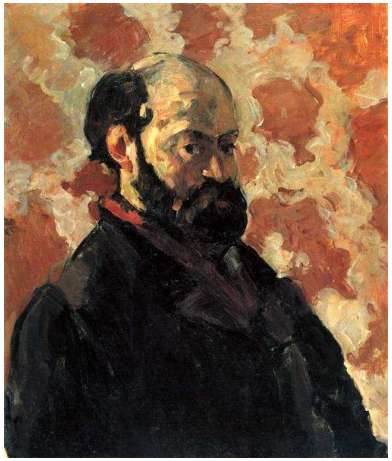
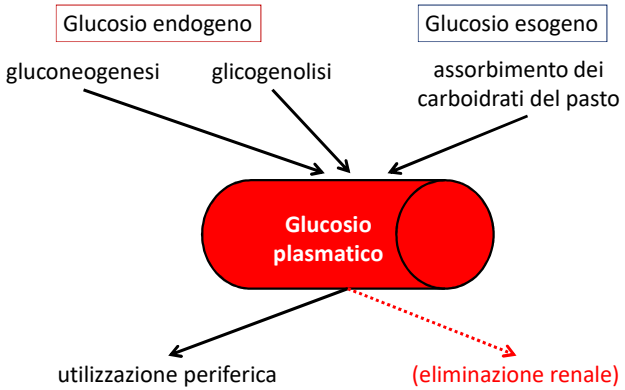


Paul Cezanne, autoritratto (1875)

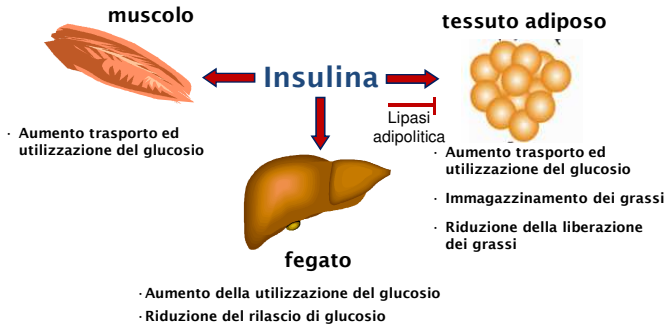
Il diabete



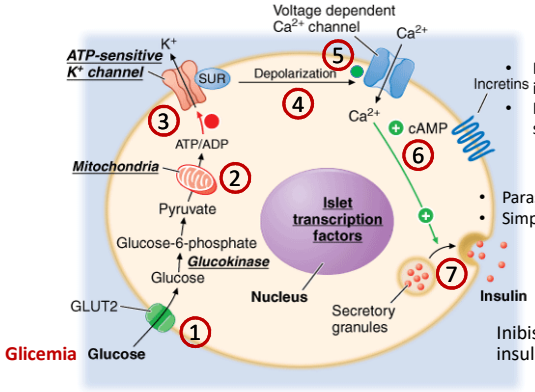
Nonostante l'alternanza di periodi di alimentazione e digiuno, la glicemia rimane in una **ristretta banda di oscillazione:**

4-7 mM o 70-99 mg/dl

Principali effetti dell'insulina



La regolazione della secrezione di insulina



Incretine (GLP-1)

- Biogenesi e secrezione insulina
- Proliferazione e sopravvivenza β-cellule

SN autonomo

- Parasimpatico (M2, Ca^{2+}) ↑
- Simpatico (α2, Gi) ↓ (β, Gs) ↑

Leptina

Inibisce la secrezione di insulina

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Metabolism Nature | Vol 590 | 11 February 2021 | 221

New-found brake calibrates insulin action in β-cells

Rohit N. Kulkarni

Insulin is produced by pancreatic β-cells. The identification of a regulator of insulin signalling in these cells cements the long-standing idea that this pathway has a key role in β-cell biology. See p.326

Article

Inceptor counteracts insulin signalling in β-cells to control glycaemia

326 | Nature | Vol 590 | 11 February 2021

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Ansarullah[1,2,10], Chirag Jain[1,2,10], Fataneh Fathi Far[1,2,10], Sarah Homberg[1,2,10], Katharina Wißmiller[1,2,10], Felizitas Gräfin von Hahn[1,2,10], Aurelia Raducanu[1,2], Silvia Schirge[1,2], Michael Stern[1,2,3], Sara Bilekova[1,2], Johanna Siehler[1,2], Julius Wiener[4,5], Lena Oppenländer[1,2], Amir Morshedi[1], Aimée Bastidas-Ponce[1,2,3], Gustav Collden[6], Martin Irmler[2,7], Johannes Beckers[2,7,8], Annette Feuchtinger[9], Michal Grzybek[2,10], Christin Ahlbrecht[2,11,12], Regina Feederle[11], Oliver Plettenburg[2,11,12], Timo D. Müller[2,8], Matthias Meier[4,5], Matthias H. Tschöp[2,3,8], Ünal Coskun[2,10,14] & Heiko Lickert[1,2,3]✉

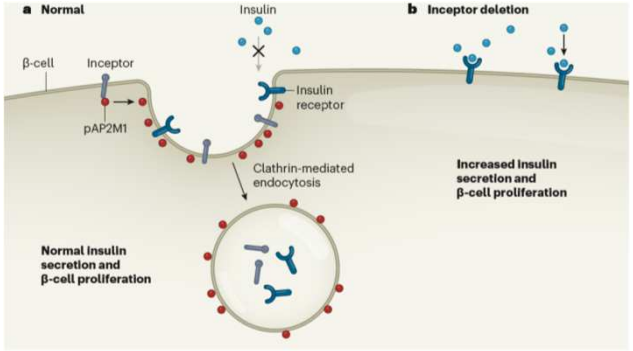
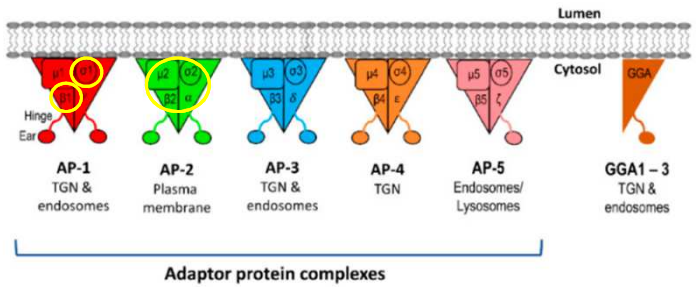


Figure 1 | A newly discovered regulator of insulin signalling. Insulin is produced in and secreted from pancreatic β-cells, but it has been unclear how insulin signalling is regulated in these cells. Ansarullah *et al.*[3] have discovered a previously unknown regulator of insulin signalling in β-cells, the protein inceptor. **a**, The group finds that inceptor binds to pAP2M1, a subunit of the AP2 protein complex. This triggers a process called clathrin-mediated endocytosis, in which inceptor and insulin receptors (along with the related insulin-like growth factor 1 receptors, not shown) are engulfed by the cell membrane and enter the cell. Insulin therefore cannot bind to its receptor. This insulin desensitization restrains insulin signalling to fine-tune insulin secretion from, and proliferation of, β-cells, maintaining normal responses to glucose. **b**, Deletion of inceptor prevents internalization of insulin receptors through this pathway, thereby allowing unrestrained insulin action and leading to enhanced insulin secretion and an increase in β-cell proliferation.

Review *Cells* **2019**, *8*, 531; doi:10.3390/cells8060531

Cargo Sorting at the *trans*-Golgi Network for Shunting into Specific Transport Routes: Role of Arf Small G Proteins and Adaptor Complexes

Jing Zhi Anson Tan and Paul Anthony Gleeson *



σ1 – MEDNIK
β1 – MEDNIK-like

AP-2 – inceptor

Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Cell Biology

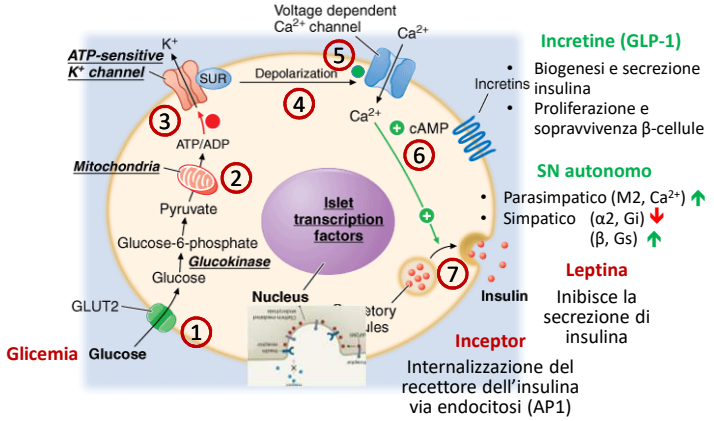
New directions for the clathrin adaptor AP-1 in cell biology and human disease

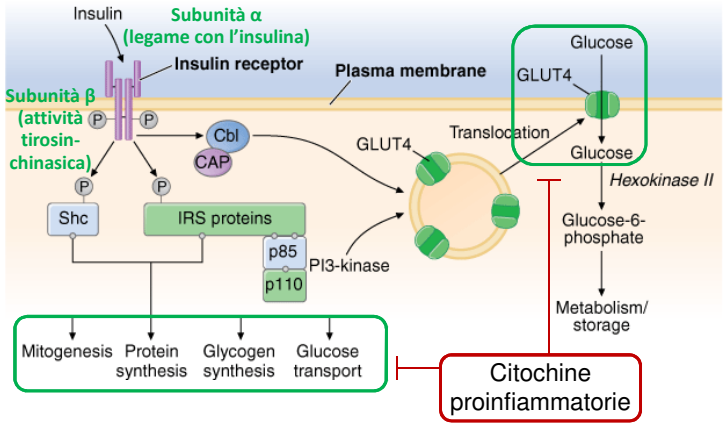
Mara C. Duncan

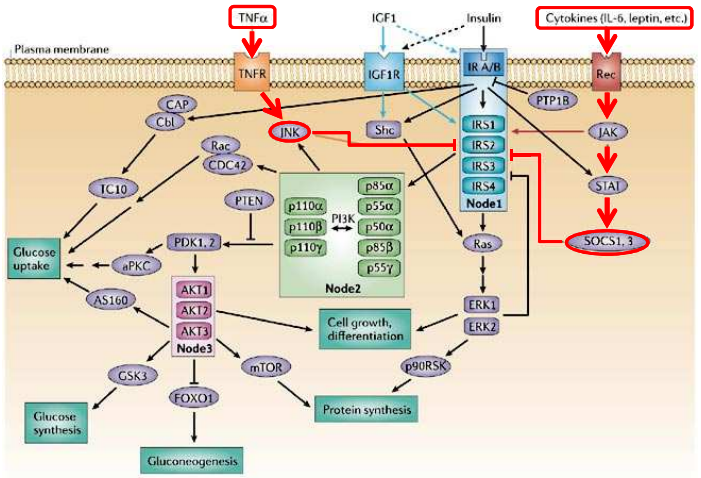
Current Opinion in Cell Biology 2022, 76:102079

AP-1 complexes are evolutionarily conserved adaptor complexes that localize to the trans-Golgi network (TGN) and endosomes. Several excellent resources are available for a detailed description of the subunit structures, regulation, and physical interactions of AP-1, and the reader is referred to those for a background on the subject [2,4–7]. An AP-1 complex is composed of four subunits termed β, γ, μ, and σ. In most organisms, each subunit is encoded by multiple alternate genes. Thus, most organisms express a family of AP-1 complexes composed of different combinations of the alternate gene products. For example, humans potentially express 12 different AP-1 complexes based on different combinations of the single β-subunit (β1) with two alternate γ-subunits (γ1 and γ2), two alternate μ-subunits (μ1A and μ1B), and three alternate σ-subunits (σ1A, σ1B, and σ1C). However, it is not yet known whether all of these complexes form *in vivo*, much less whether they perform redundant or distinct functions.

1. La regolazione della secrezione di insulina

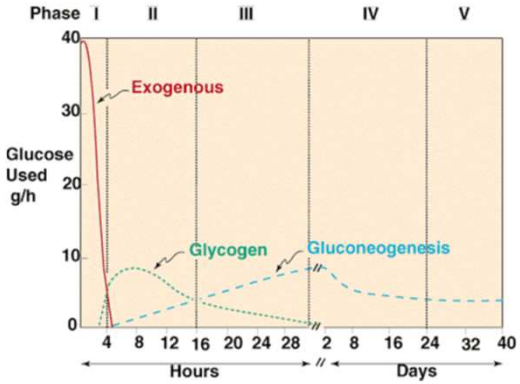






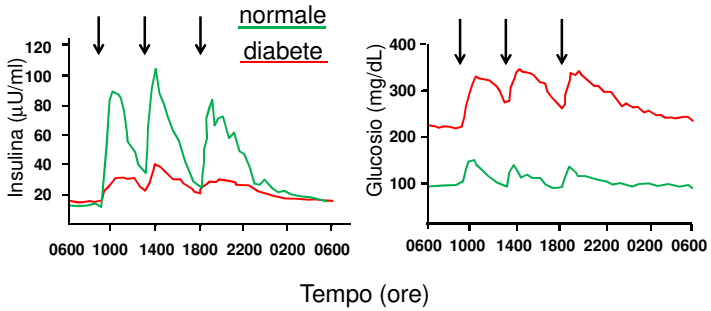
Taniguchi *et al. (2006)*
Nat Rev Mol Cell Biol **7**, 85–96

Diabete Mellito
definizione, classificazione, patogenesi



Diabete Mellito: Definizione

Disordine metabolico ad eziologia multipla caratterizzato da una iperglicemia cronica con disturbi del metabolismo dei carboidrati, lipidi e proteine, conseguente ad una alterazione della secrezione o della azione della insulina.



