoon
- pulsatility in opposite phase with ACTH and cortisol
- Effects: - appetite inhibition
- - effects on GH-RH and GnRH



Leptin-deficient patients before treatment

- Three first-degree cousins from one large Turkish pedigree
- Shown to be leptin-deficient
- Initial body weight, 125 kg on average
- Daily leptin injection for ten months
- J. Licinio, M. Ozata, E. Ravussin, et al.

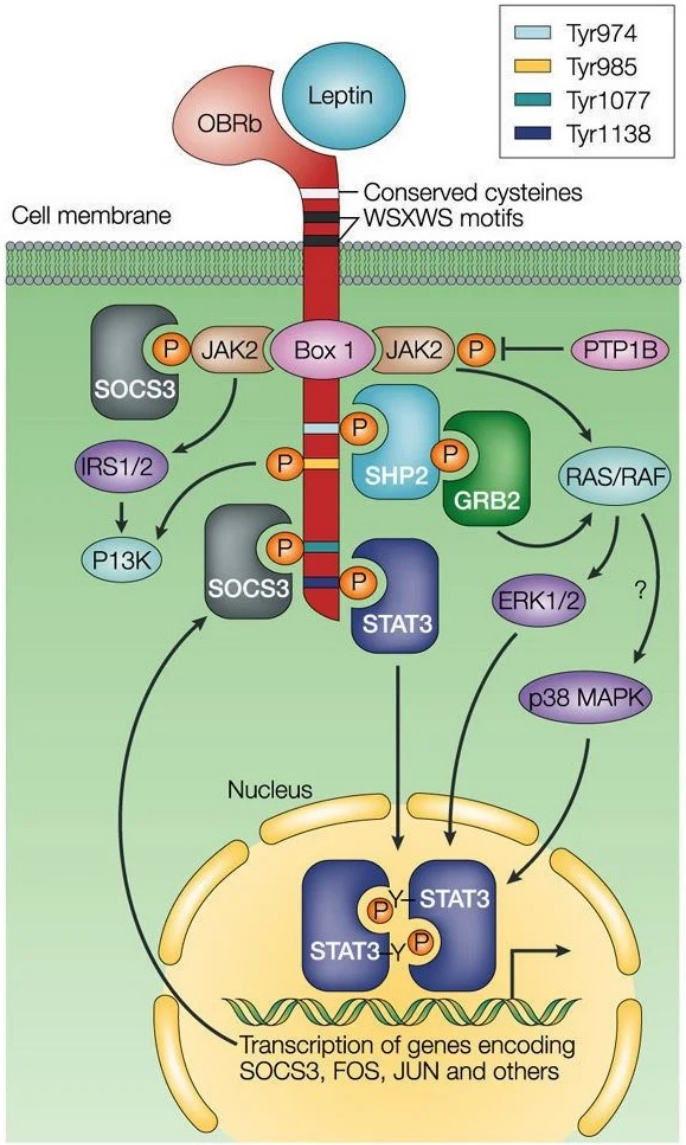
After three months of treatment

After ten months of treatment

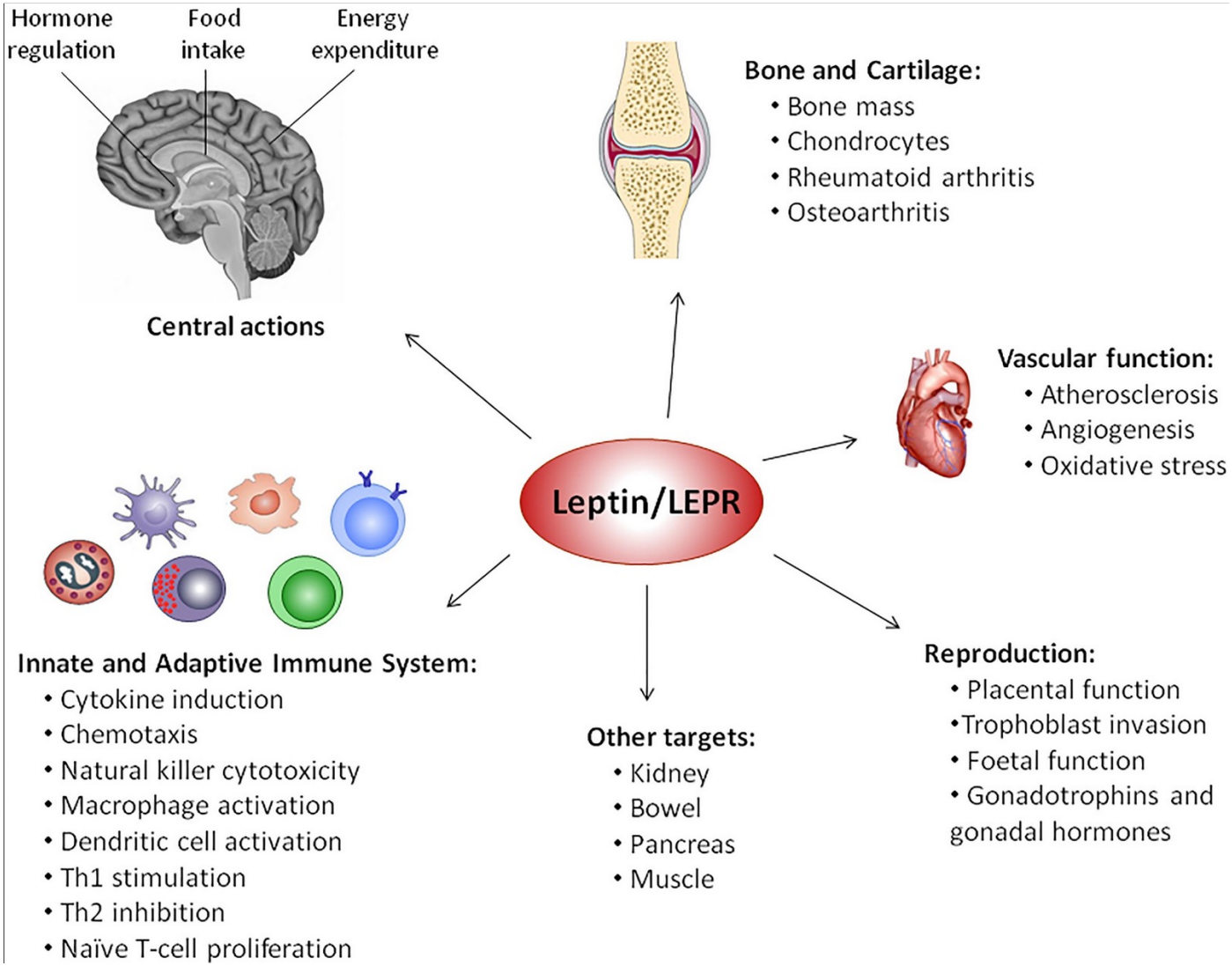
Ten months later, the cousins have lost nearly half their body weight.

Leptin receptor (CD295)

Type I cytokine receptor



The Emerging Leptin Biology



Leptin

- central role in appetite and body weight homeostasis by inducing anorexigenic factors (as cocaine-amphetamine-related transcript) and suppressing orexigenic neuropeptides (as neuropeptide Y) on hypothalamus

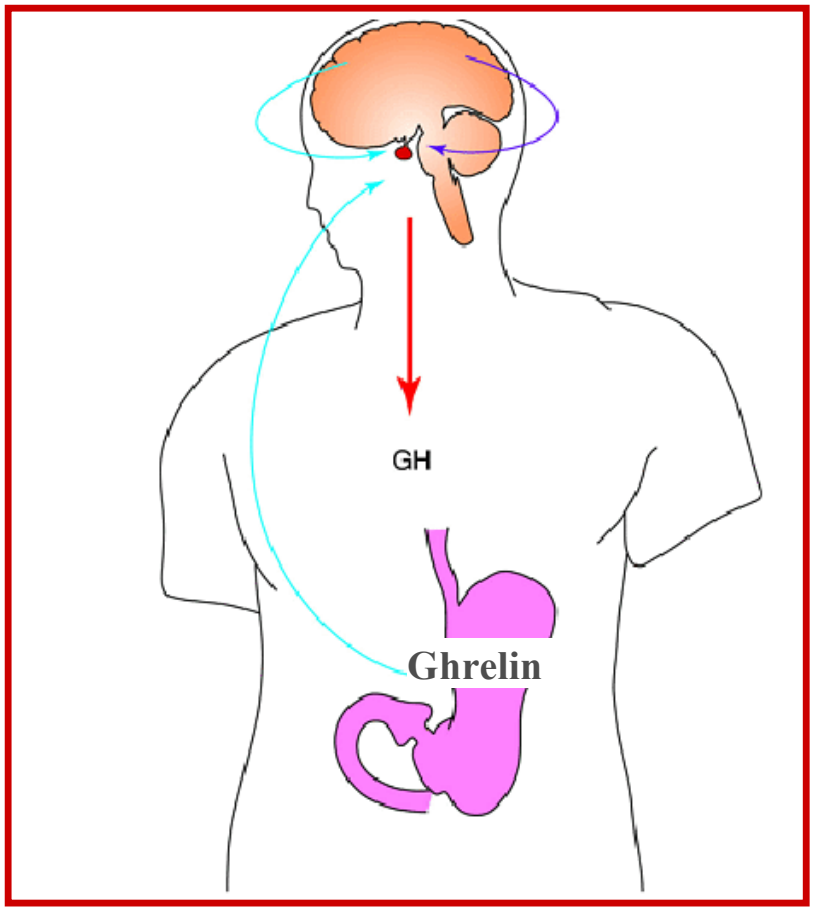
- also affects other physiological functions, namely bone metabolism, inflammation, infection and immune responses

