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GENOVA
Hotel NH Collection Marina
15-16 dicembre 2023

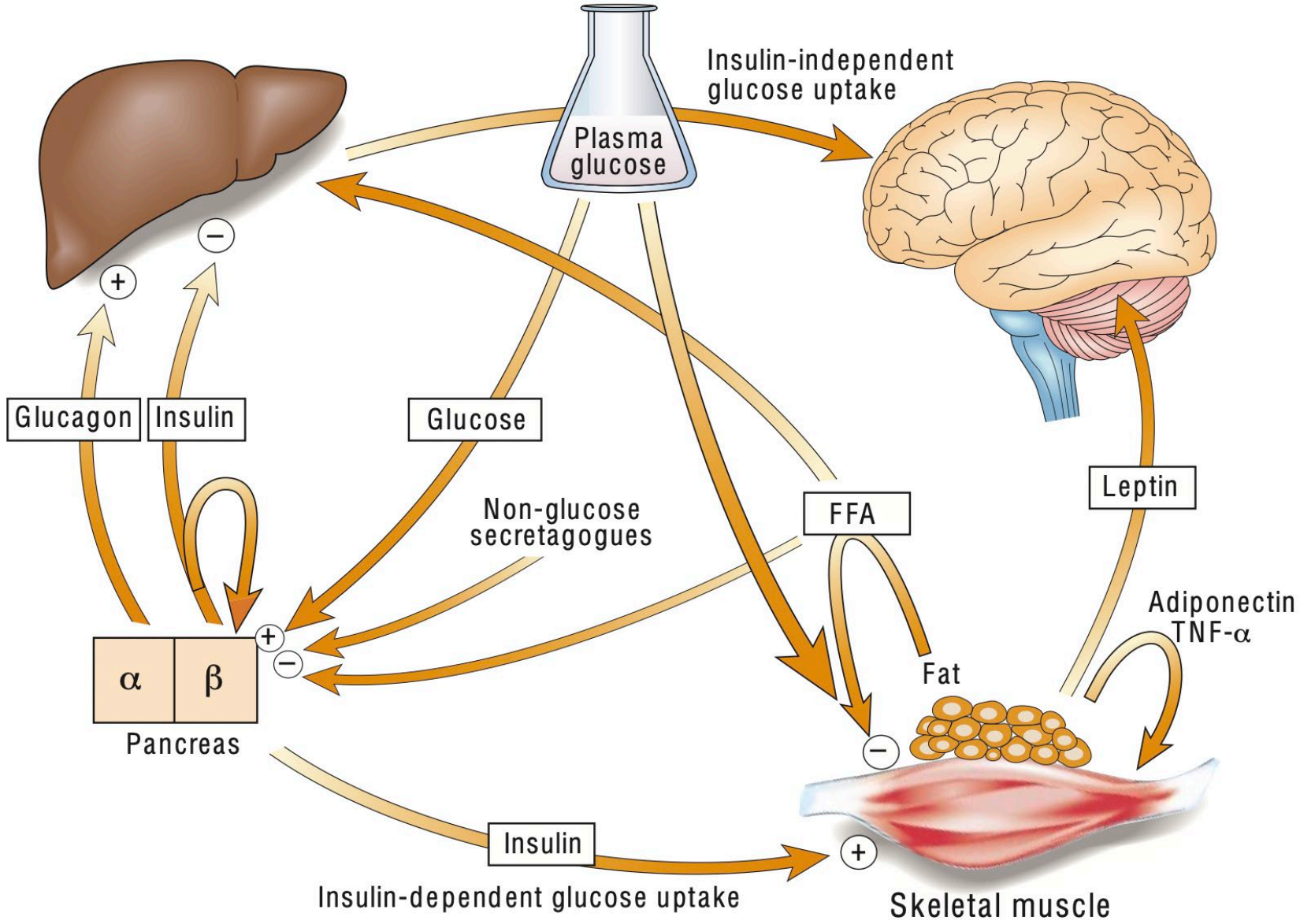
Nuovi indici di insulino-resistenza e nuove prospettive terapeutiche per l'obesità pediatrica