Criteri diagnostici
Organizzazione Mondiale della Sanità, 1999

Glicemia a digiuno

	Concentrazione del glucosio (mg/dl)
Normale	**70-99**
Alterata glicemia a digiuno	**100-125**
Diabete mellito	**≥ 126**

Da WHO. WHO report WHO/NCD/99.2, 1999.

Criteri diagnostici
Organizzazione Mondiale della Sanità, 1999

Glicemia post-prandiale (2 ore dopo il pasto/OGTT)

	Concentrazione del glucosio (mg/dl)
Normale	< 140
Alterata tolleranza al glucosio	140-199
Diabete mellito	≥ 200

Da WHO. WHO report WHO/NCD/99.2, 1999.

Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus

Abbreviated Report of a WHO Consultation

2. GLYCATED HAEMOGLOBIN (HbA1c) FOR THE DIAGNOSIS OF DIABETES

Recommendation

HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement.

An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests.

Quality of evidence assessed by GRADE: moderate

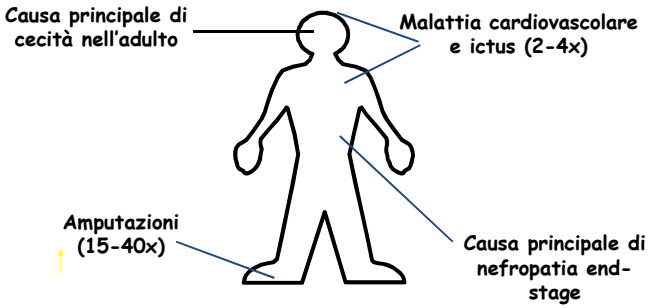
Strength of recommendation based on GRADE criteria: conditional

Some of the factors that influence HbA1c and its measurement*. Adapted from Gallagher et al (*24*)

1. Erythropoiesis Increased HbA1c: iron, vitamin B12 deficiency, decreased erythropoiesis. Decreased HbA1c: administration of erythropoietin, iron, vitamin B12, reticulocytosis, chronic liver disease.
2. Altered Haemoglobin Genetic or chemical alterations in haemoglobin: haemoglobinopathies, HbF, methaemoglobin, may increase or decrease HbA1c.
3. Glycation Increased HbA1c: alcoholism, chronic renal failure, decreased intra-erythrocyte pH. Decreased HbA1c: aspirin, vitamin C and E, certain haemoglobinopathies, increased intra-erythrocyte pH. Variable HbA1c: genetic determinants.
4. Erythrocyte destruction Increased HbA1c: increased erythrocyte life span: Splenectomy. Decreased A1c: decreased erythrocyte life span: haemoglobinopathies, splenomegaly, rheumatoid arthritis or drugs such as antiretrovirals, ribavirin and dapsone.
5. Assays Increased HbA1c: hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiate use. Variable HbA1c: haemoglobinopathies. Decreased HbA1c: hypertriglyceridaemia.

* Some of the above interfering factors are "invisible" in certain of the available assays

Morbilità e Mortalità del Diabete



negli USA → 4ª causa principale di morte per malattia
7ª causa principale di morte

American Diabetes Association, Vital Statistics 2004

La patogenesi del diabete mellito

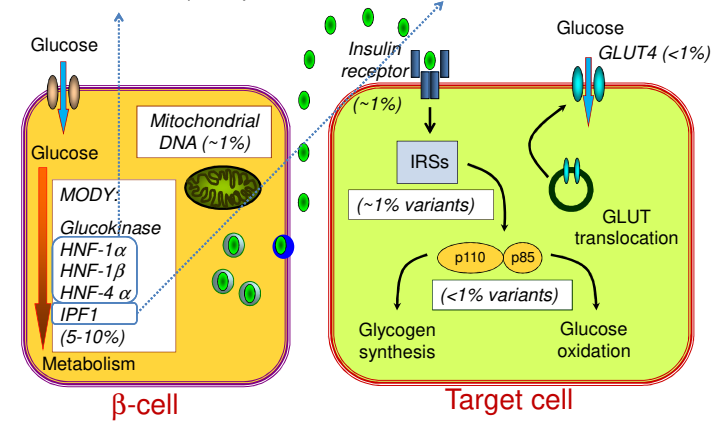
Classificazione

- **Tipo 1**
- **Tipo 2**
- **Altre forme specifiche**
  - *difetti genetici della funzione della β-cellula*
  - *difetti genetici dell'azione della insulina*
  - *malattie del pancreas esocrino*
  - *endocrinopatie*
  - *indotto da farmaci*
  - *infezioni*
  - *forme non comuni di DM immuno-mediate*
  - *altre sindromi genetiche associate a volte con DM*
- **Diabete gestazionale**

Da WHO. WHO report WHO/NCD/99.2, 1999.

Hepatocyte Nuclear Factors (fattori trascrizionali non solo epatici). Variants of the genes can cause several relatively rare forms of Maturity Onset Diabetes of the Young (MODY), an inherited, early onset form of diabetes. Mutations in the HNF4α, HNF1α, or HNF1β genes are linked to MODY1, MODY3, and MODY5 respectively

Insulin promoter factor 1 is a homeodomain protein which in the adult mouse pancreas is selectively expressed in the β-cells and which binds to and transactivates the insulin promoter



Cause monogeniche di DM

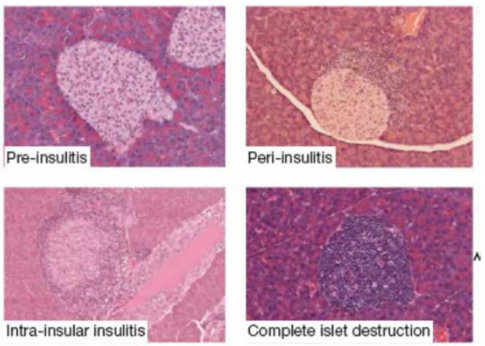
MODY (AD)
- Fattori di trascrizione (HNF-1α, HNF 1β, HNF-4α)
- Glucochinasi

- DIABETE NEONATALE
- subunità del canale KATP (Kir 6.2)
- Glucochinasi (AR)

Le forme più comuni (tipo I e tipo II) hanno patogenesi complessa, multifattoriale

Diabete mellito tipo 1

"Tipo 1" indica un processo di carenza dell'insulina per **distruzione delle β-cellule** che può portare ad una forma di diabete mellito nel quale la somministrazione di insulina esogena è essenziale per la sopravvivenza, allo scopo di prevenire lo sviluppo di **chetoacidosi**, coma e morte.



Non-obese diabetic (NOD) mouse

Bluestone et al. (2010) Nature 464, 1293

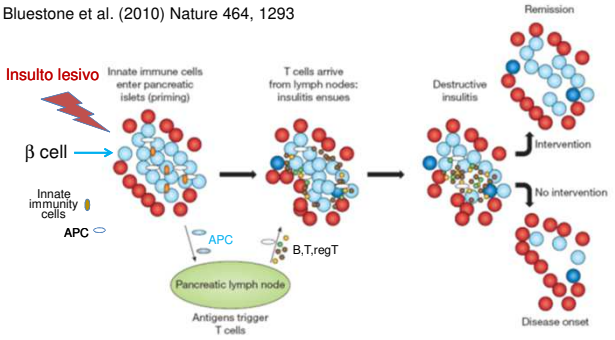
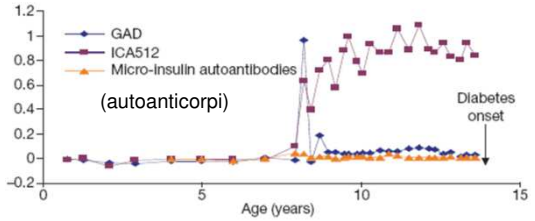
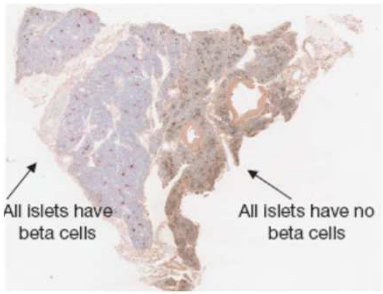


Figure 2 | Immunologic history of type 1 diabetes. An as-yet-undefined immunologic insult occurs in an individual with genetic predisposition and initiates a chronic low-grade immunologic process (priming). The initiating events involve infiltration of innate immune cells (such as monocytes and natural killer cells with autoreactive B cells) (orange ovals) into the pancreatic islets. The principal site of antigen presentation is thought to be the pancreatic lymph node where islet antigens are presented by antigen-presenting cells (white ovals) to T cells (brown dots). Blue ovals are antigen-presenting cells loaded with islet antigens. B cells (green dots) and dendritic cells may be among the early antigen-presenting cells. The cellular infiltration of islets ensues but the insulitis is uneven. Islets with infiltration may be situated near to islets without cells. The process specifically targets insulin-producing β-cells (light blue circles), while other endocrine cells (red circles) within the islet are spared. In the lymph nodes, the cycle of antigen presentation, activation of adaptive immune cells, licensing of effector T cells and epitope spreading continues with the loss of β-cells over time. There is evidence for a regenerative attempt of β-cells in the midst of the islet inflammation (dark blue circles). Tertiary lymphoid organs are thought to develop within the islets, which may lead to amplification of the adaptive immune response. Regulatory T cells (yellow dots) may arrest this process in its early and late stages but are not able to contain the amplified process in the late stages despite an increase in their numbers. With continued loss of β-cells, hyperglycaemia can be detected. The loss of metabolic function at presentation may be both functional and anatomic, because immune therapies can restore cells that have lost the capacity to produce insulin but have not been destroyed. Without intervention, however, β-cell loss continues.





Pancreas di un paziente con diabete di tipo I di lunga durata

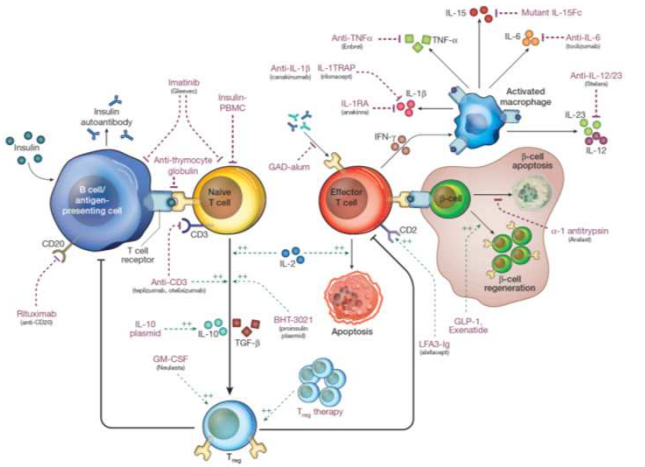
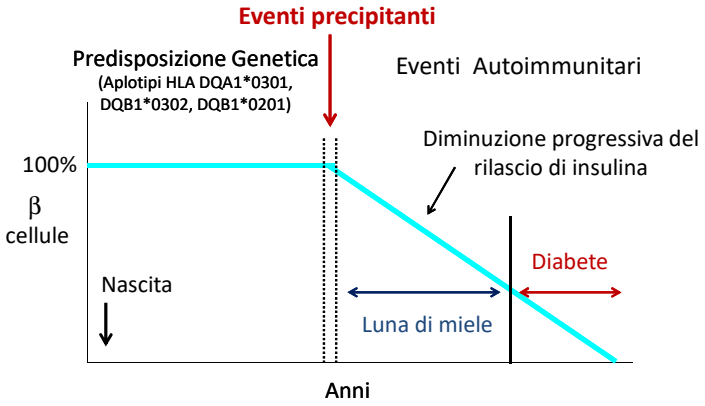


Figure 4 | Targets of immune intervention in type 1 diabetes. This schematic provides an overview of the pathogenesis of type 1 diabetes, highlighting a number of key pathways that are being targeted by current therapeutics. Although not exhaustive (see Supplementary Table 1), this figure shows that both non-specific and antigen-specific therapies are being tested, which inhibit effector cells and antigen presentation as well as boost regulatory pathways. Purple and green dotted arrows indicate the therapeutics, black arrows are immune and metabolic pathways; a green dotted arrow indicates a positive effect and a purple dotted arrow indicates a negative effect. In addition, these immunotherapies are being combined with drugs that promote β-cell survival to potentially replenish insulin-producing β-cells. The figure has been redrawn after ref. 87, with permission.