- LEPR is expressed in across the cells of innate and adaptive immune system, evoking leptin as a crucial linker of neuroendocrine and immune systems

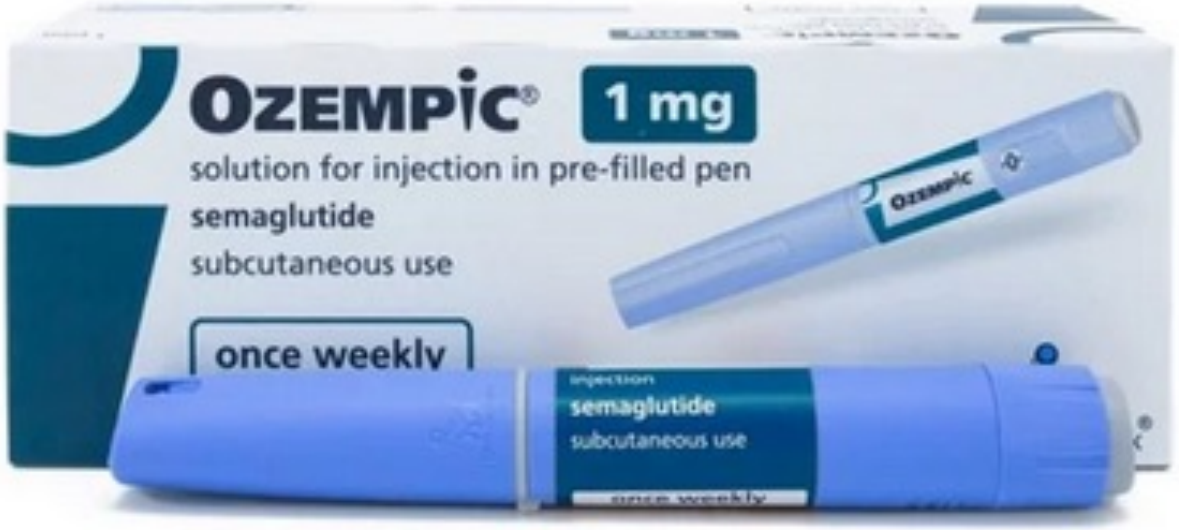
- central leptin resistance, caused by impairment of leptin transportation, leptin signaling and leptin target neural circuits, is considered the main risk factor for the obesity pathogenesis

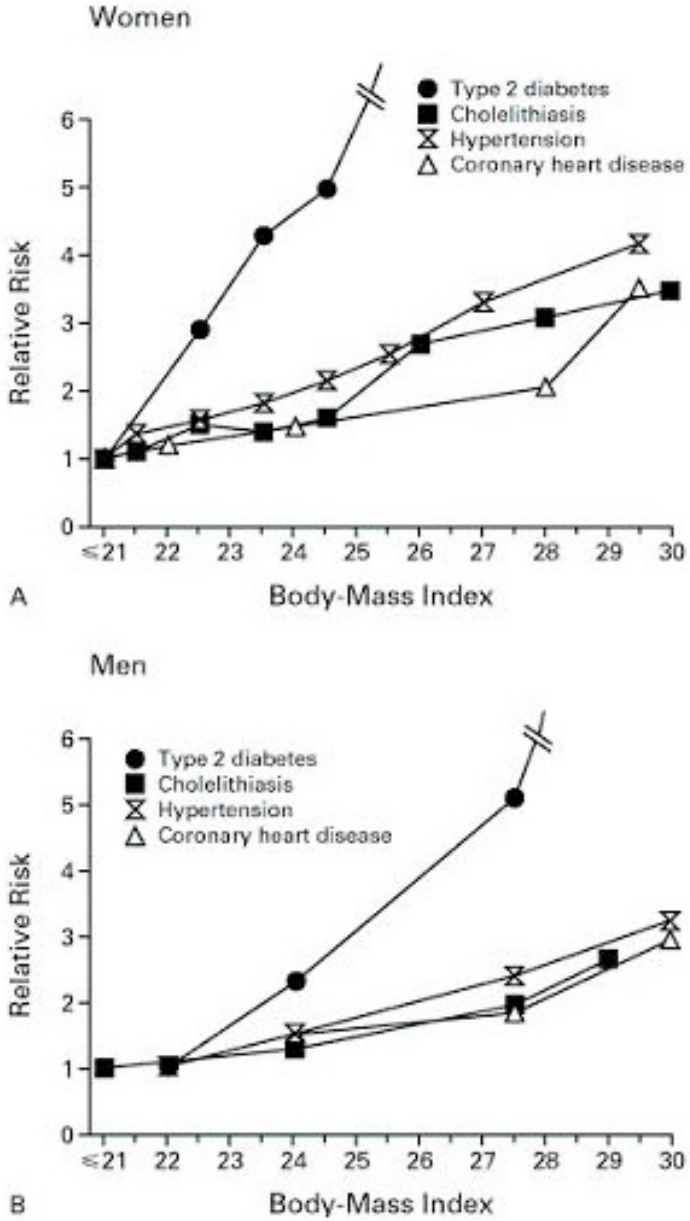
Ghrelin: Endogenous Ligand for the GH Secretagogue Receptor

- **Expressed in stomach**
- **Stimulates GH secretion**
- **Induces adiposity by decreasing fat oxidation and increasing food intake in rodents**
- **Circulating ghrelin levels are decreased in obesity**



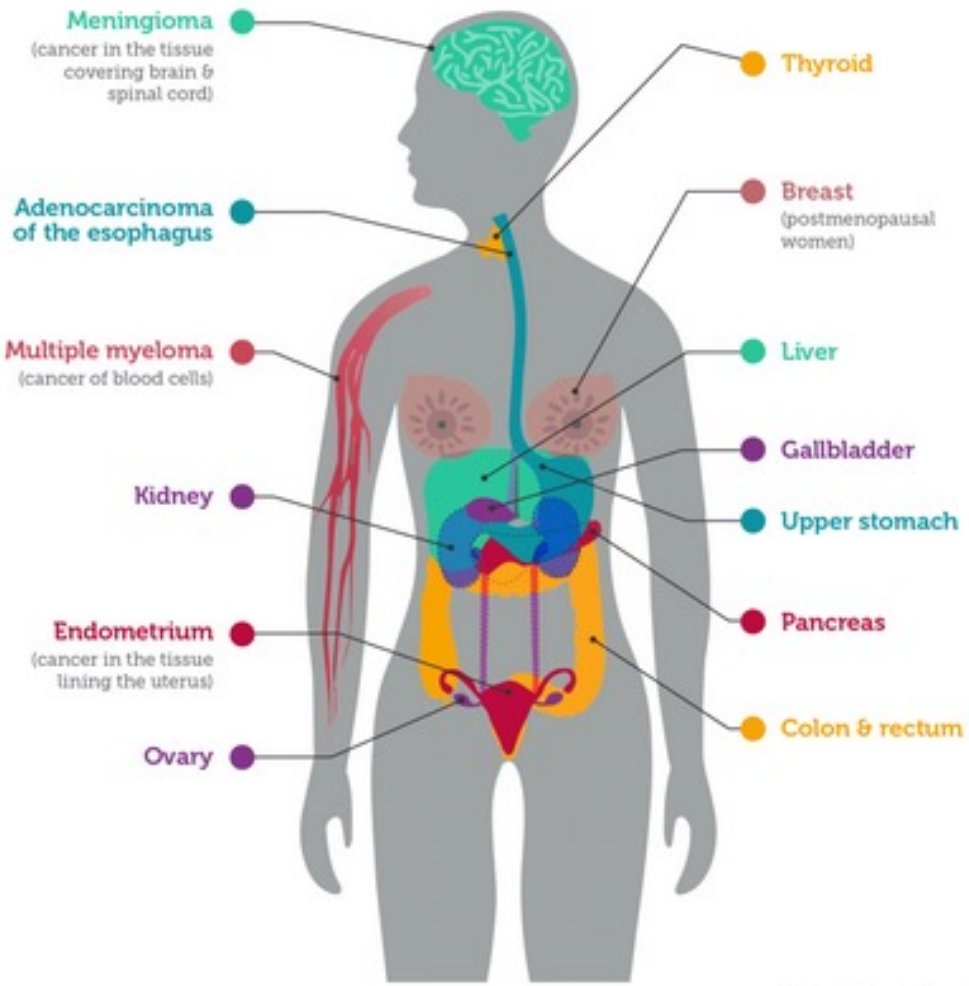
GLP-1R agonist




Women
Type 2 diabetes
Cholelithiasis
Hypertension
Coronary heart disease
Relative Risk
0
1
2
3
4
5
6
≤21
22
23
24
25
26
27
28
29
30
Body-Mass Index
A
Men
Type 2 diabetes
Cholelithiasis
Hypertension
Coronary heart disease
Relative Risk
0
1
2
3
4
5
6
≤21
22
23
24
25
26
27
28
29
30
Body-Mass Index
B