Dr. Giacomo Tantari

Il dr. Giacomo Tantari dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

INSULINA



Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature. 2001

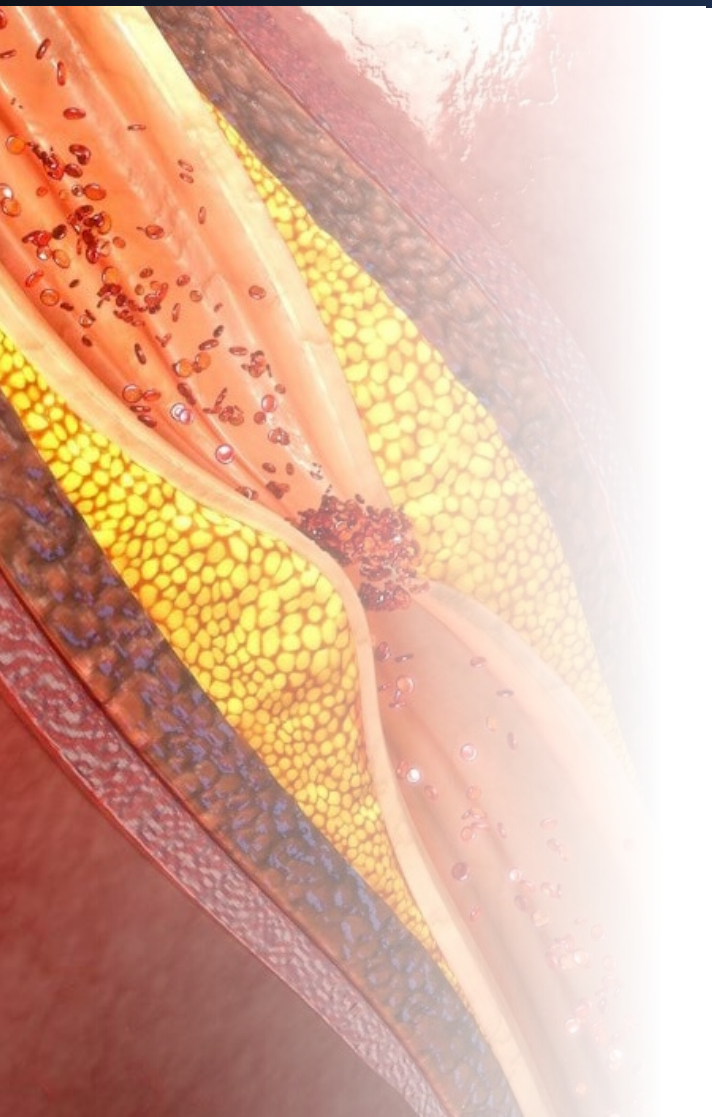
Insulino-resistenza(IR)

Disfunzione metabolica complessa caratterizzata dall'incapacità di una determinata quantità di insulina, endogena o esogena, ad aumentare l'uptake di glucosio intracellulare

Inadeguata utilizzazione di glucosio da parte delle cellule dell'organismo, in particolare fegato, tessuto muscolare ed adipociti

Lebovitz HE. Insulin resistance: definition and consequences. Exp Clin Endocrinol Diabetes. 2001.

Complicanze: disfunzione endoteliale



La disfunzione endoteliale è caratterizzata da uno **squilibrio tra agenti vasodilatatori e vasocostrittori**

L'**Endotelio Danneggiato** produce agenti che stimolano la **trombosi** *(inibitori dell'attivatore del plasminogeno, fattore di von Willebrand)* o l'**infiammazione**, *(interleuchina-6, proteina C-reattiva ultrasensibile)*