PATOGENESI DEL DIABETE TIPO 1



La triade sintomatologica del diabete:

- Poliuria (osmotica)
- Polidipsia (secondaria)
- Polifagia

Le complicanze:

- Acute
  - Chetoacidosi diabetica
  - Sindome iperglicemica iperosmolare
- Croniche
  - Macrovascolari (aterosclerosi)
  - Microvascolari
    - Retinopatia
    - Neuropatia
    - Nefropatia

Le studieremo nel diabete tipo 2

1. Chetoacidosi Diabetica (DKA)

"Si definisce chetoacidosi diabetica la triade iperglicemia, acidosi e chetosi, di cui la causa principale è la carenza assoluta o relativa di insulina"

Diabetologia (1989) 32: 399-401

Diabetologia
© Springer-Verlag 1989

Review

Oskar Minkowski: Discovery of the pancreatic origin of diabetes, 1889

R. Luft
Department of Endocrinology, Karolinska Hospital, Stockholm, Sweden

Fig. 1. This photograph of Oskar Minkowski (1858-1931) is taken from Fischer I (1933) Biographisches Lexikon. Urban & Schwarzenberg, Berlin Vienna

It is of interest to reflect back on two of the generally accepted landmark discoveries in diabetes research and to consider how they have influenced our thinking. Legend has it that on a momentous day in 1889 Oskar Minkowski noticed that urine collected from his pancreatectomized dogs attracted an inordinate number of flies. He is then said (by some) to have tasted the urine and to have been struck by its sweetness. From this simple but astute observation, he established for the first time that the pancreas produced some entity essential for control of the blood sugar concentration, which, when absent, resulted in diabetes mellitus. A second milestone was reached some 30 years later when Frederick Banting and his colleagues identified the active pancreatic principle as insulin. Thus, in 1921 the concept of an insulin-glucose axis as a central component of fuel homeostasis came into being. In keeping with its etymological derivation, diabetes mellitus has been viewed ever since as a disorder primarily associated with abnormal glucose metabolism.

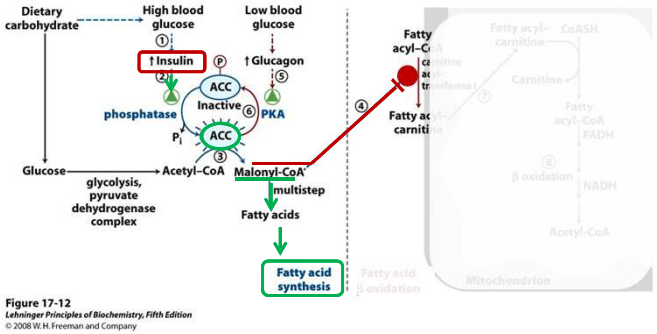
Now let us suppose that Minkowski had lacked a sense of taste but had a good nose. Presumably, instead of detecting sugar in the diabetic urine he would have smelled the acetone. Although this might have left him even more bemused as to the swarm of flies, he would surely have concluded that removal of the pancreas causes fatty acid metabolism to go awry. Extending this hypothetical scenario, the major conclusion of Banting's work might then have been that the preeminent role of insulin is in the control of fat metabolism. No doubt, soon thereafter hyperglycemia (high blood sugar concentration) and glycosuria (spillage of glucose in the urine) would have been recognized as additional untoward effects of insulin deficiency and would likely have been considered secondary to disordered fat metabolism. It might well be asked whether such a viewpoint deserves more consideration than it has received hitherto.

What If Minkowski Had Been Ageusic? An Alternative Angle on Diabetes

J. Denis McGarry

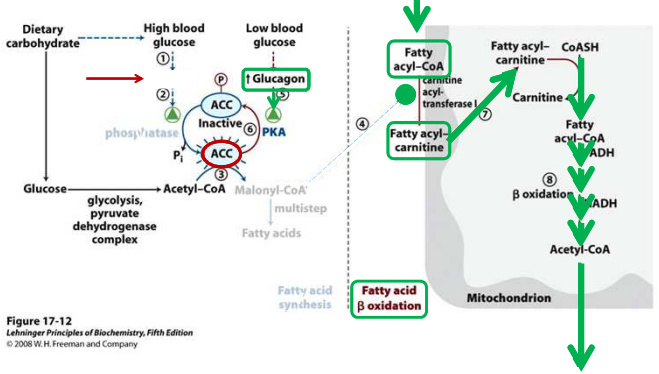
Despite decades of intensive investigation, the basic pathophysiological mechanisms responsible for the metabolic derangements associated with diabetes mellitus have remained elusive. Explored here is the possibility that traditional concepts in this area might have carried the wrong emphasis. It is suggested that the phenomena of insulin resistance and hyperglycemia might be more readily understood if viewed in the context of underlying abnormalities of lipid metabolism.

Science (1992) 258, 766-770



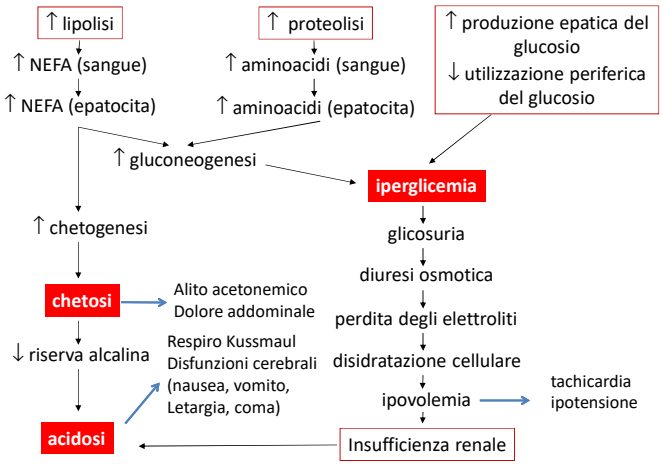
Idrolisi trigliceridi tessuto adiposo

Acidi grassi



Corpi chetonici

Riduzione dell'insulina + aumento degli ormoni contro-regolatori



Manifestazioni cliniche del diabete di tipo 1 scompensato

iperglicemia	Stanchezza, malessere generale	
diuresi osmotica	poliuria, sete, polidipsia	disidratazione, ipotensione
perdita elettroliti	crampi, aritmie cardiache	anomalie ECG
iperosmolarità	sonnolenza	disfunzioni cerebrali
chetoacidosi	perdita di peso	perdita della massa muscolare
	bradipnea	respiro Kussmaul
	dolori addominali	ipostenia

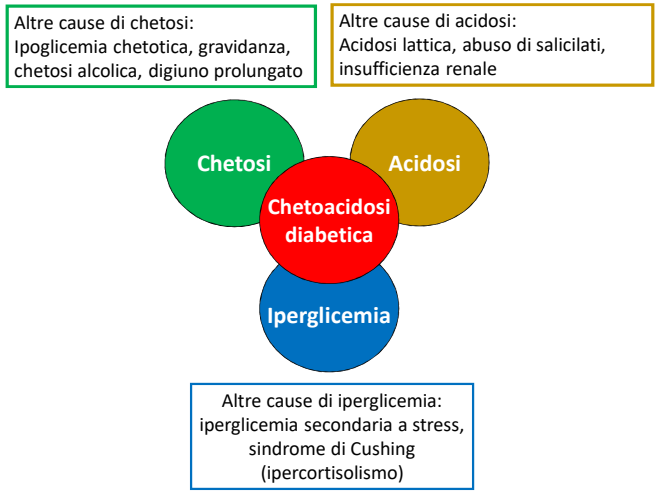
2. Sindrome iperglicemica iperosmolare

Definizione

Si definisce Sindrome Iperglicemica Iperosmolare (SII) quella complicanza metabolica acuta del diabete mellito caratterizzata da:

- iperosmolarità *(osmolarità plasmatica > 320 mosm/kg)*
- grave iperglicemia *(glicemia > 600 mg/dl)*
- marcata disidratazione
- assenza di acidosi *(pH plasmatico sempre >7.3 e bicarbonato > 15 mEq/l)*

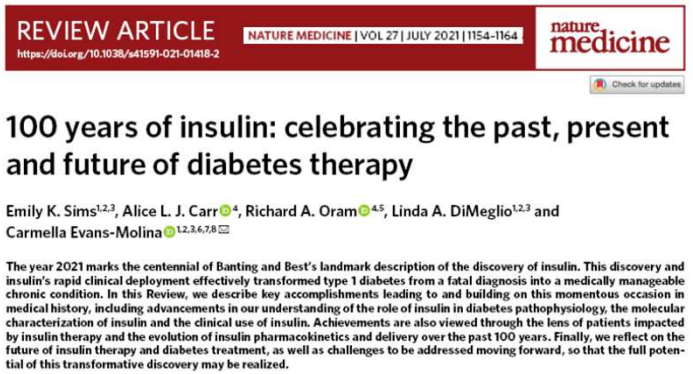
Ipotensione, tachicardia, alterato stato mentale
NO nausea, vomito, dolore addominale, respiro Kussmaul



Sindrome iperglicemica iperosmolare

Principali caratteristiche cliniche

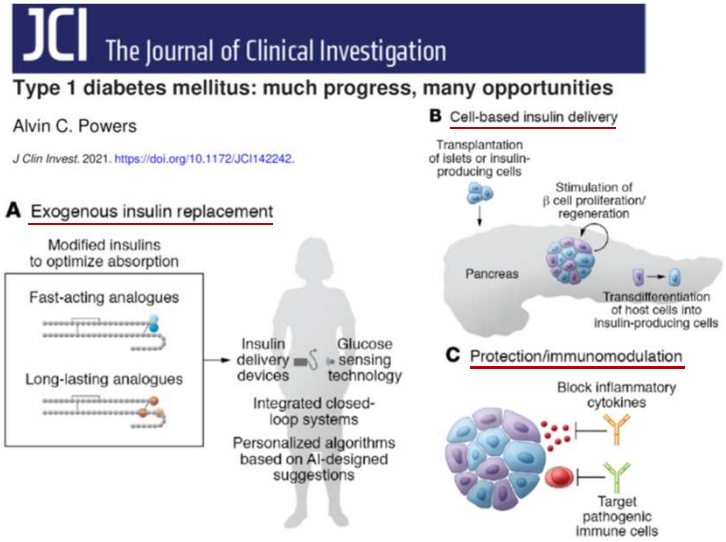
- Lenta evoluzione
- Poliuria
- Sete intensa
- Disidratazione ingravescente
- Progressivo ottundimento del sensorio
- Tachicardia, ipotensione
- Shock
- Convulsioni
- Coma


REVIEW ARTICLE
NATURE MEDICINE | VOL 27 | JULY 2021 | 1154–1164
https://doi.org/10.1038/s41591-021-01418-2
nature medicine

100 years of insulin: celebrating the past, present and future of diabetes therapy

Emily K. Sims[1,2,3], Alice L. J. Carr[4], Richard A. Oram[4,5], Linda A. DiMeglio[1,2,3] and Carmella Evans-Molina[1,2,3,6,7,8]

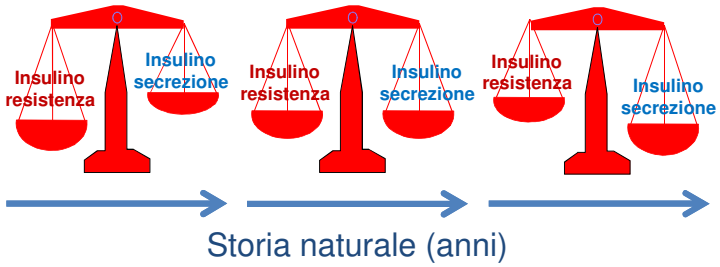
The year 2021 marks the centennial of Banting and Best's landmark description of the discovery of insulin. This discovery and insulin's rapid clinical deployment effectively transformed type 1 diabetes from a fatal diagnosis into a medically manageable chronic condition. In this Review, we describe key accomplishments leading to and building on this momentous occasion in medical history, including advancements in our understanding of the role of insulin in diabetes pathophysiology, the molecular characterization of insulin and the clinical use of insulin. Achievements are also viewed through the lens of patients impacted by insulin therapy and the evolution of insulin pharmacokinetics and delivery over the past 100 years. Finally, we reflect on the future of insulin therapy and diabetes treatment, as well as challenges to be addressed moving forward, so that the full potential of this transformative discovery may be realized.



Fernando Botero

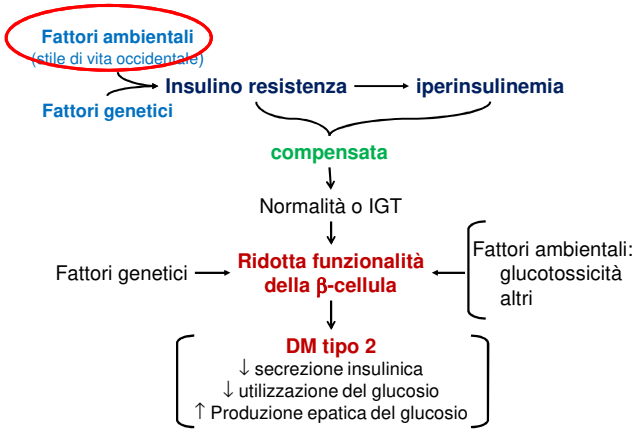
Diabete mellito tipo 2

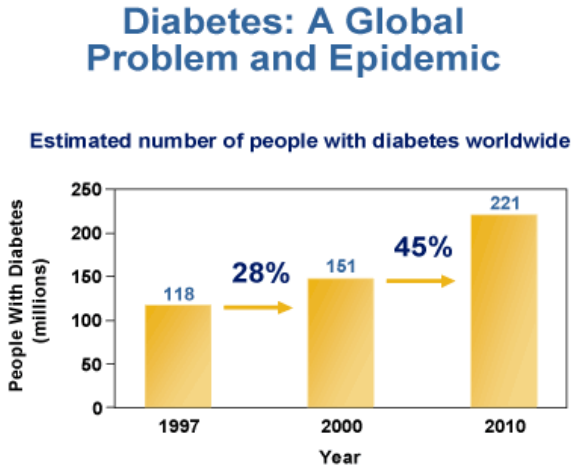
- Caratterizzato da un disordine della azione insulinica (insulino resistenza) e della secrezione insulinica, ciascuna delle quali può essere la forma predominante.
- Generalmente entrambe le alterazioni sono presenti al momento della manifestazione clinica della malattia

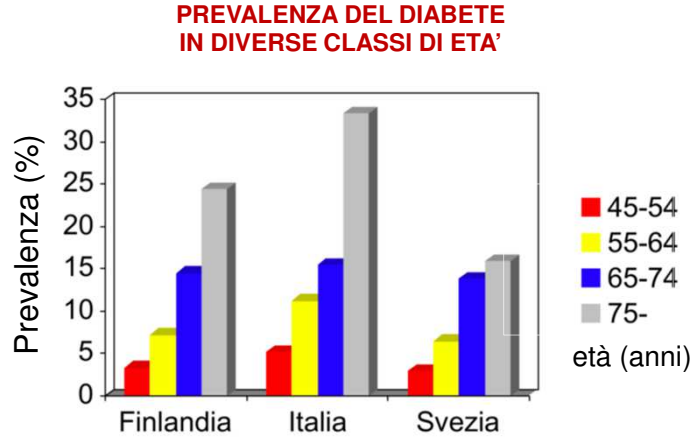


Da WHO. WHO report WHO/NCD/99.2, 1999.