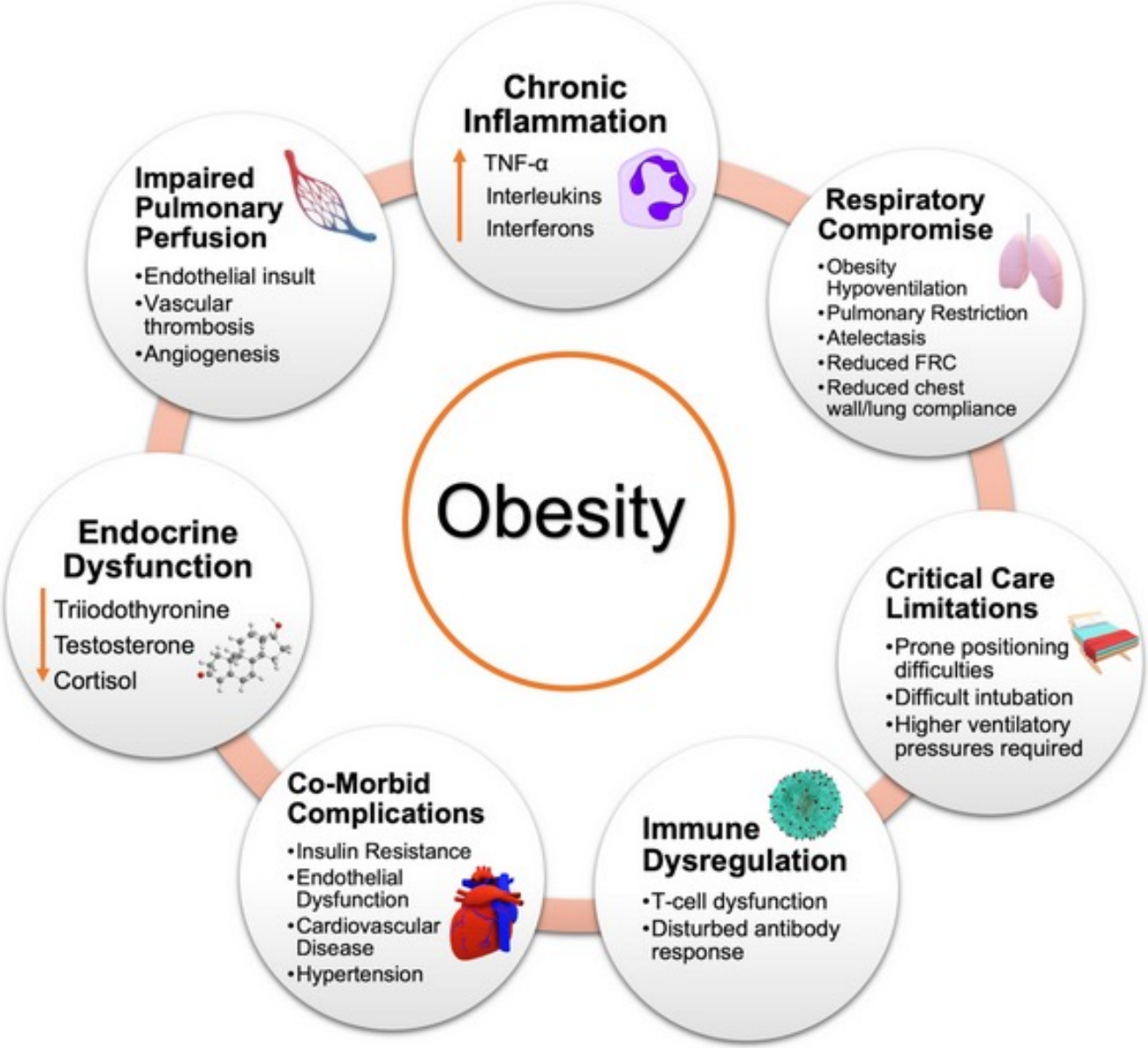
NATIONAL CANCER INSTITUTE

Cancers Associated with Overweight & Obesity

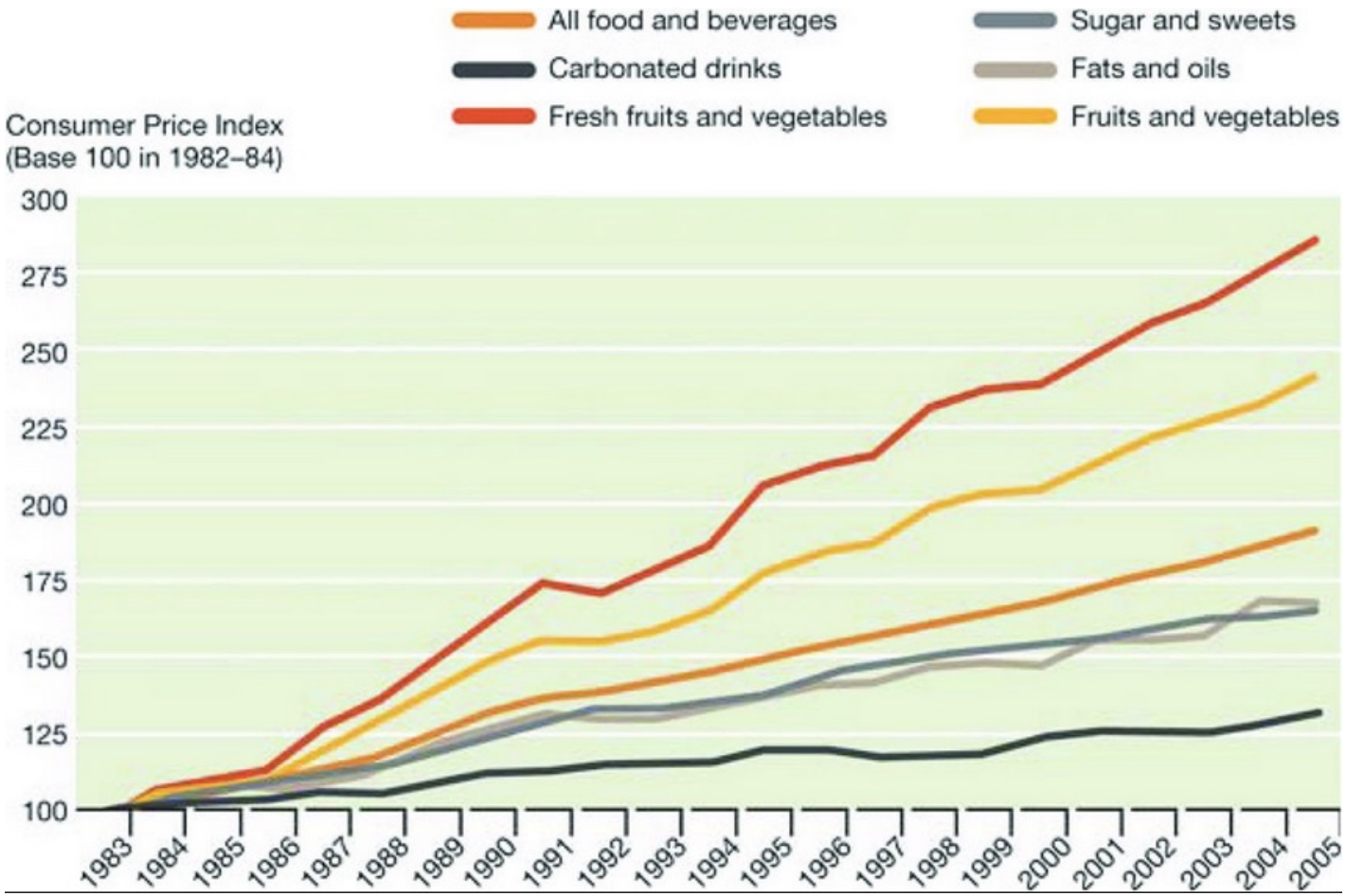


cancer.gov/obesity-fact-sheet

Adapted from Centers for Disease Control & Prevention

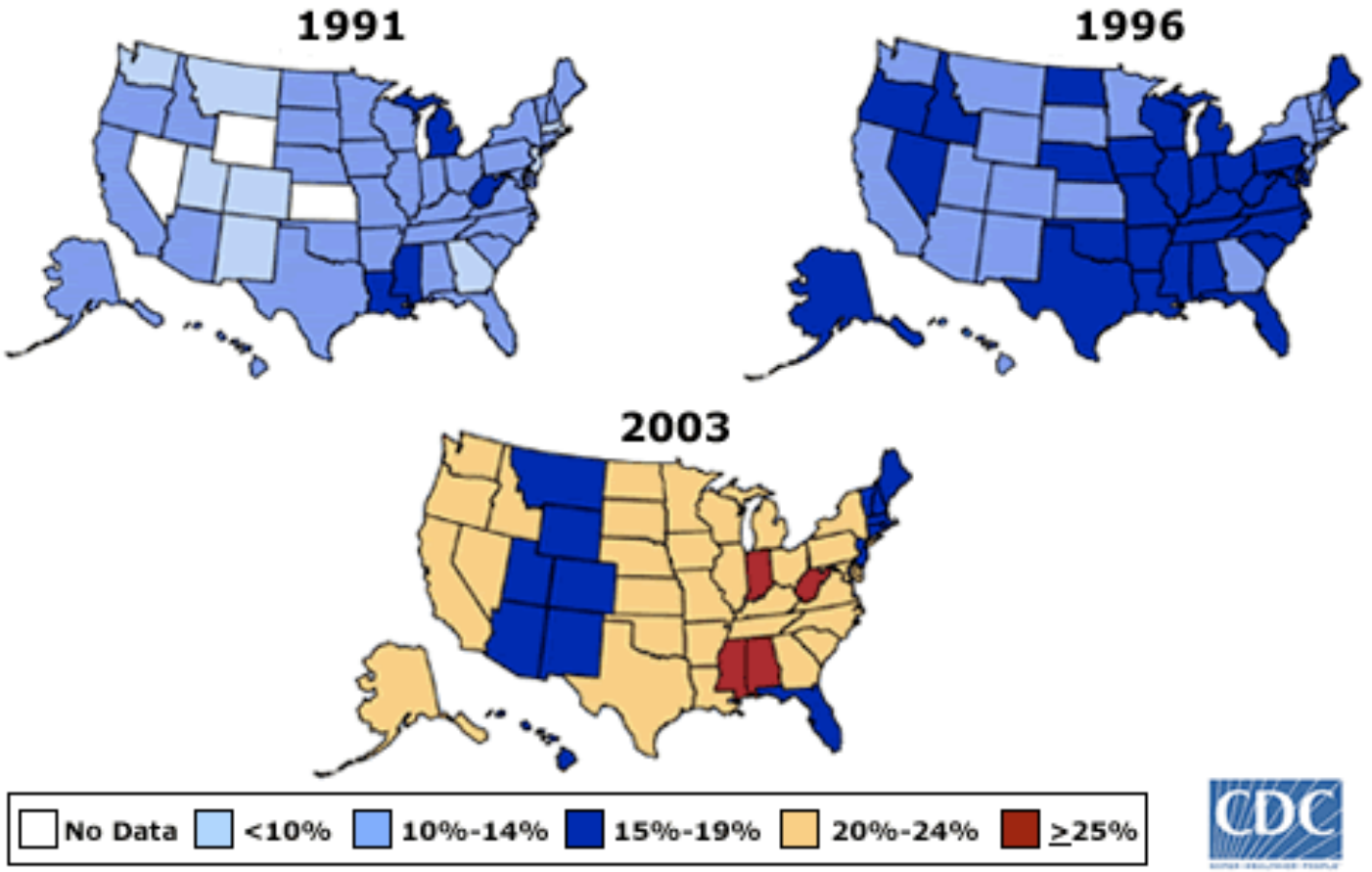

Obesity
Chronic Inflammation
TNF-α
Interleukins
Interferons
Respiratory Compromise
•Obesity Hypoventilation
•Pulmonary Restriction
•Atelectasis
•Reduced FRC
•Reduced chest wall/lung compliance
Critical Care Limitations
•Prone positioning difficulties
•Difficult intubation
•Higher ventilatory pressures required
Immune Dysregulation
•T-cell dysfunction
•Disturbed antibody response
Co-Morbid Complications
•Insulin Resistance