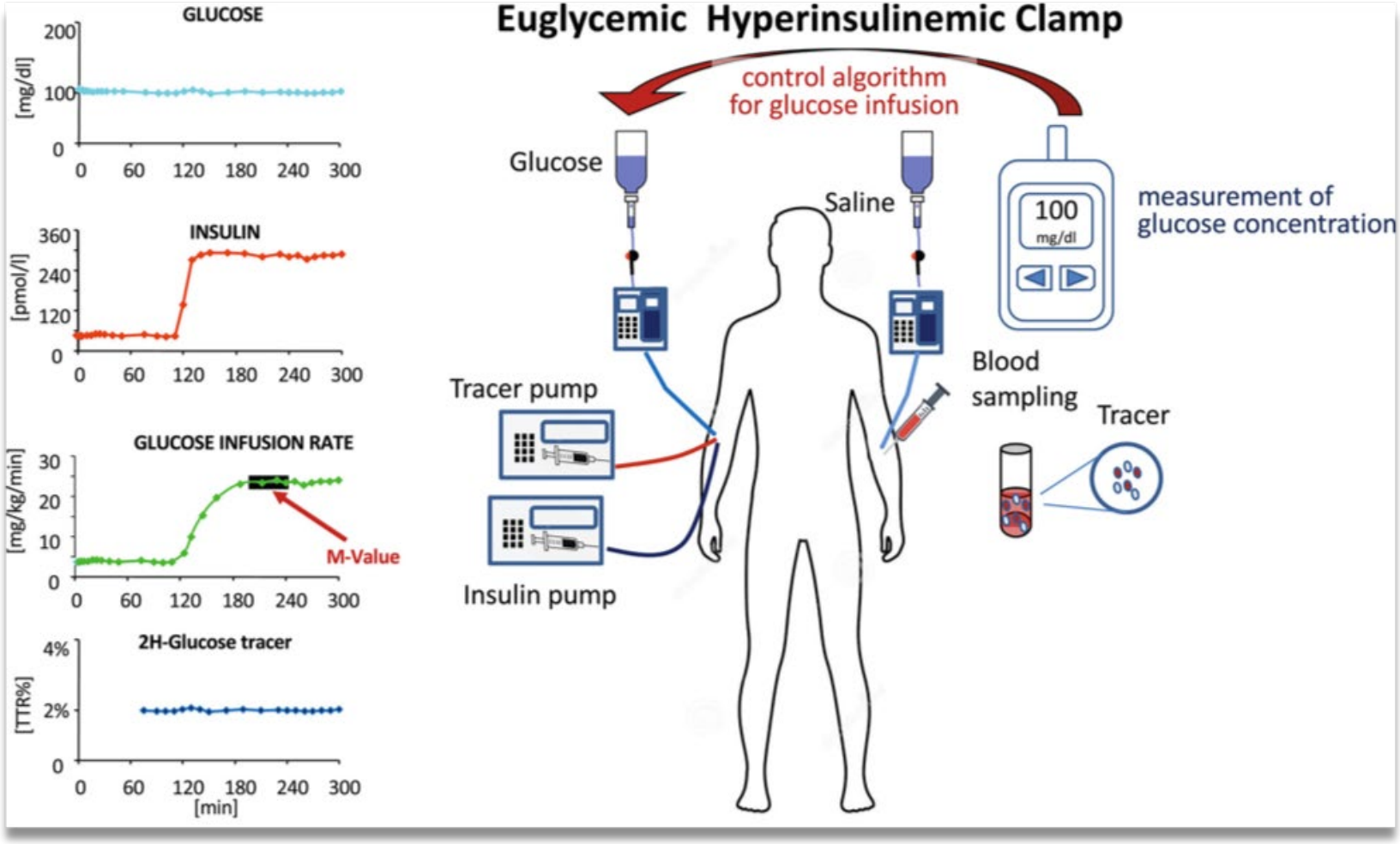
L'ED rappresenta il ***primum movens*** nella patogenesi dell'**aterosclerosi** e della **trombosi** con sviluppo di **malattie cardiovascolari** *(coronaropatia, ictus emorragico o ischemico, arteriopatia periferica e tromboembolismo venoso).*