PATOGENESI DEL DIABETE TIPO 2







Adapted from different references

- Il Diabete di tipo 2 è associato all'obesità

  Perchè gli obesi diventano insulino-resistenti?

  Come si sviluppa la disfunzione secretiva?

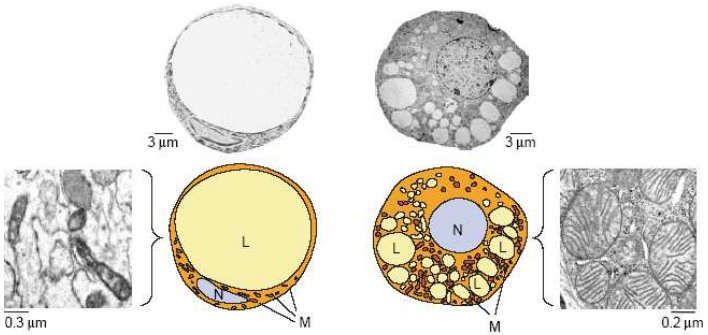
La complessa relazione tra obesità e diabete (diabesity)

Tre importanti concetti preliminari:

1. Il tessuto adiposo come produttore di ormoni (adipochine): l'organo endocrino adiposo
2. L'autoregolazione del metabolismo energetico: i sensori cellulari dei livelli di ATP/ADP/AMP
3. Il ruolo di adipochine, insulina e leptina nel controllo dell'assunzione di cibo

L’organo endocrino adiposo e le sue alterazioni nell’obesità

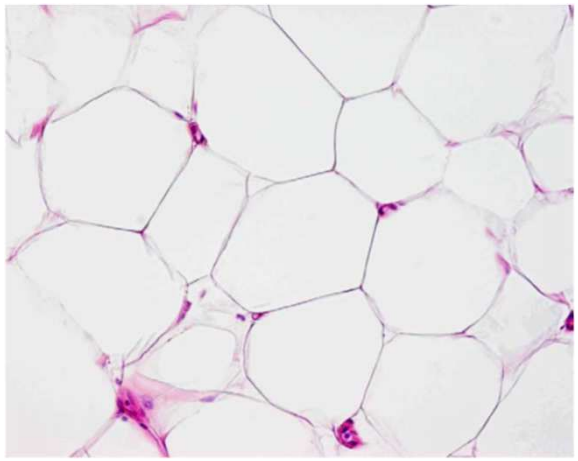
La prima distinzione: grasso bianco e grasso bruno



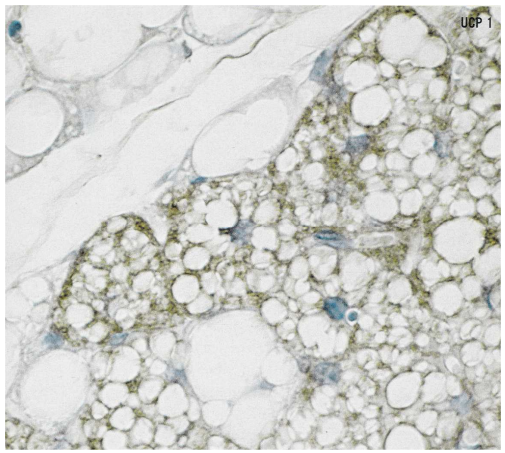
White adipocyte
- Lipids (L) in a single vacuola
- Peripheral nucleus (N)
- Few mitochondria (M), poorly developed
- No *UCP1* gene expression

Brown adipocyte
- Lipids (L) in multiple vacuolae
- Central nucleus (N)
- Many mitochondria (M), highly developed
- *UCP1* gene expression

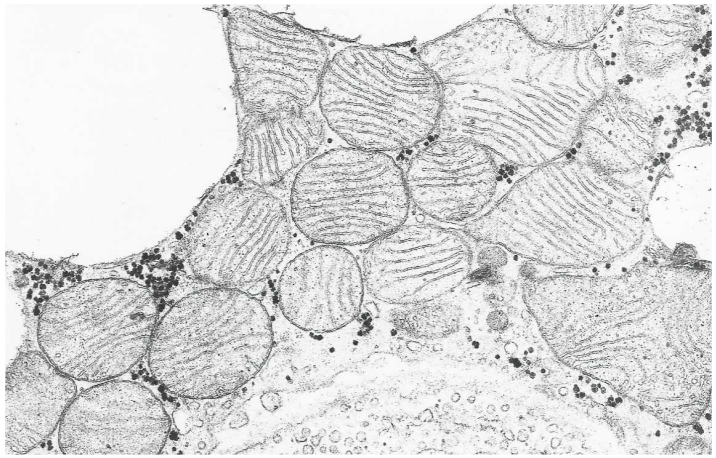
Il tessuto adiposo bianco (uomo)

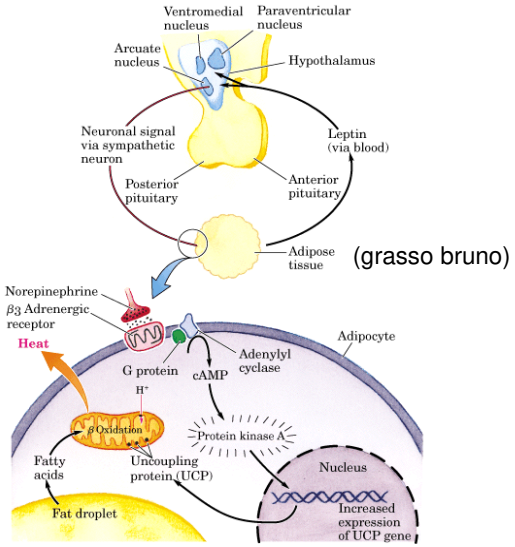


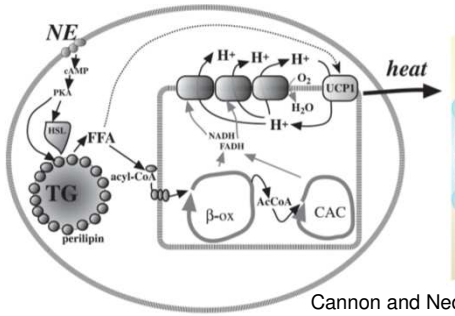
Il tessuto adiposo bruno (ratto)



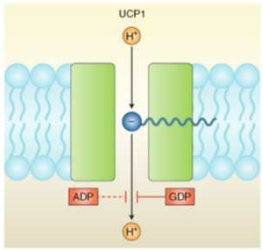
I mitocondri nel grasso bruno







Nat Metab (2019) 1, 752-753



Cannon and Nedergaard (2004)
Physiol. Rev. 84, 277-359

FIG. 4. Norepinephrine-induced stimulation of thermogenesis in brown adipocytes: events downstream of the protein kinase A (PKA) activation illustrated in Fig. 2. HSL, hormone-sensitive lipase; TG, triglyceride droplet; AcCoA, acetyl CoA. Free fatty acids (FFA) activated to acyl CoAs by acyl-CoA synthetase are first transferred to acyl-carnitine by the highly expressed muscle form of carnitine palmitoyltransferase I (M-CPT I), which is the CPT I form found in both brown and white adipose tissue (205) and which is very sensitive to inhibition by malonyl CoA. The acyl-carnitine probably enters the mitochondria through the carnitine transporter (not as yet explicitly described in brown adipose tissue) and is probably reconverted to acyl CoA by CPT II. The ensuing β-oxidation (β-ox) of the fatty acids (acyl CoAs) as well as the activity of the citric acid cycle (CAC) lead to the formation of the reduced electron carriers FADH and NADH, which are then oxidized by the electron transport chain (respiratory chain; here indicated by the series of gray boxes), ultimately through oxygen consumption. This results in a pumping out of protons from the mitochondria and the formation of a proton-motive force that drives the protons back into the mitochondrial matrix through the uncoupling protein UCP1. The energy stored in the proton-motive force is then released as heat.

REVIEW GENES & DEVELOPMENT 27:234–250 © 2013 by Cold Spring Harbor Laboratory Press

Adaptive thermogenesis in adipocytes: Is beige the new brown?

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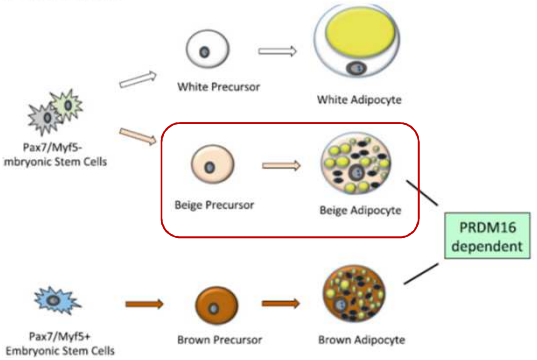
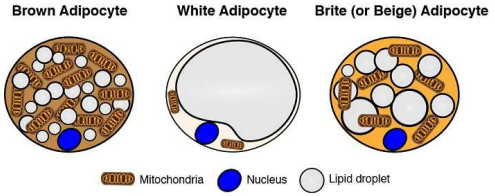
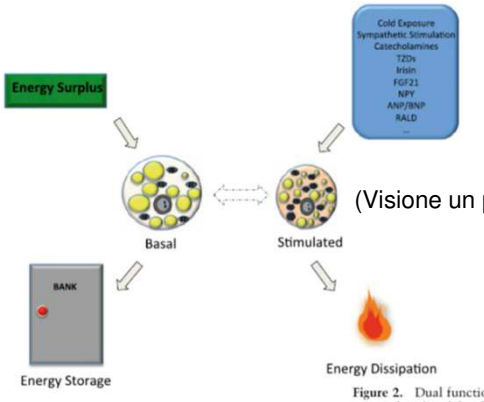




	Brown	White	Brite/beige
UCP1 Expression	Positive	Negative	Positive
Mitochondrial Density	High	Low	Medium
LD Morphology	Multi-locular	Uni-locular	Multi-locular
Primary Function	Thermogenesis Endocrine	Energy storage Endocrine	Thermogenesis? Endocrine?

D. Guertin, University of Massachusetts Medical School
https://www.umassmed.edu/guertinlab/research/adipocytes/



(Visione un po' ottimistica)

Figure 2. Dual functions of beige fat cells. Beige fat cells have a very low basal level of UCP1 but can robustly respond to cAMP to activate a thermogenic program to levels similar to those seen in the brown cells. When energy intake exceeds energy expenditure, the surplus energy can be stored in beige fat cells in the form of lipid, and beige fat cells take on a more "white" morphology. Many stimuli—including cold, sympathetic stimulation, TZDs, and hormones (including recently identified exercised induced polypeptide irisin)—can activate beige fat cells and result in increased energy dissipation.

Journal of Clinical Investigation
Vol. 41, No. 9, 1962

A CASE OF SEVERE HYPERMETABOLISM OF NONTHYROID ORIGIN WITH A DEFECT IN THE MAINTENANCE OF MITOCHONDRIAL RESPIRATORY CONTROL: A CORRELATED CLINICAL, BIOCHEMICAL, AND MORPHOLOGICAL STUDY

By ROLF LUFT,* DENIS IKKOS,* GENARO PALMIERI,* LARS ERNSTER† AND BJÖRN AFZELIUS‡

(From the Department of Endocrinology and Metabolism, Karolinska Sjukhuset, and the Departments of Physiological Chemistry and Biophysics, Wenner-Gren Institute, University of Stockholm, Sweden)

Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 8731–8738, September 1994

Il morbo di Luft,
la prima malattia mitocondriale
nella storia della medicina

Review

The development of mitochondrial medicine

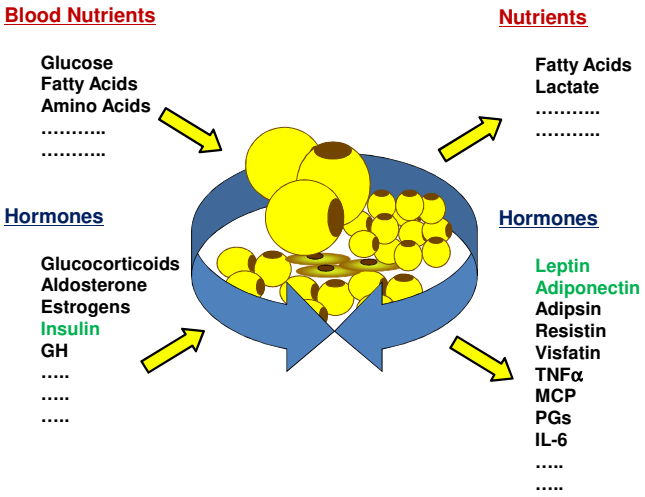
Rolf Luft

The Rolf Luft Research Institute, Department of Molecular Medicine, Karolinska Hospital, S-171 76 Stockholm, Sweden

The Birth of Mitochondrial Medicine (1959–1962): Luft Disease

The first patient found to have a mitochondrial disease was a 30-year-old woman who developed clinical symptoms at the age of 7. Her dominant symptoms were *enormous perspiration* combined with markedly increased fluid intake but without polyuria; *extremely high caloric intake* (above 3000 kcal per day) at a stable body weight of 38 kg and a body height of 159 cm; and *general weakness*, particularly prominent in her musculature. The dominating laboratory finding was a basal metabolic rate (BMR, a measure of oxygen consumption) of +180%. Thyroid function was normal. Subtotal thyroidectomy with administration of thyroid-depressing drugs was followed by classical myxedema but with a BMR of +100%.