•Endothelial Dysfunction
•Cardiovascular Disease
•Hypertension
Endocrine Dysfunction
Triiodothyronine
Testosterone
Cortisol
Impaired Pulmonary Perfusion
•Endothelial insult
•Vascular thrombosis
•Angiogenesis

Development of relative prices for various foods in the United States from 1983 to 2005

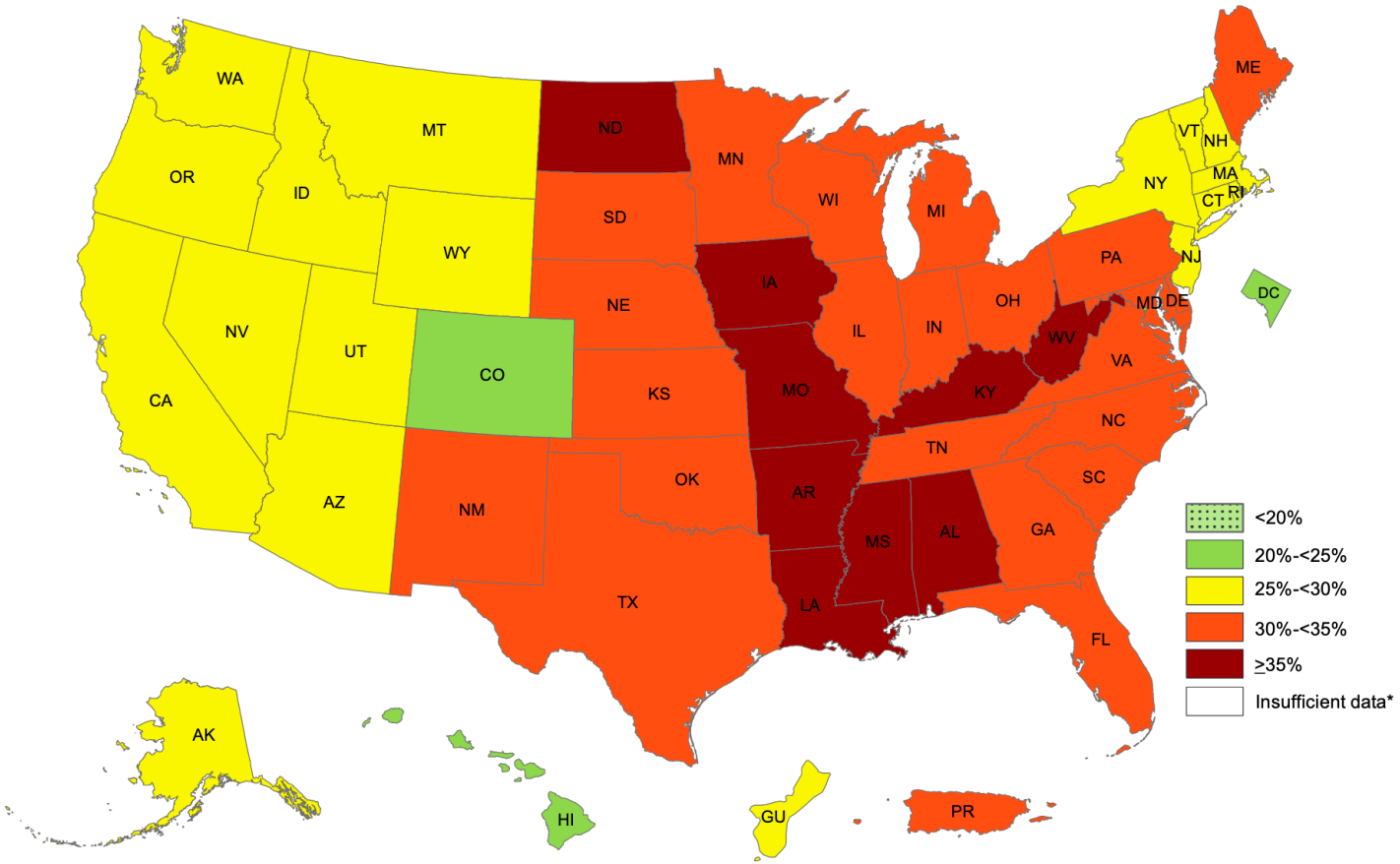


Obesity Trends* Among US Adults
CDC's Behavioral Risk Factor Surveillance System
1991-2003

(*BMI≥30, or ~ 30 lbs overweight for 5'4" women)



2018



https://www.cdc.gov/obesity/data/prevalence-maps.html#overall

Changes in lifestyle

- Shift from carbohydrate to fat consumption:

  Fat contains approximately 9 kcal/g while carbohydrates and protein contain 4 kcal/g