Biochemical studies of isolated skeletal muscle mitochondria from the patient (Figs. 1 and 2) demonstrated a nearly maximal rate of respiration in the presence of substrate alone without addition of ADP + P_i, but an almost normal phosphorylating efficiency (expressed as the P/O ratio) in the presence of ADP and P_i. The mitochondria also exhibited high ATPase activity, which was only slightly stimulated by 2,4-dinitrophenol, a known uncoupler of respiration from phosphorylation. These features of "loosely coupled" respiration—deficient respiratory control with a partially maintained ability to synthesize ATP—accounted for the symptoms of the patient: abnormal production of heat, which the body tried to relieve by increased perspiration, and enormous caloric intake to compensate for the increased combustion.


Blood Nutrients
Glucose
Fatty Acids
Amino Acids
.....
.....
Hormones
Glucocorticoids
Aldosterone
Estrogens
Insulin
GH
.....
.....
.....
Nutrients
Fatty Acids
Lactate
.....
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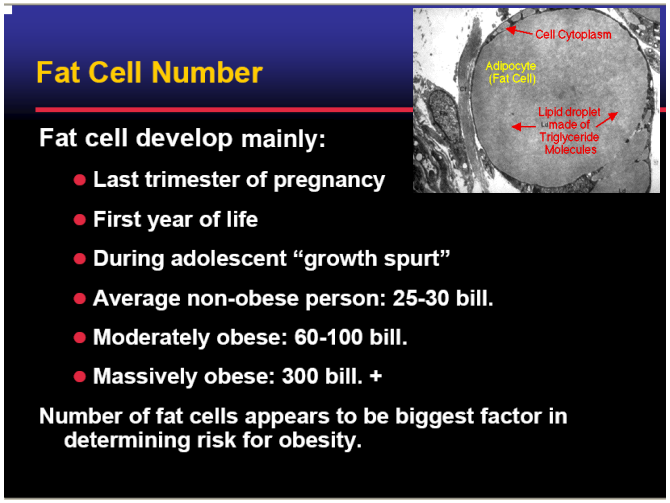
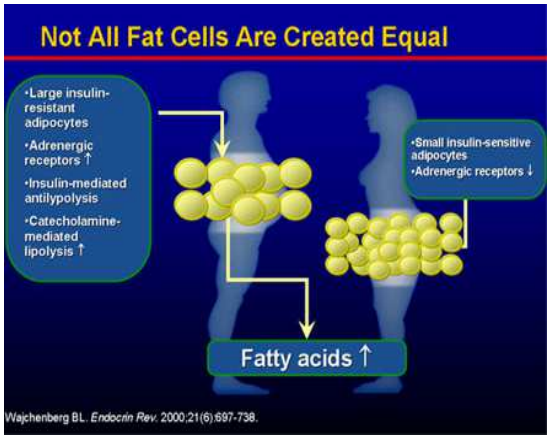
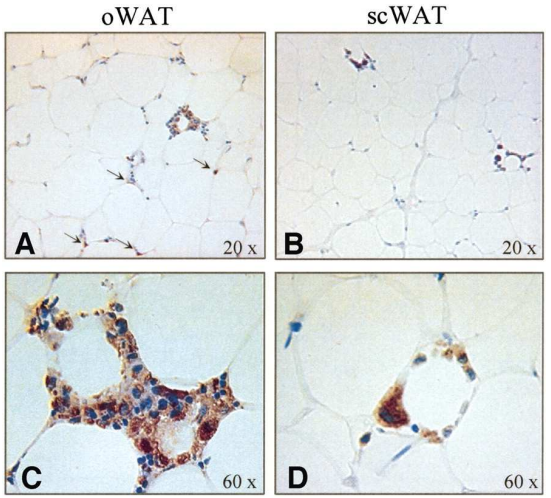
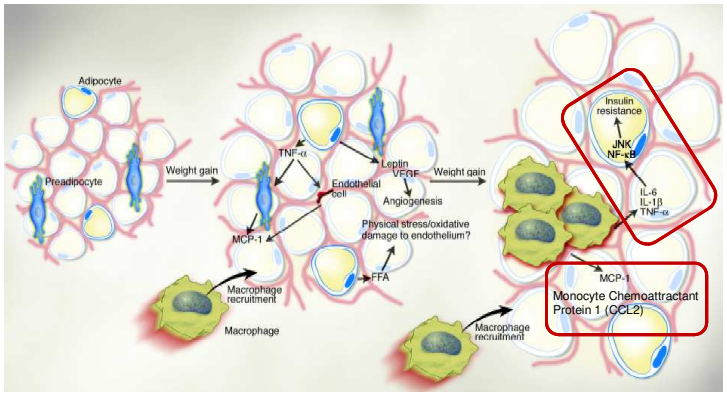
Hormones
Leptin
Adiponectin
Adipsin
Resistin
Visfatin
TNFα
MCP
PGs
IL-6
.....
.....


Fat Cell Number
Fat cell develop mainly:
Last trimester of pregnancy
First year of life
During adolescent "growth spurt"
Average non-obese person: 25-30 bill.
Moderately obese: 60-100 bill.
Massively obese: 300 bill. +
Number of fat cells appears to be biggest factor in determining risk for obesity.
Cell Cytoplasm
Adipocyte (Fat Cell)
Lipid droplet made of Triglyceride Molecules

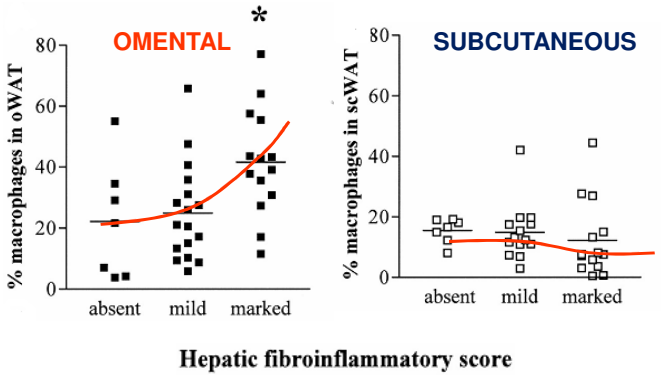

Not All Fat Cells Are Created Equal
•Large insulin-resistant adipocytes
•Adrenergic receptors ↑
•Insulin-mediated antilypolysis
•Catecholamine-mediated lipolysis ↑
•Small insulin-sensitive adipocytes
•Adrenergic receptors ↓
Fatty acids ↑
Wajchenberg BL. Endocrin Rev. 2000;21(6):697-738.


oWAT
scWAT
A
20 x
B
20 x
C
60 x
D
60 x

Obese adipose tissue is characterized by inflammation and progressive infiltration by macrophages

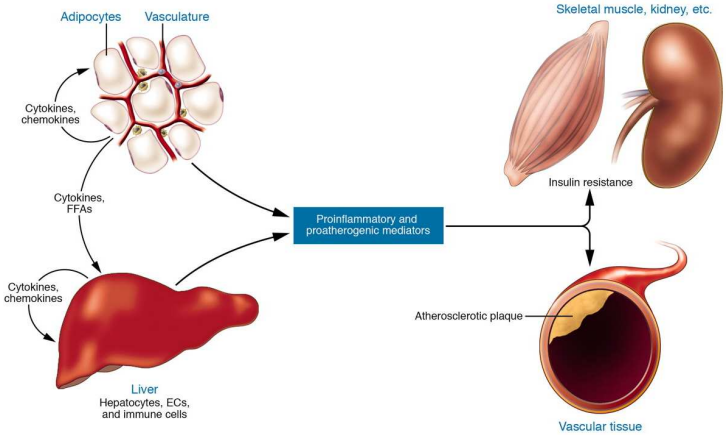


Wellen and Hotamisligil, J Clin Invest 112:1785–1788, 2003



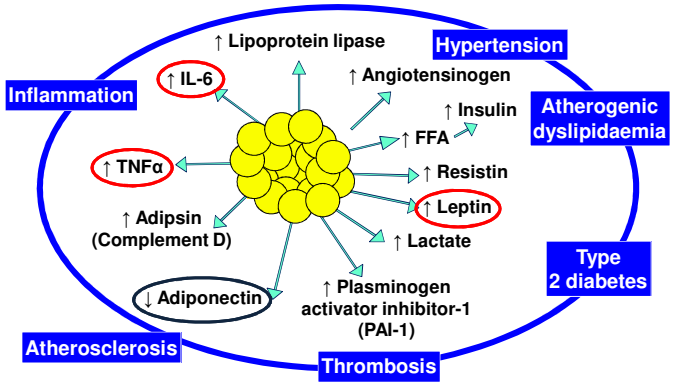
Cancello et al. ***Diabetes*** 55:1554-1561, 2006

Local, portal, and systemic effects of inflammation in insulin resistance and atherogenesis



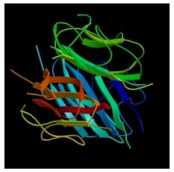
Shoelson, S. E. et al. J. Clin. Invest. 2006;116:1793-1801

Nell'obesità viscerale il repertorio di adipochine viene alterato



Lyon 2003; Trayhurn et al 2004; Eckel et al 2005

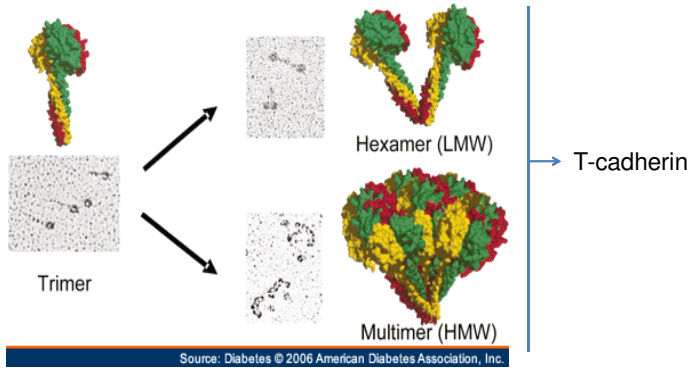
Adiponectin



- The protein, discovered in 1995, is also called ADIPOQ, gelatine-binding 28, Acrp30.
- It is a peptide hormone made by adipocytes. Its actions include:
  - Increased FA uptake by myocytes and of the rate of FA oxidation.
  - Decreased rate of synthesis and increased rate of oxidation of FA in the liver.
  - Decreased rates of gluconeogenesis in the liver.

  It acts through AMP-dependent protein kinase (AMPK).
- Obese subjects who suffer from Type II diabetes show **reduced levels of adiponectin**.
- Drugs (thiazolidinediones) used to treat Type II diabetes elevate adiponectin expression.

Adiponectin - structure



10308–10313 | PNAS | July 13, 2004 | vol. 101 | no. 28

T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin

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Acrp30/adiponectin is reduced in the serum of obese and diabetic individuals, and the genetic locus of adiponectin is linked to the metabolic syndrome. Recombinant adiponectin, administered to diet-induced obese mice, induced weight loss and improved insulin sensitivity. In muscle and liver, adiponectin stimulates AMP-activated protein kinase activation and fatty acid oxidation. To expression-clone molecules capable of binding adiponectin, we transduced a C2C12 myoblast cDNA retroviral expression library into Ba/F3 cells and panned infected cells on recombinant adiponectin linked to magnetic beads. We identified T-cadherin as a receptor for the hexameric and high-molecular-weight species of adiponectin but not for the trimeric or globular species. Only eukaryotically expressed adiponectin bound to T-cadherin, implying that post-translational modifications of adiponectin are critical for binding. An adiponectin mutant lacking a conserved N-terminal cysteine residue required for formation of hexamer and high-molecular-weight species did not bind T-cadherin in coimmunoprecipitation studies. Although lacking known cellular functions, T-cadherin is expressed in endothelial and smooth muscle cells, where it is positioned to interact with adiponectin. Because T-cadherin is a glycosylphosphatidylinositol-anchored extracellular protein, it may act as a coreceptor for an as-yet-unidentified signaling receptor through which adiponectin transmits metabolic signals.

Atherosclerosis 292 (2020) 1–9

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journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

Adiponectin, a unique adipocyte-derived factor beyond hormones

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[c] Division of Osaka Health Support Center, Sumitomo Mitsui Banking Corporation, 6-5, Kitahama 4-chome, Chuo-ku, Osaka, Osaka, 541-0041, Japan
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- It circulates at very high concentrations, constituting approximately 0.01–0.05% of total serum proteins. Its concentration is approximately 3–6 orders of magnitude greater than ordinary hormones and cytokines, including leptin, insulin, and interleukins. Despite its abundance, circulating adiponectin levels significantly change in a number of health conditions and have an impact on the etiology and onset of various diseases.
- Circulating adiponectin concentrations inversely correlate with body fat mass, particularly visceral fat mass, despite its specific production from adipocytes. Other adipose-derived factors, such as leptin, positively correlate with body fat mass.

Diabetologia (2003) 46:459–469
DOI 10.1007/s00125-003-1074-z

Diabetologia

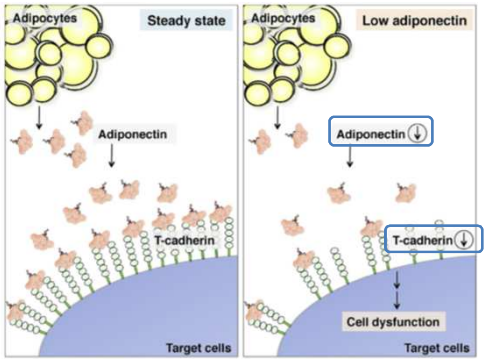
Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex

M. Cnop[1,5], P. J. Havel[2], K. M. Utzschneider[1], D. B. Carr[3], M. K. Sinha[4], E. J. Boyko[1], B. M. Retzlaff[1], R. H. Knopp[1], J. D. Brunzell[1], S. E. Kahn[1]

[1] Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, Veterans Affairs Puget Sound Health Care System (151) and University of Washington, Seattle, USA
[2] Department of Nutrition, University of California, Davis, CA, USA
[3] Department of Obstetrics and Gynecology, University of Washington, USA
[4] Linco Research Inc., St. Charles, MO, USA
[5] Laboratory of Experimental Medicine and Division of Endocrinology, Université Libre de Bruxelles, Brussels, Belgium

Studio su 182 soggetti

Results. Adiponectin concentrations were higher in women than in men (7.4±2.9 vs 5.4±2.3 μg/ml, $p<0.0001$) as were leptin concentrations (19.1±13.7 vs 6.9±5.1 ng/ml, $p<0.0001$). Women were more insulin sensitive (S_I: 6.8±3.9 vs 5.9±4.4×10^{-5} min^{-1}/(pmol/l), $p<0.01$) and had more subcutaneous (240±133 vs 187±90 cm^2, $p<0.01$), but less intra-abdominal fat (82±57 vs 124±68 cm^2, $p<0.0001$). By simple regression, adiponectin was positively correlated with age ($r=0.227$, $p<0.01$) and S_I ($r=0.375$, $p<0.0001$), and negatively correlated with BMI ($r=-0.333$, $p<0.0001$), subcutaneous ($r=-0.168$, $p<0.05$) and intra-abdominal fat ($r=-0.35$, $p<0.0001$). Adiponectin was negatively correlated with triglycerides ($r=-0.281$, $p<0.001$) and positively correlated with HDL cholesterol ($r=0.605$, $p<0.0001$) and Rf, a measure of LDL particle buoyancy ($r=0.474$, $p<0.0001$). By multiple regression analysis, adiponectin was related to age ($p<0.0001$), sex ($p<0.005$) and intra-abdominal fat ($p<0.01$). S_I was related to intra-abdominal fat ($p<0.0001$) and adiponectin ($p<0.0005$). Both intra-abdominal fat and adiponectin contributed independently to triglycerides, HDL cholesterol and Rf.
Conclusion/interpretation. These data suggest that adiponectin concentrations are determined by intra-abdominal fat mass, with additional independent effects of age and sex. Adiponectin could link intra-abdominal fat with insulin resistance and an atherogenic lipoprotein profile. [Diabetologia (2003) 46:459–469]



Maeda et al. (2020)

Fig. 2. Working model of T-cadherin-dependent adiponectin accumulation.
Under steady state conditions, adiponectin is specifically secreted from adipocytes and circulates abundantly in the bloodstream. Adiponectin accumulates on cells expressing T-cadherin, such as the cardiovasculature, by stabilizing and binding the T-cadherin protein on the cell surface. This T-cadherin-dependent accumulation of adiponectin protects against cellular damage, similar to "car wax". However, chronic hypoadiponectinemia (low level of circulating adiponectin), observed in the majority of visceral fat obesity, decreases T-cadherin protein levels on the cell surface and reduces adiponectin accumulation, resulting in ~~cellular and organ protection~~ decreased such as against atherosclerosis.

Hypoadiponectinemia has been identified as one of the risk factors for atherosclerosis and diabetes in human subjects and adiponectin has multi-functional beneficial properties, such as anti-atherogenic and anti-inflammatory effects. However, previous clinical studies, including meta-analyses, reported a relationship between high adiponectin levels and mortality, named the "adiponectin paradox" [103–113]. The

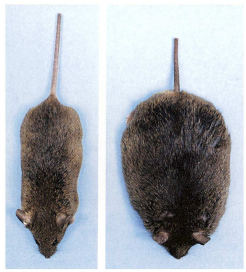
Circulating adiponectin concentrations have been shown to increase, particularly with renal dysfunction [114,115], heart failure [103,107], and sarcopenia [116,117], which are high risk factors for all-cause and cardiovascular mortalities. Under these morbid conditions, many known and unknown responses, such as increases in natriuretic peptides that directly act on adipocytes to produce adiponectin [118], are induced in the whole body. Furthermore, circulating adiponectin concentrations inversely correlate with the estimated glomerular filtration rate (eGFR) [119]. However, several systematic reviews and meta-analyses have implicated high adiponectin concentrations in all-cause and/or cardiovascular mortalities even after adjustments for eGFR or natriuretic peptides levels [109,113].

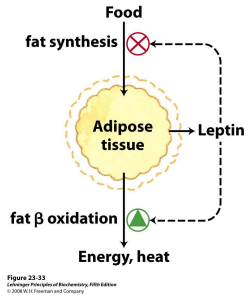
The T-cadherin genotype has a significant impact on plasma adiponectin concentrations and the hazard ratio of total mortality was shown to decrease after adjustments by the T-cadherin genotype [109], suggesting that the "adiponectin paradox" reflects "adiponectin resistance". In terms of the adiponectin/T-cadherin system, we propose that T-cadherin expression levels decrease in subjects liable for severe events and these reductions in tissue T-cadherin levels deteriorate the organ-protective effects of adiponectin while superficially increasing circulating adiponectin concentrations, which may be referred to as "adiponectin resistance". However, the mechanisms underlying T-cadherin regulation remain unclear, and, thus, further investigations are needed, particularly in human subjects, to obtain a deeper understanding of the "adiponectin paradox" and "adiponectin resistance".

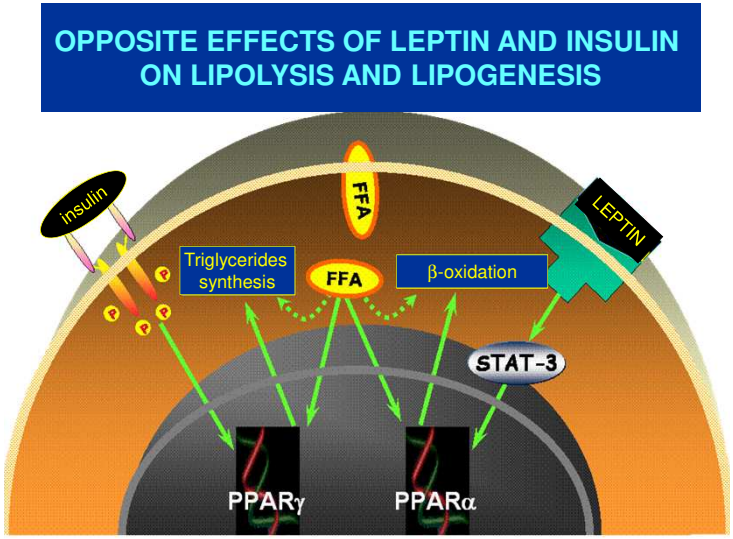
Il controllo dell'assunzione di cibo: la cooperazione leptina/insulina

Leptin

- 16 kDa peptide hormone encoded by the Ob gene
- Mainly produced by **differentiated adipocytes**, less by stomach, skeletal muscle, liver, placenta
- It passes through the blood/brain barrier by a saturable transport mechanism and it acts on the CNS, in particular the hypothalamus
- Main effects: **suppression of food intake** and **stimulation of energy expenditure**







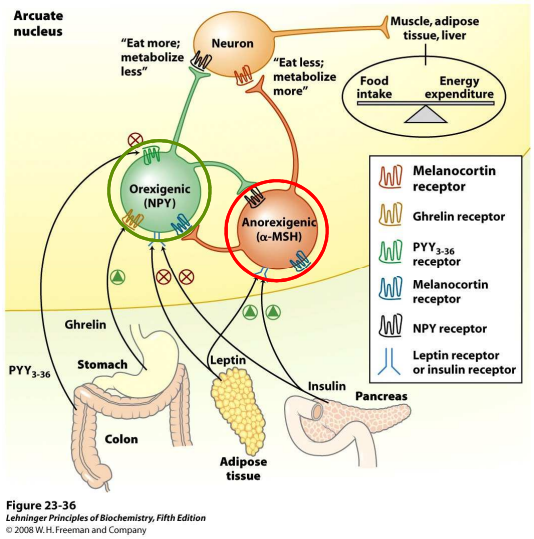


Figure 23-36
Lehninger Principles of Biochemistry, Fifth Edition
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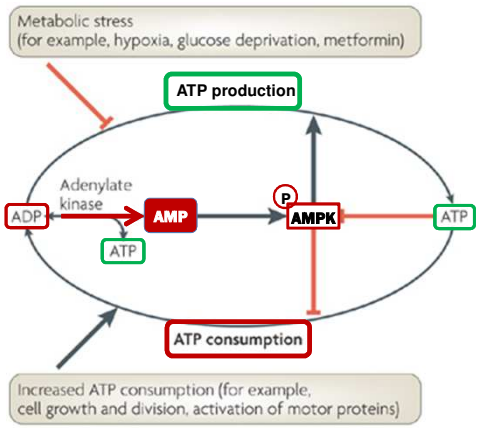
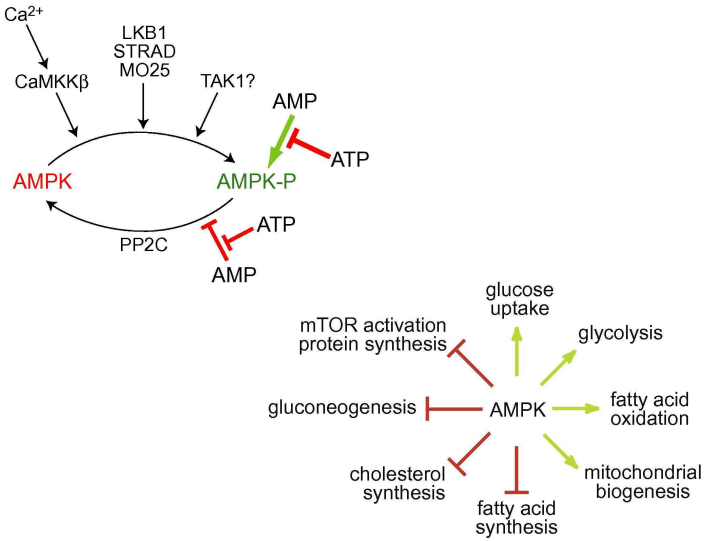
L'autoregolazione del metabolismo energetico:
funzione e regolazione delle AMPK, proteine chinasi AMP-dipendenti



Nature Reviews | Molecular Cell Biology

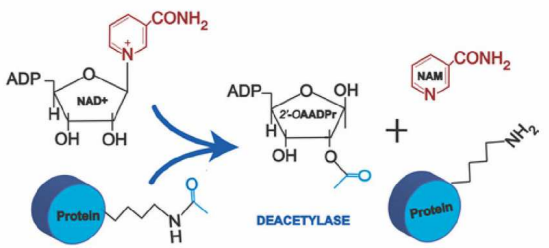


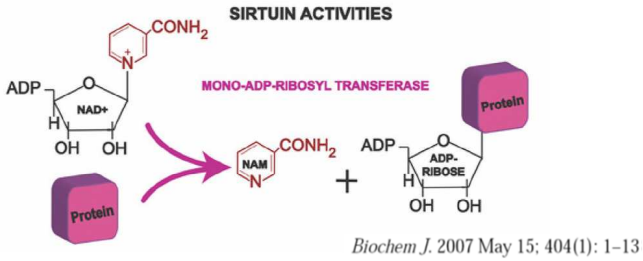
Sirtuine

- Scoperte in lievito (Sir2, Silent mating-type information regulation 2)
- Deacetilasi di proteine

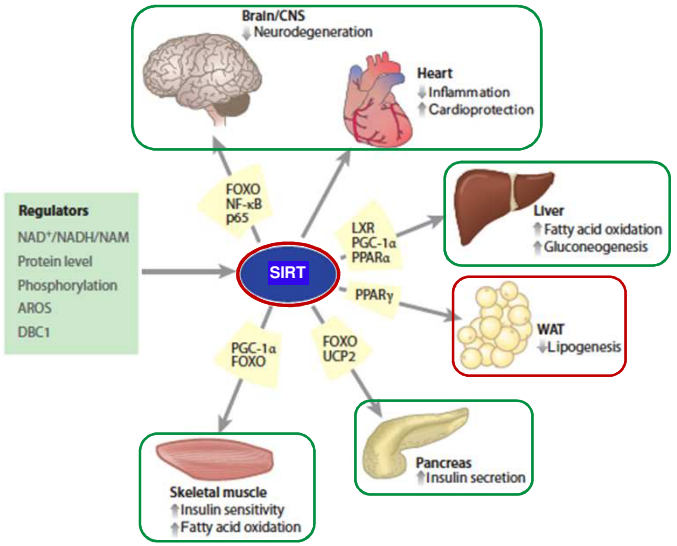
Table 1 Summary of the mammalian sirtuins