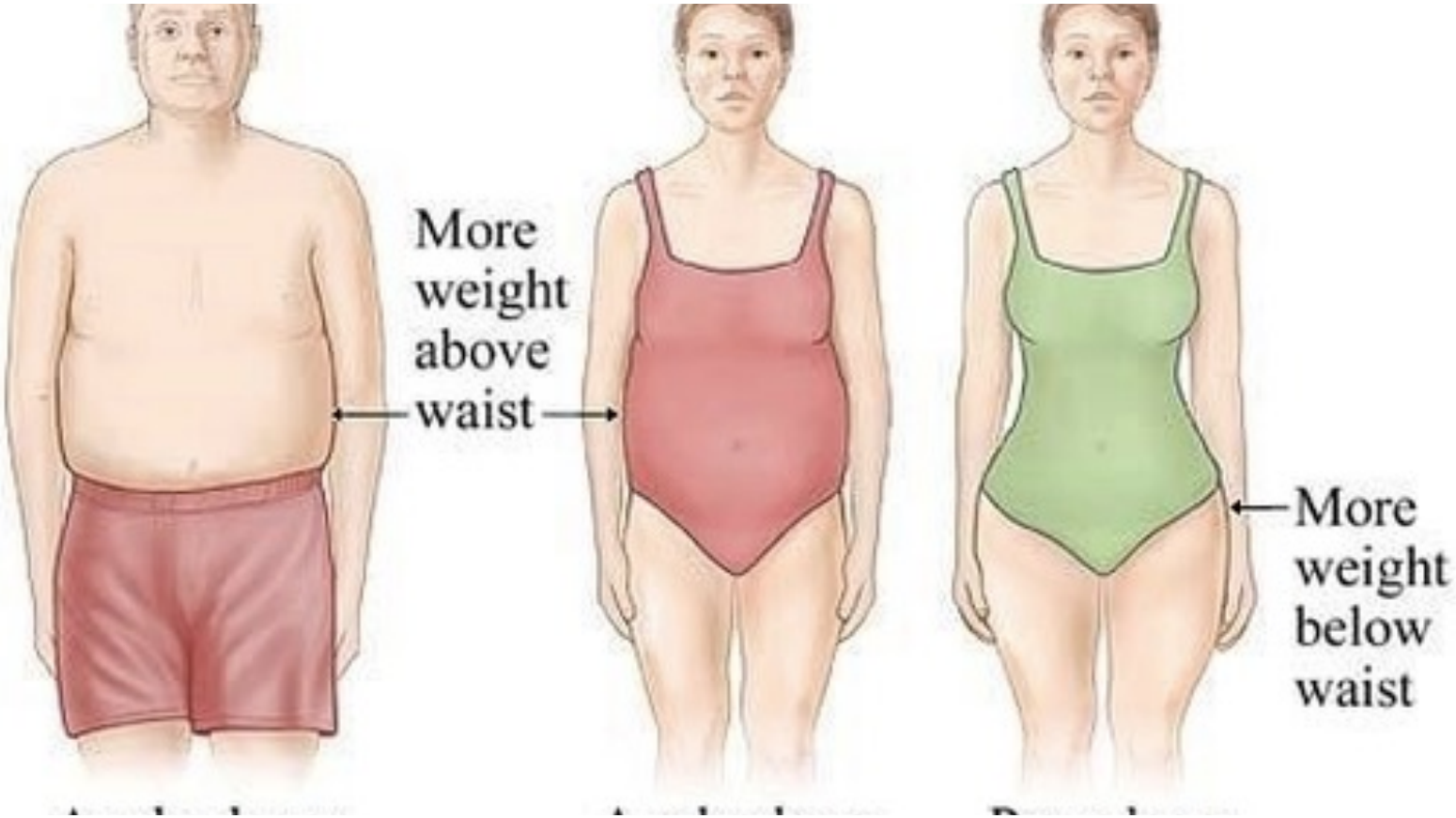
- Television

- Car ownership

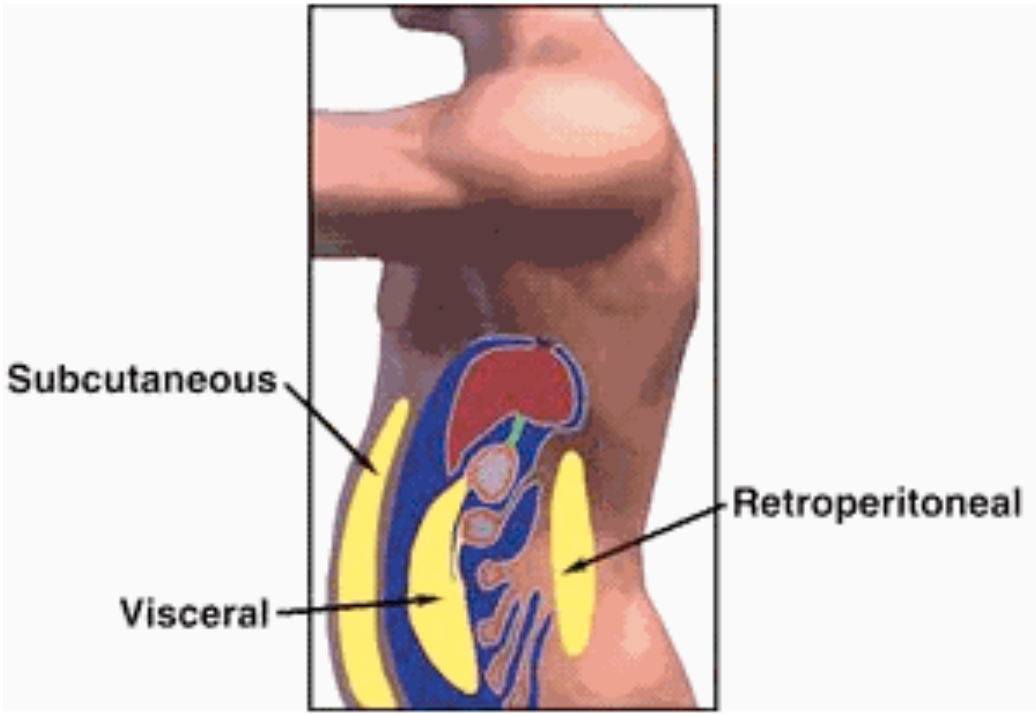
Central versus peripheral obesity

- Abdomen versus hips and thighs
- The more visceral fat the greater the risk of developing cardiovascular and metabolic complications of obesity.
- Differences in the distribution of body fat explain why individuals from Asian backgrounds are at higher risk of the complications of obesity for any given BMI than white Europeans, as Asians tend to have greater central fat distribution.
- Percentage body fat: men: 15-20%, women 25-30%
- Women develop peripheral obesity, while men develop central obesity

Apple versus pear



Visceral Fat



drains into the portal circulation

Metabolic Syndrome

- Complex condition linked to obesity
- Characterized by related clinical features:
  - Obesity
  - Glucose intolerance
  - Insulin resistance
  - Dyslipidemia
  - Hypertension
- Abnormal regulation of energy metabolism
- Diabetes Time-Bomb!

The New International Diabetes Federation (IDF) Definition

For a person to be defined as having the metabolic syndrome they must have:

Central obesity (defined as waist circumference ≥ 94 cm for Europid men and 80 cm for Europid women, with ethnicity-specific values for other groups **plus any two of the following four factors:**

- **Raised TG level:** ≥150mg/dL (1.7 mmol/L) or **specific treatment of this lipid abnormality**
- **Reduced HDL cholesterol:** <40mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women, or **specific treatment for this lipid abnormality**
- **Raised blood pressure:** systolic BP ≥130 or diastolic BP ≥85m Hg, **or treatment for previously diagnosed hypertension**
- **Raised fasting plasma glucose** (FPG) ≥100 mg/dL (5.6 mmol/L), **or previously diagnosed Type 2 diabetes**

Insulin resistance

- Exists when normal insulin concentrations fail to produce a normal biological response

Defect on insulin action: this results in fasting hyperinsulinemia to maintain euglycemia

-Even before fasting hyperinsulinemia develops, postprandial hyperinsulinemia exists.

Major cause: increased plasma albumin-bound fatty acids

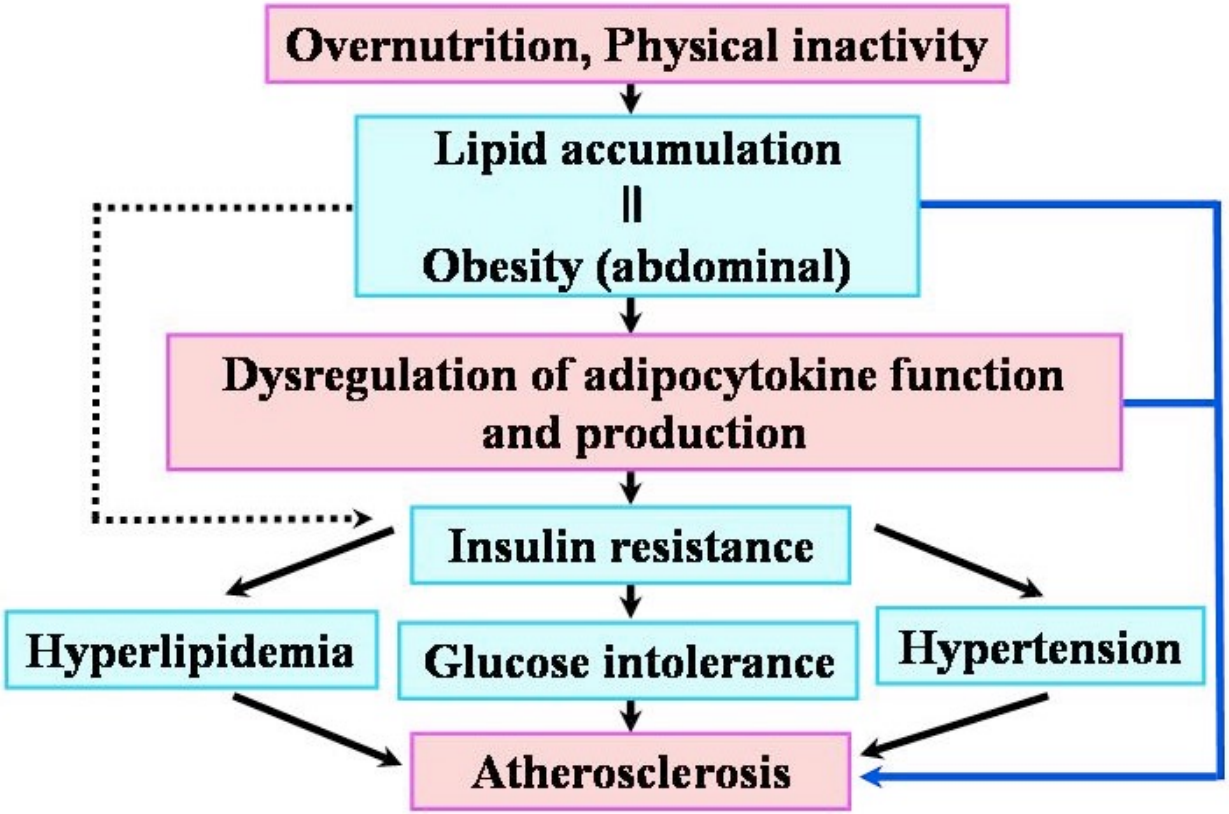
Released from:

-adipose tissue triglycerides through the action of the cAMP-dependent enzyme hormone sensitive lipase

-triglyceride rich lipoproteins through the action of lipoprotein lipase

The most sensitive pathway of insulin action is the inhibition of lipolysis in adipose tissue: vicious cycle!