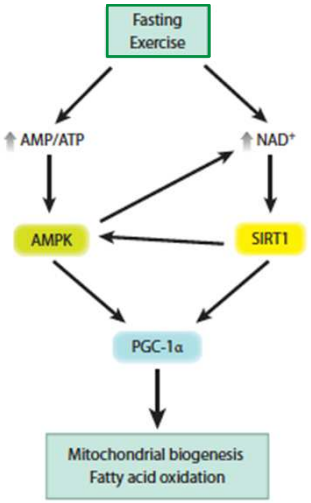
Sirtuin	Location	Interactions	Biology	Null phenotype
SIRT1	Nucleus	FOXO, PGC-1α NF-κB, Ku70, etc.	Metabolism, stress	Developmental defects, lethal in some backgrounds
SIRT2	Cytosol	Tubulin, H4, FOXO	Cell cycle	Developmentally normal
SIRT3	Mitochondria	AceCS2, GDH complex I	Thermogenesis, ATP production	Developmentally normal
SIRT4	Mitochondria	GDH, IDE, ANT	Insulin secretion	Developmentally normal
SIRT5	Mitochondria	CPS1	Urea cycle	Developmentally normal
SIRT6	Nucleus	Histone H3, NF-κB	Base excision repair, metabolism	Premature aging
SIRT7	Nucleolus	Pol I	rDNA transcription	Smaller size, short lifespan, heart defects





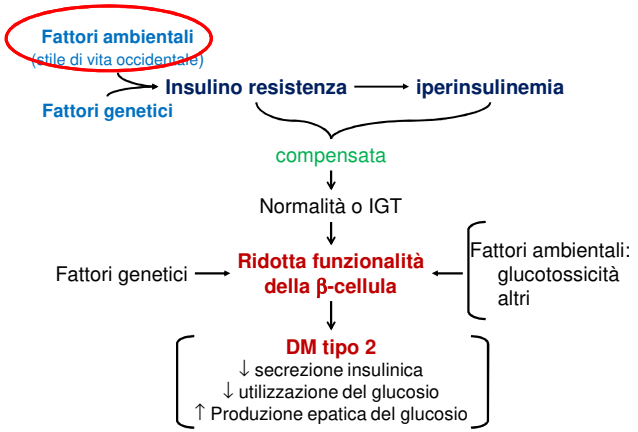
Biochem J. 2007 May 15; 404(1): 1–13





Lo sviluppo della insulino-resistenza

PATOGENESI DEL DIABETE TIPO 2



Rhoden and Shulman (2019) Nature 576, 51-60

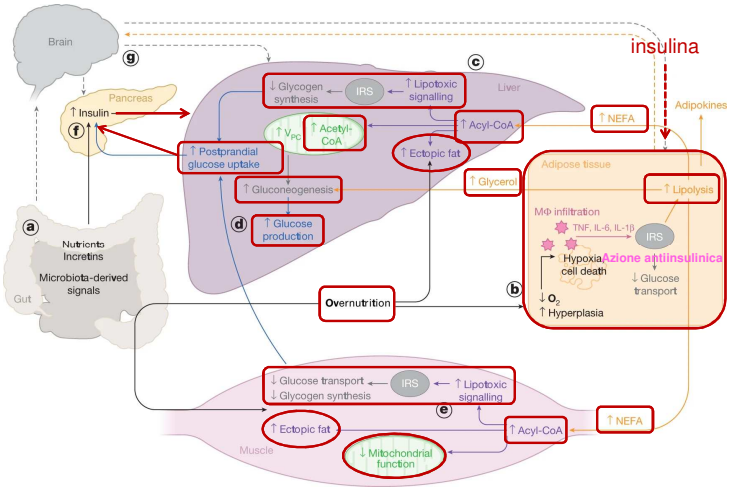
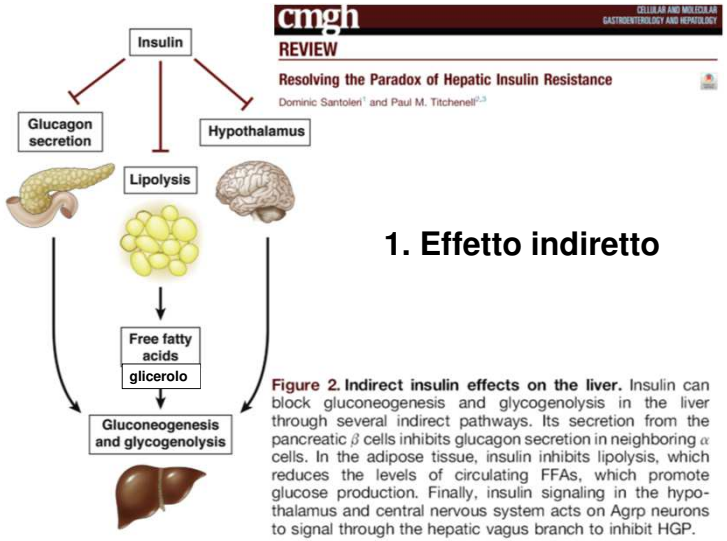


Fig. 3 | A unified concept of insulin resistance in humans. a, Overnutrition leads to adipose tissue hypertrophy and hyperplasia and ectopic TAG deposition, mainly in muscle and liver—key features of insulin resistance. **b**, Adipose dysfunction, possibly due to local hypoxia ultimately resulting in apoptosis and cell death, recruits and transforms macrophages to release, for example, TNF and interleukins (IL-1β and IL-6). Local inflammatory reaction increases lipolysis directly or via inhibiting insulin signalling with subsequent release of NEFA and glycerol from WAT. Chronically, adipose dysfunction alters adipocytokine secretion favouring systemic low-grade inflammation. **c**, In liver, glycerol as substrate and NEFA-derived acetyl-CoA, allosterically activating pyruvate carboxylase flux (V_{PC}), stimulate gluconeogenesis and fasting glucose production. NEFA and glycerol, as substrates of TAG accumulation, initiate NAFLD in the absence of adequate mitochondrial function and generate lipotoxic metabolites that inhibit insulin signalling. **d**, Hepatocellular insulin resistance not only chronically upregulates

non alcoholic fatty liver disease

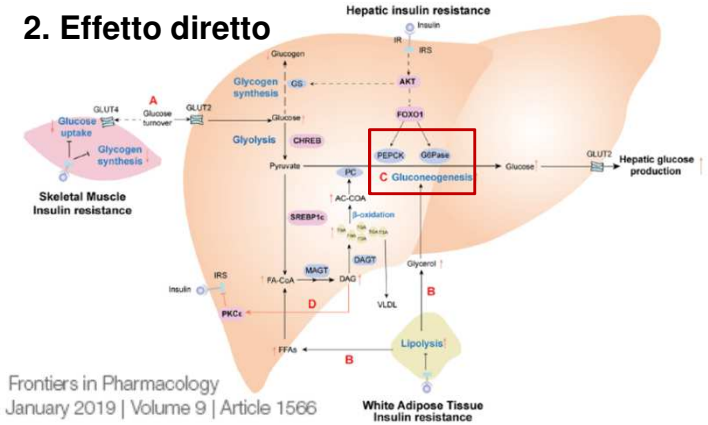
gluconeogenesis, but also decreases insulin-stimulated net glycogen synthesis and glucose uptake, in turn raising postprandial glucose production. **e**, In muscle, increased NEFA availability, accelerated by—possibly inherited—inadequate mitochondrial fat oxidation, also favours lipid synthesis, inhibiting insulin-stimulated glucose transport and glycogen synthesis. This, combined with lower non-insulin-mediated glucose uptake due to sedentary lifestyle, contributes to the postprandial glucose rise. **f**, These different mechanisms, along with direct stimulation by nutrients and enteroendocrine signals (such as GLP-1 and GIP) increase the insulin:glucagon secretion ratio, resulting in normoglycaemia at the expense of hyperinsulinaemia. **g**, Chronically, both acquired and inherited factors impair insulin secretion, with subsequent postprandial and fasting hyperglycaemia. The brain may also contribute to regulation of peripheral metabolism via afferent (for example, leptin from WAT (orange dashed line)) and efferent (for example, to liver (grey dashed line)) signalling.



1. Effetto indiretto

Figure 2. Indirect insulin effects on the liver. Insulin can block gluconeogenesis and glycogenolysis in the liver through several indirect pathways. Its secretion from the pancreatic β cells inhibits glucagon secretion in neighboring α cells. In the adipose tissue, insulin inhibits lipolysis, which reduces the levels of circulating FFAs, which promote glucose production. Finally, insulin signaling in the hypothalamus and central nervous system acts on Agrp neurons to signal through the hepatic vagus branch to inhibit HGP.

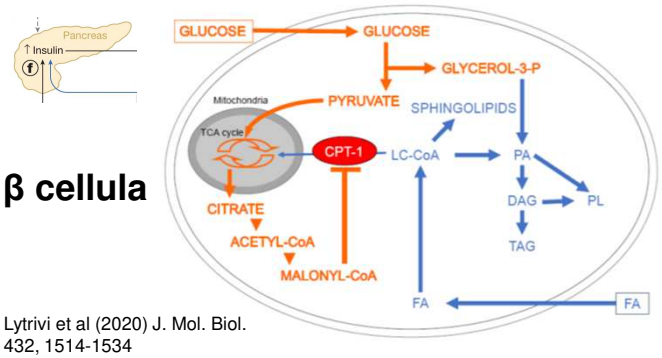
2. Effetto diretto



Hepatic insulin resistance refers to **impaired suppression of glucose production by insulin in hepatocytes**. Insulin mediates its inhibitory effects on glucose production by inhibiting two key gluconeogenic enzymes, **phosphoenolpyruvate carboxykinase (PEPCK) and the glucose-6 phosphatase (G6Pase).**

Mechanisms of β-Cell Lipo- and Glucolipotoxicity in Type 2 Diabetes

β cellula



Lytrivi et al (2020) J. Mol. Biol. 432, 1514-1534

Fig. 5. Effects of glucose on intracellular lipid metabolism in the β-cell. In the presence of simultaneously elevated levels of glucose and FFAs, the increase in cytosolic malonyl-CoA resulting from glucose metabolism inhibits carnitine palmitoyltransferase 1 (CPT-1). Transport of long-chain acyl-CoA (LC-CoA) in the mitochondria is blocked, and FFA metabolism is diverted towards the synthesis of lipid-derived signaling molecules such as sphingolipids, diacylglycerols (DG), phosphatidic acid (PA), phospholipids (PL), and triacylglycerols (TG).
Adapted from Ref. [51] with permission.

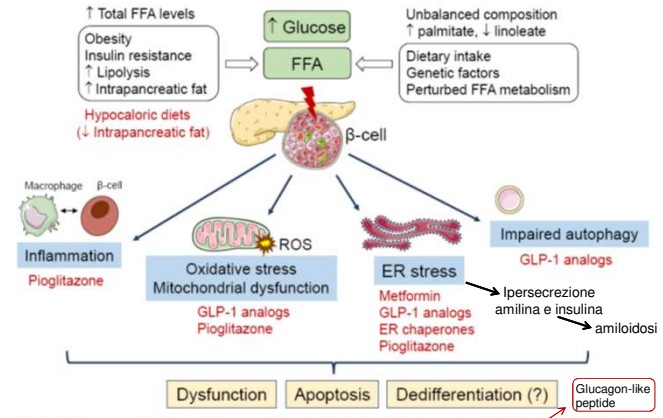
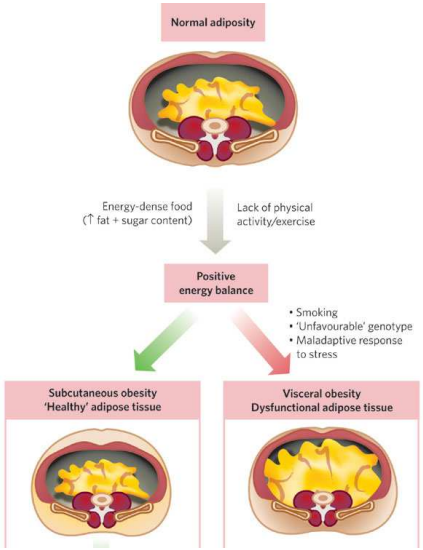
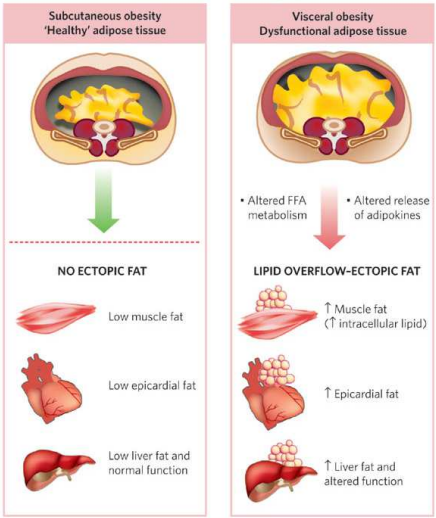


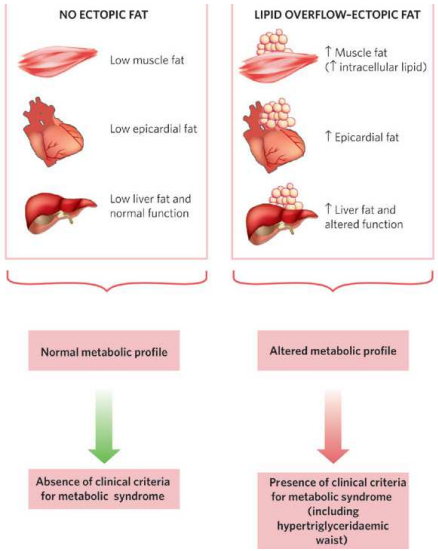
Fig. 6. Molecular mechanisms of lipo- and glucolipotoxic β-cell demise and potential treatments. A prolonged increased FFA supply and/or unbalanced FFA composition, alone or in combination with high glucose, elicits stress responses in pancreatic β-cells. These include ER stress, oxidative stress with excessive ROS production, mitochondrial dysfunction, inflammation, and impaired autophagic flux. Crosstalk between these pathways may give rise to feed-forward mechanisms, aggravating glucolipotoxic stress. Collectively, these phenomena culminate in β-cell dysfunction, apoptosis, and possibly dedifferentiation. *In vitro* data suggest that metformin, GLP-1 analogs, thiazolidinediones, and ER chaperones mitigate lipo- and glucolipotoxicity. These therapies (shown in red) target distinct stress pathways. The graphic illustrations used in this figure are from Servier Medical art (https://smart.servier.com).