Pathophysiology of the metabolic syndrome



Glucose Intolerance

insulin fails to

1. adequately inhibit glucose production by liver and kidney
2. mediate glucose uptake into muscle and adipose tissue

FFA can stimulate insulin secretion but increased or prolonged exposure has the opposite effect.

Non esterified fatty acids (NEFA)

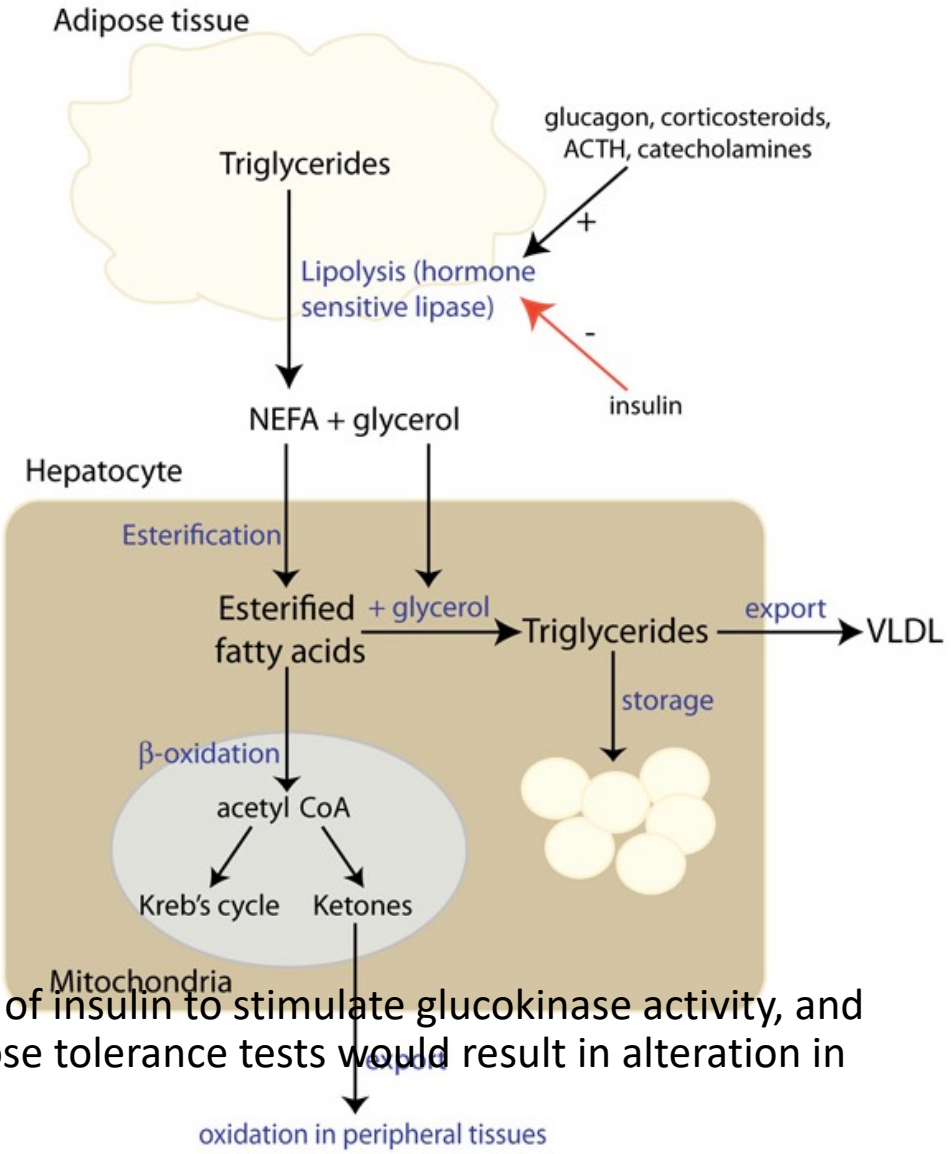
-induce insulin resistance

-impair β-cell function

- T½ in the blood: 2-4 minutes

- After a fatty meal: lipoprotein lipase in the capillaries of adipose tissue hydrolyses circulating triglycerides (chylomicrons)

- decrease insulin-mediated glucose transport by decreasing activity of PI3Kinase, a key insulin-regulated enzyme, that is responsible for translocation of GLUT4 to plasma membrane

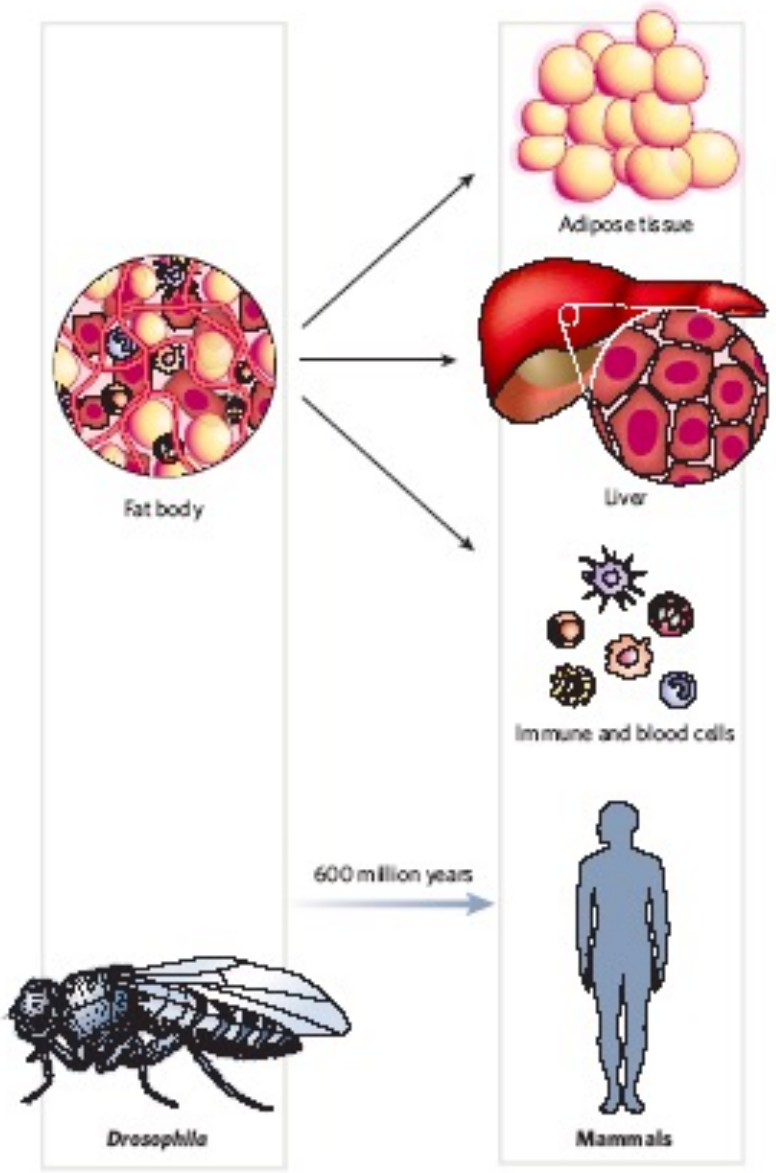


- induce hepatic insulin resistance by interfering with the ability of insulin to stimulate glucokinase activity, and the unsuppressed NEFAs during the early part of the oral glucose tolerance tests would result in alteration in rates of gluconeogenesis and glycogenolysis

Inflammation

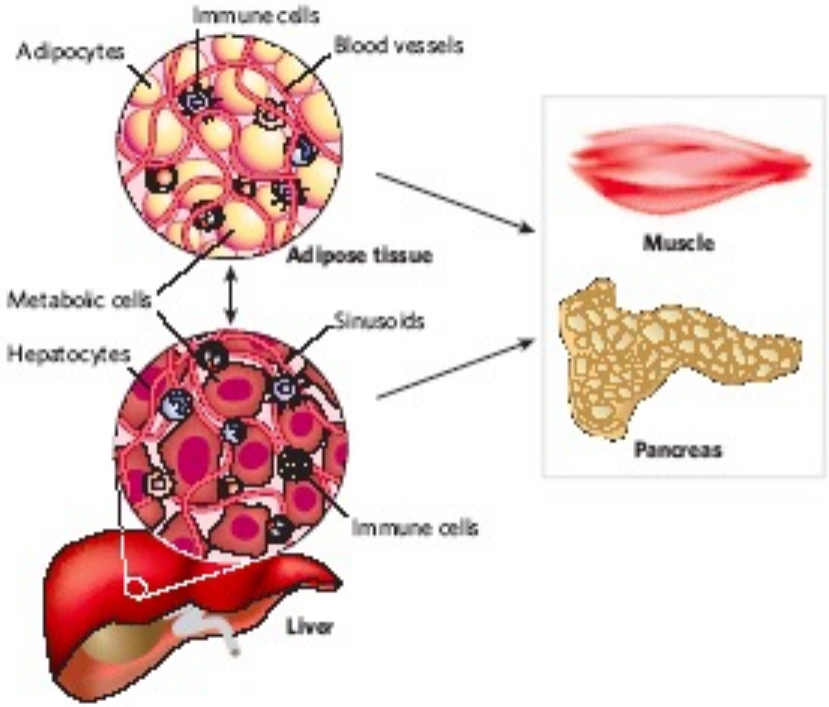
= response of the body invoked to deal with injuries

- tumor, rubor, dolor, calor
- long-term consequences of prolonged inflammation are often be not beneficial
- many of the same mediators are observed in diabetes. But the classic features of inflammation are not observed.
- => low grade, chronic inflammation, “metabolically triggered inflammation”



Evolution of adipose tissue, the liver and the haematopoietic system into distinct organs in mammals

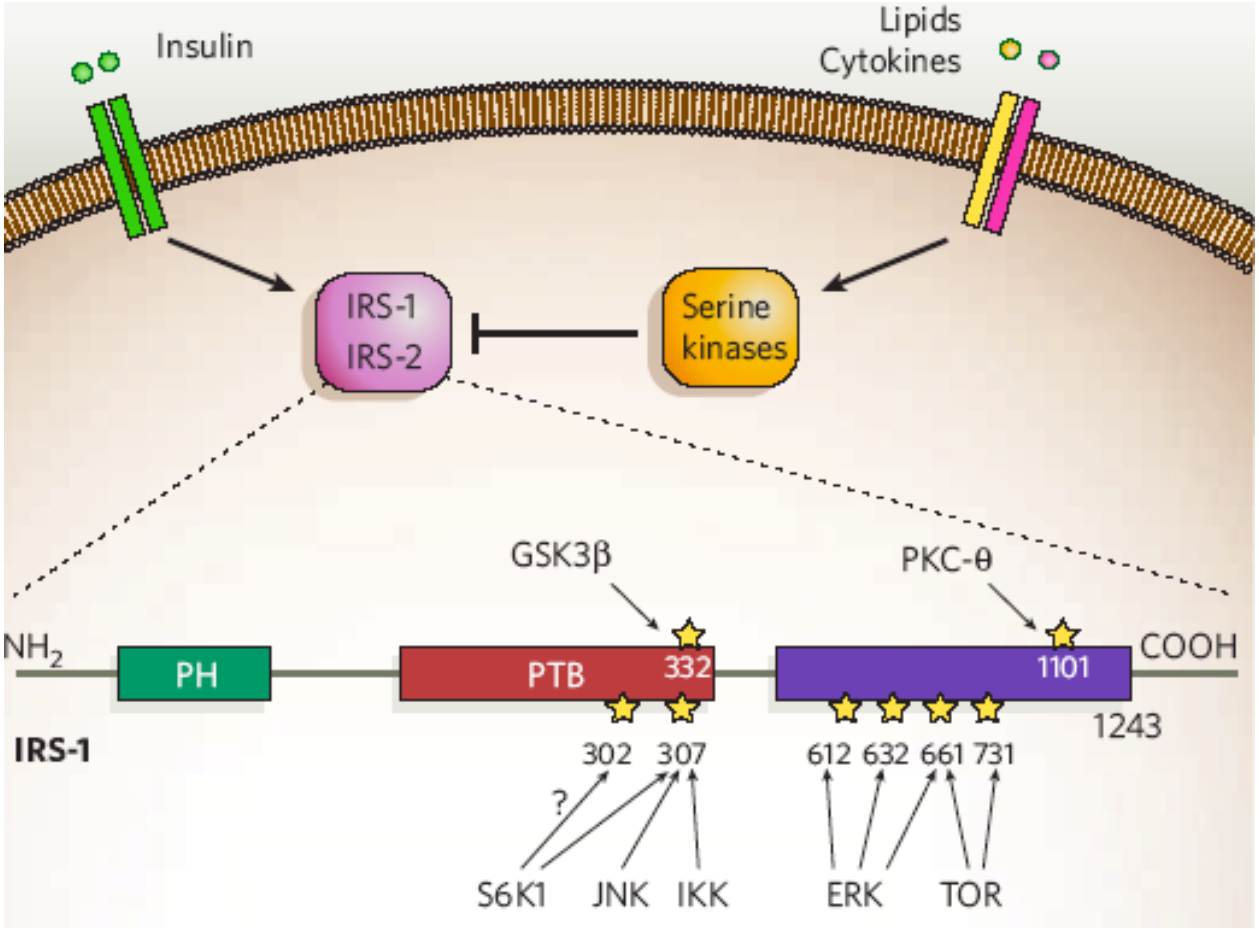
Proximity of metabolic and immune cells



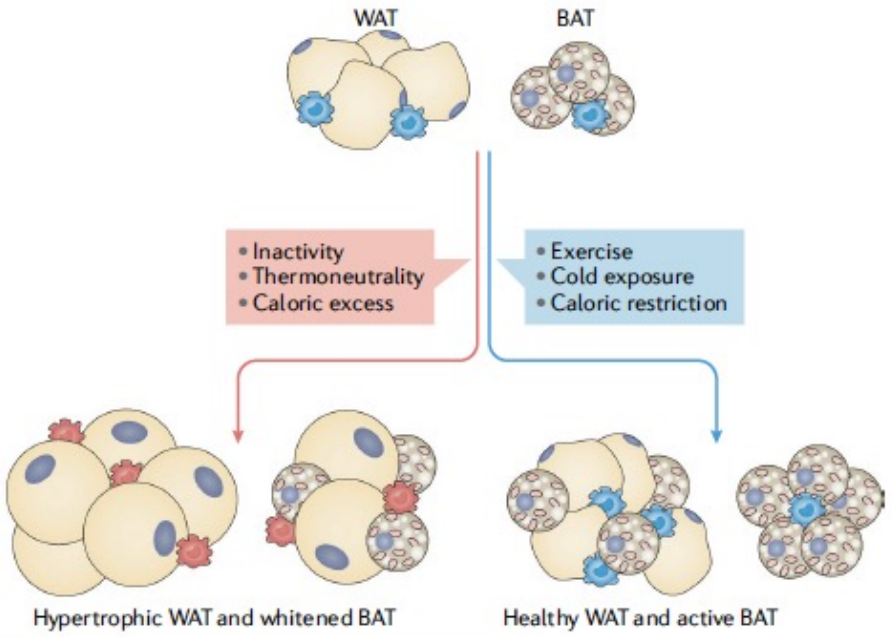
Coordination of metabolic and immune responses

- Energy resources need to be redistributed during the mounting of an immune or inflammatory response
- Blocking insulin signaling diverts energy sources from synthetic pathways
- All stress and immune response pathways are potentially involved in the disturbance of insulin action
- These systems did not evolve in the presence of continuous nutrient surplus such as we are now experiencing
- Exposure to pathogens or pathogen-associated components can disrupt systemic metabolic function from flies to humans.
- Chronic disturbance of metabolic homeostasis, such as occurs in malnutrition or over nutrition, could lead to aberrant immune responses.

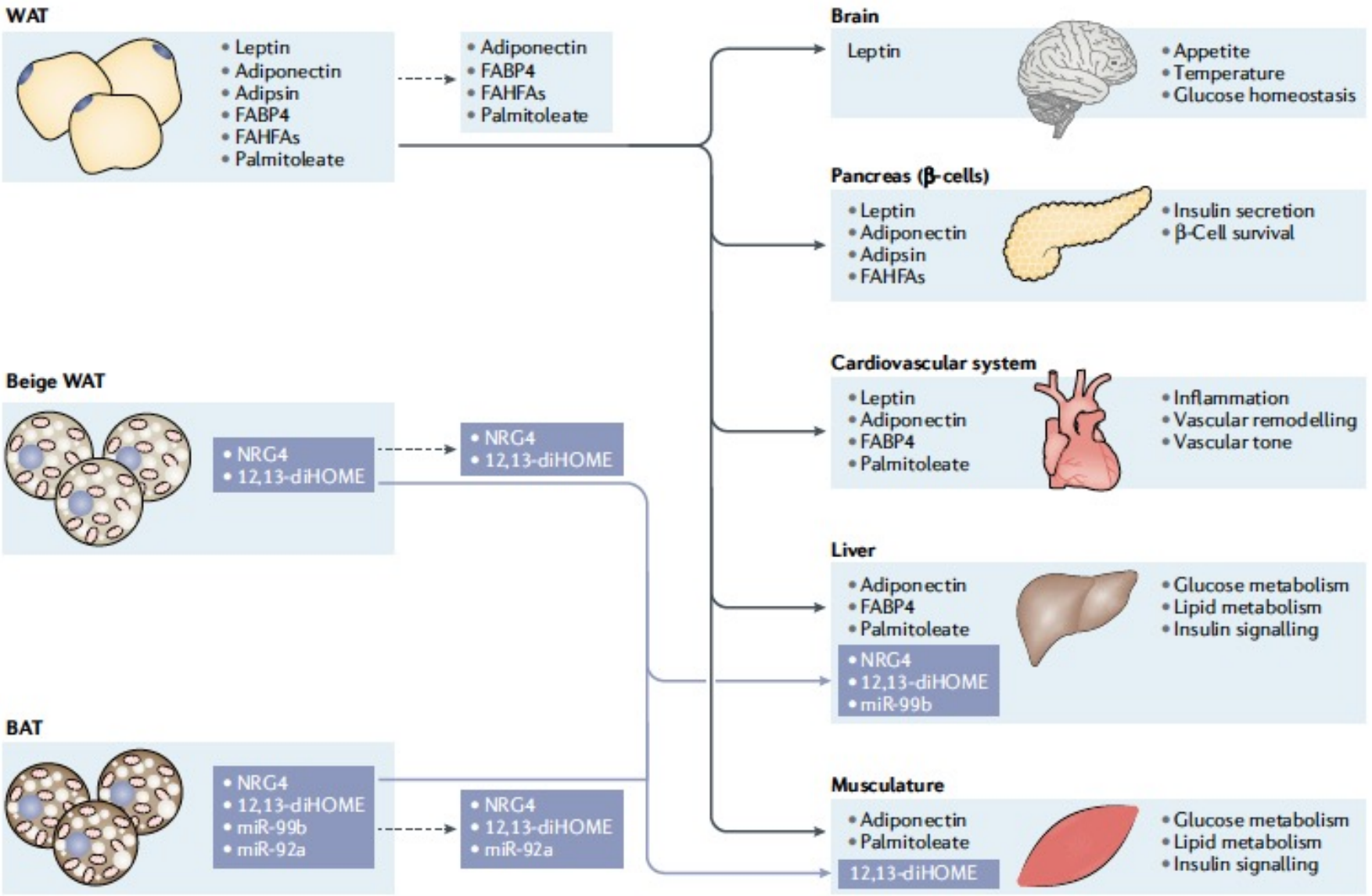
Interface of insulin and inflammatory signaling