Obesità ⟷ Insulino-resistenza

Il concetto di sindrome metabolica







The IDF consensus worldwide definition of the metabolic syndrome

Table 1: The new International Diabetes Federation (IDF) definition

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:

Central obesity *(defined as waist circumference* ≥ 94cm for Europid men and ≥ 80cm for Europid women, *with ethnicity specific values for other groups)*

plus any two of the following four factors:

- ***raised TG level***: > 150 mg/dL (1.7 mmol/L), *or* ***specific treatment for this lipid abnormality***
- ***reduced HDL cholesterol***: < 40 mg/dL (0.9 mmol/L) in males and < 50 mg/dL (1.1 mmol/L) in females, ***or specific treatment for this lipid abnormality***
- ***raised blood pressure:*** systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, ***or treatment of previously diagnosed hypertension***
- ***raised fasting plasma glucose*** (FPG) ≥ 100 mg/dL (5.6 mmol/L), ***or previously diagnosed type 2 diabetes***
  If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

This editorial was published on February 10, 2021, at NEJM.org.

DOI: 10.1056/NEJMe2101705

STEP 1 for Effective Weight Control — Another First Step?

Julie R. Ingelfinger, M.D., and Clifford J. Rosen, M.D.

Medications approved for weight loss by the Food and Drug Administration, the European Medicines Agency, and other regulatory bodies have had a troubling history, with withdrawal of several approved drugs owing to serious adverse events; among these are various amphetamines (addiction), fenfluramine (cardiac toxicity), and, most recently, lorcaserin (cancer risk).[4,5] During clinical trials for the two most recently approved agents for treating type 2 diabetes — the glucagon-like peptide-1 (GLP-1) agonists and sodium–glucose cotransporter-2 (SGLT-2) inhibitors (Table 1) — weight loss was noted to be substantial.[5-9] However, a major limiting factor with regard to treating obesity with the GLP-1 agonists was their daily subcutaneous administration.

1961 patients with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or higher (or ≥27 with at least one coexisting condition) were randomly assigned, in a 1:1 ratio, to receive a once-weekly subcutaneous preparation of the GLP-1 agonist semaglutide (2.4 mg) or placebo for 68 weeks.[10]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group*

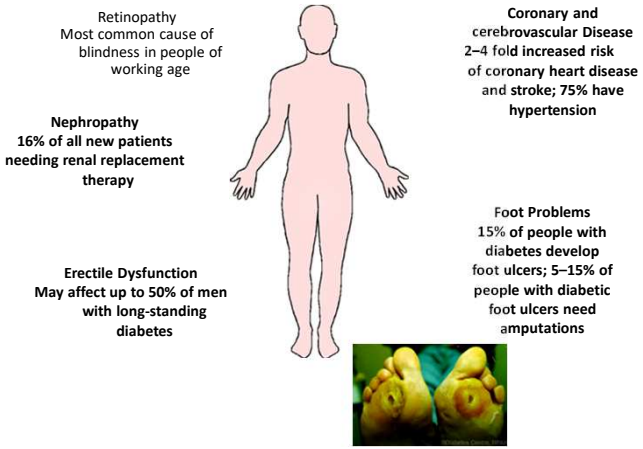
This article was published on February 10, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2032183

RESULTS

The mean change in body weight from baseline to week 68 was −14.9% in the semaglutide group as compared with −2.4% with placebo, for an estimated treatment difference of −12.4 percentage points (95% confidence interval [CI], −13.4 to −11.5; P<0.001). More participants in the semaglutide group than in the placebo group achieved weight reductions of 5% or more (1047 participants [86.4%] vs. 182 [31.5%]), 10% or more (838 [69.1%] vs. 69 [12.0%]), and 15% or more (612 [50.5%] vs. 28 [4.9%]) at week 68 (P<0.001 for all three comparisons of odds). The change in body weight from baseline to week 68 was −15.3 kg in the semaglutide group as compared with −2.6 kg in the placebo group (estimated treatment difference, −12.7 kg; 95% CI, −13.7 to −11.7).

Chronic Complications of Diabetes



Le complicanze croniche dipendono dalla durata e dalla gravità dell'iperglicemia

Le complicanze:

- Acute
  - Chetoacidosi diabetica
  - Sindome iperglicemica iperosmolare
- Croniche
  - Macrovascolari (aterosclerosi)
  - Microvascolari
    - Retinopatia (edema, ischemia, neoangiogenesi)
    - Neuropatia (degenerazione assonale multifocale)
    - Nefropatia (proteinuria, espansione matrice mesangiale e glomerulosclerosi)

1. Advanced glycosylation products (AGE)

- autoossidazione intracellulare del glucosio a **gliossale** e prodotti derivati
- reazione con residui amminici proteine (**arg in particolare**)
- formazione degli AGE

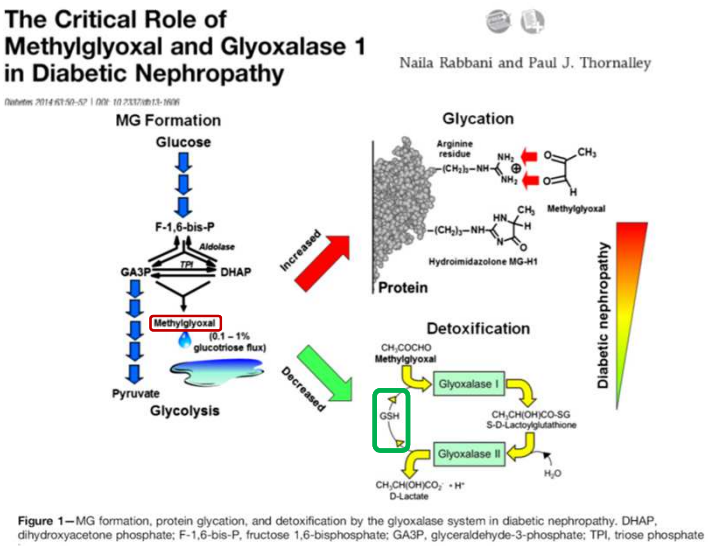
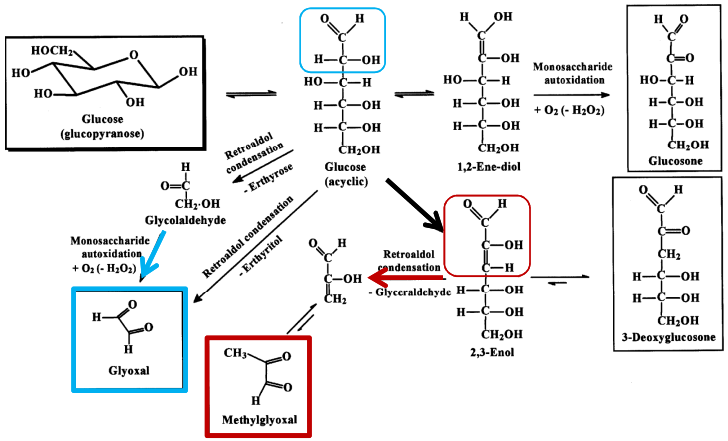
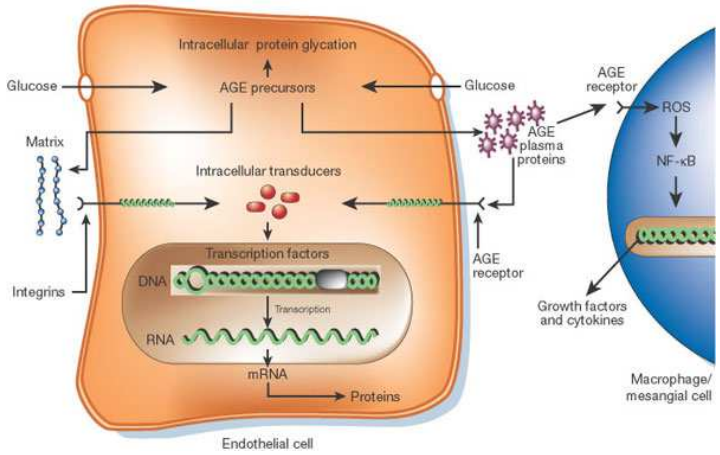


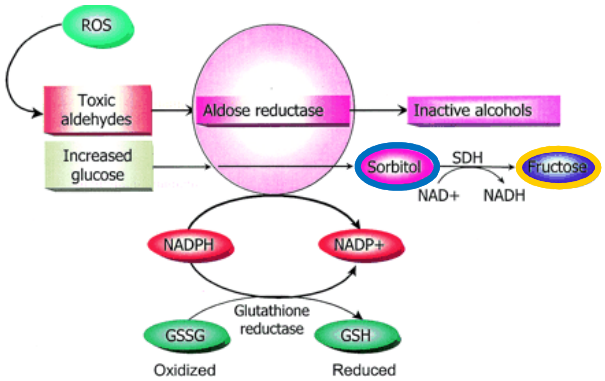
Figure 1—MG formation, protein glycation, and detoxification by the glyoxalase system in diabetic nephropathy. DHAP, dihydroxyacetone phosphate; F-1,6-bis-P, fructose 1,6-bisphosphate; GA3P, glyceraldehyde-3-phosphate; TPI, triose phosphate



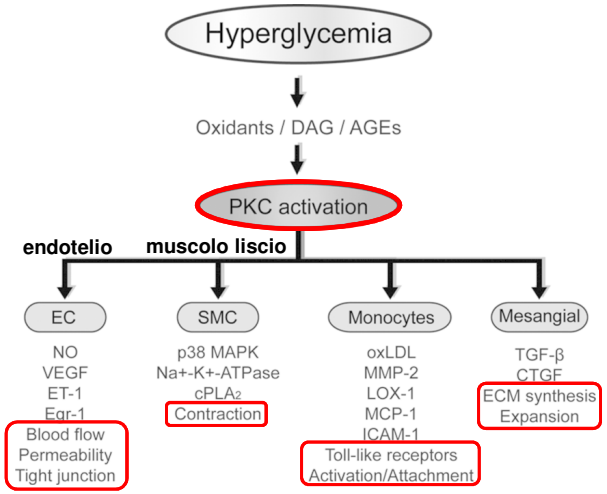


2. Produzione di sorbitolo via aldoso reduttasi

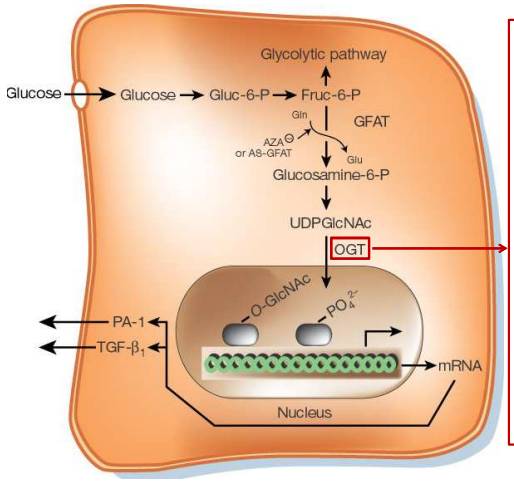
- Effetto osmotico (?)
- Alterazione dell'equilibrio redox (stress ossidativo)



3. Attivazione delle protein chinasi C



4. Aumentato flusso attraverso la via delle esosamine



O-linked N-acetylglucosamine (O-GlcNAc) transferase **(OGT)** catalyzes the addition of a single N-acetylglucosamine in O-glycosidic linkage to **serine or threonine** residues. Since both phosphorylation and glycosylation compete for similar serine or threonine residues, the two processes may compete for sites, or they may alter the substrate specificity of nearby sites by steric or electrostatic effects

Effetti

- **Produzione di fattori di crescita**
  - VEGF-A (retinopatia proliferativa)
  - TGF-β (nefropatia)
- **Produzione di molecole endocrine**
  - angiotensina II, endotelina
- **Disfunzione cellulare**
  - ROS
  - induzione di apoptosi o necroptosi
- **Risposta infiammatoria cronica**
  - danno cellulare
  - fibrosi