Endocrine factors released by healthy and unhealthy adipose tissue



Saturated FFAs	↑	↓
Anorexigenic peptide	↑ Leptin	↓ Leptin
Anti-inflammatory lipids	↓ Palmitoleate, FAHFAs	?
Anti-inflammatory peptides	↓ Adiponectin, omentin, NRG4	↑ Adiponectin, NRG4
Proinflammatory peptides	↑ RBP4, FABP4, resistin, IL-6	↑ IL-6
Prothermogenic molecules	↓ CXCL14	↑ CXCL14, 12,13-diHOME

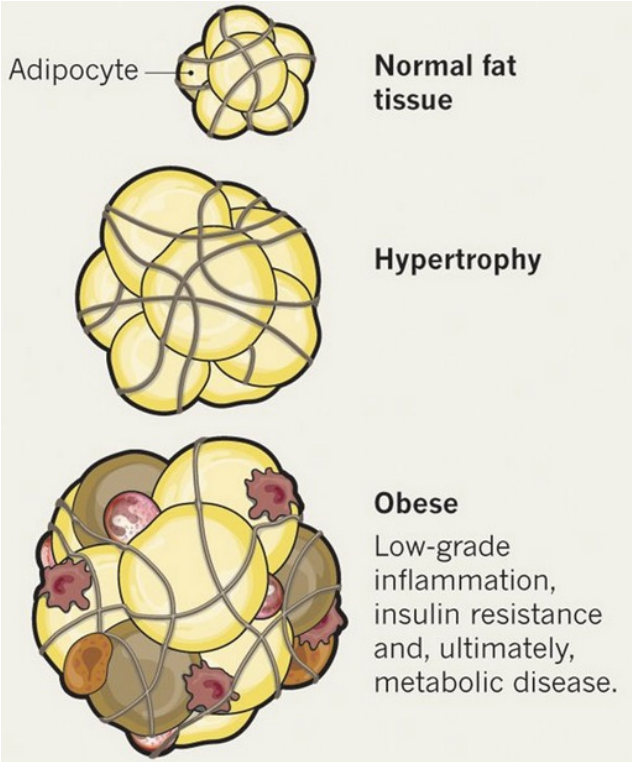


Ludger Scheja, Joerg Heeren

Evolution of adipocytes

- Vertebrate radiation
- Mammals, birds, reptiles, amphibians and many fish have them!
  - in many different locations
- Some are largely structural
  - heels, fingers, toes
  - periorbital

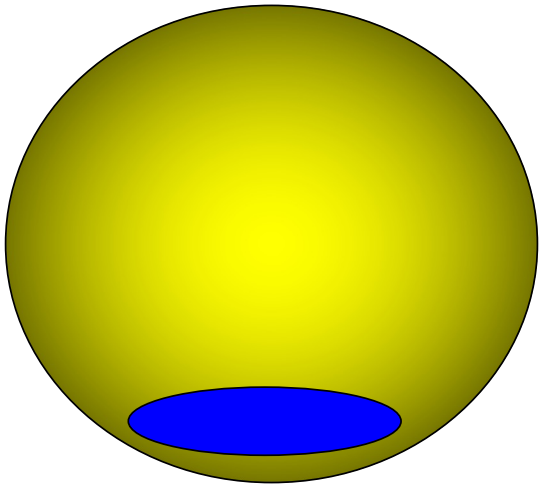
Adipose tissue turning bad



Cells overloaded with lipids rapidly outgrow oxygen supply, leading to cell death and inflammation.

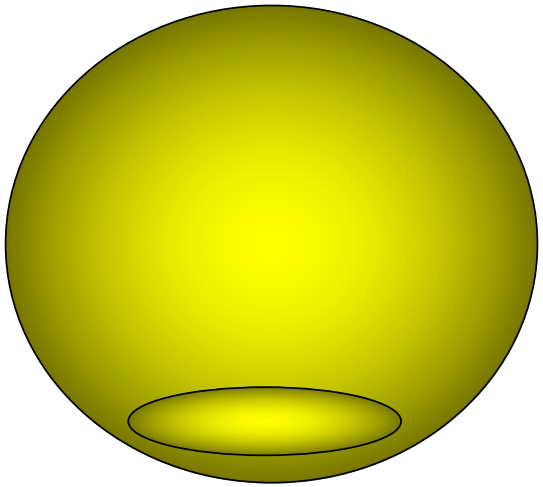
Macrophages, lymphocytes, neutrophils and other immune cells.

Fat cells: Adipocytes



- Regulate fat mass
- Regulate nutrient homeostasis
- Immune response
- Blood pressure control
- Haemostasis
- Bone mass
- Thyroid function
- Reproductive function

The fat cell is an endocrine factory



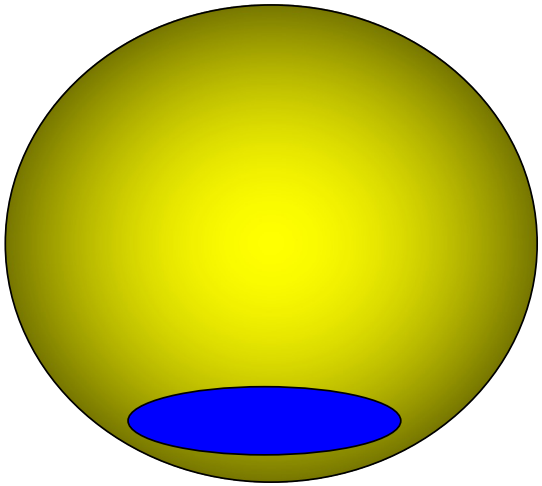
- Non esterified fatty acids (NEFA) from stored triglycerides
- Glycerol
- Hormones
  - Leptin
  - Adiponectin
  - Cortisol
  - Angiotensinogen
  - Resistin
- Proinflammatory cytokines

  TNFα (Tumor Necrosis Factor α)

  IL-6 (interleukin-6)

  MCP-1 (monocyte chemoattractant protein)

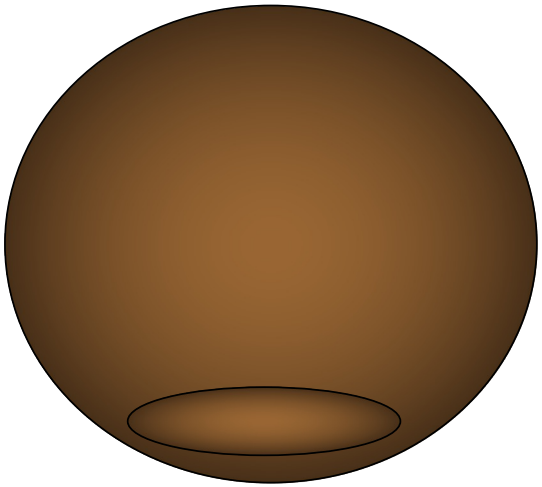
Fat cells: Adipocytes



- Continually absorb or release substances in response to the body's energy needs
- Are better adapted to preserving calories than shedding them
- Release fatty acids into the circulation

Triacylglycerols contain more energy per unit mass than do carbohydrates and can be stored anhydrously.
Glycogen has only 1/2 the energy content per unit of pure mass, and must be stored in association with water.

Brown fat



- Only in mammals
- Express uncoupling protein UCP-1
  - Dissipates the proton gradient accross the inner mitochondrial membrane that is produced by the action of the electron transport chain

  $\Rightarrow$Heat is generated at the expense of ATP
- In humans:
  - Surrounds heart and vessels in infants

Obesity: genetic and epigenetic factors

- Twin studies
- Genome-wide association studies
- Fetal programming
  - Dutch Hunger winter, Army recruits