Indici di insulino-resistenza

Clamp euglicemico/iperinsulinemico

Gold standard per misurare la sensibilità all'insulina

Invasivo, laborioso, non applicabile nella pratica clinica quotidiana pediatrica



Indici di insulino-resistenza

Necessità di sviluppare indici più semplici e riproducibili anche per studi di follow-up

Table 4. Percentiles of HOMA-IR, HOMA-β% and QUICKI indexes in healthy Italian children and adolescents, grouped by sex and pubertal Tanner's Stage (TS)

	N	2.5th	5th	10th	25th	Median	75th	90th	95th	97.5th
Males (N=85)										
HOMA-IR										
TS 1	46	0.28	0.40	0.45	0.65	1.19	1.64	2.11	2.20	2.44
TS 2-3	27	0.29	0.62	0.68	0.90	1.13	2.13	2.76	3.08	3.61
TS 4-5	12	0.73	0.73	0.79	1.12	1.68	2.41	2.47	2.72	2.72
HOMA-β%										
TS 1	46	32.8	43.3	45.1	64.6	89.6	118.7	133.3	154.7	683.9
TS 2-3	27	24.1	36.1	41.2	63.2	98.4	163.7	249.1	363.4	523.4
TS 4-5	12	51.2	51.2	57.2	111.1	165.0	232.2	261.5	403.4	403.4
QUICKI										
TS 1	46	0.33	0.34	0.34	0.35	0.37	0.41	0.44	0.45	0.49
TS 2-3	27	0.32	0.32	0.33	0.34	0.38	0.39	0.41	0.42	0.48
TS 4-5	12	0.33	0.33	0.33	0.33	0.35	0.38	0.40	0.40	0.40
Females (N=57)										
HOMA-IR										
TS 1	27	0.51	0.55	0.61	0.92	1.36	1.71	2.12	2.20	2.89
TS 2-3	18	0.37	0.37	0.38	0.61	1.38	1.82	4.02	5.39	5.39
TS 4-5	12	0.42	0.42	0.88	1.08	1.91	3.50	3.64	4.36	4.36
HOMA-β%										
TS 1	27	38.1	46.6	56.5	75.2	122.1	154.8	184.7	192.1	232.5
TS 2-3	18	24.5	24.5	34.4	53.2	112.8	171.1	548.8	1078.2	1078.2
TS 4-5	12	32.8	32.8	55.5	132.8	236.7	316.3	421.8	487.4	487.4
QUICKI										
TS 1	27	0.33	0.34	0.34	0.35	0.36	0.39	0.42	0.43	0.43
TS 2-3	18	0.30	0.30	0.31	0.35	0.36	0.42	0.46	0.46	0.46
TS 4-5	12	0.31	0.31	0.32	0.32	0.35	0.38	0.39	0.45	0.45

Indici di insulino-resistenza

OGTT: **Test di tolleranza al carico di glucosio orale** utilizzato da più di 100 anni.

Basale

↓ + 1.75 mg/kg glucosio (Max 75 gr) - ADA LG

Ad ogni prelievo→ glucosio sierico e insulina sierica

1° campione – 30 min

↓

2° campione – 60 min

↓

3° campione – 90 min

↓

4° campione – 120 min

Valutazione della tolleranza glucidica a 2 ore dal carico
Normale tolleranza glucidica: glicemia < 140 mg/dl,
Ridotta tolleranza glucidica (IGT) = glicemia 140-200 mg/dl
Diabete Mellito (DM) = glicemia >= 200 mg/dl

Insulino-resistenza:
1. Somma totale insulinica OGTT: > 300 µU/ml (Ong, Y.Y., et al.)
2. Somma totale insulinica OGTT: > 535 µU/ml (La Valle et al.)

Indici di insulino-resistenza

SPISE: Single Point Insulin Sensitivity Estimator

È un nuovo marcatore di insulino-resistenza basato su una formula matematica che comprende BMI, valori ematici di trigliceridi a digiuno e colesterolo HDL.

→ **Miglior capacità predittiva di IR rispetto agli indici HOMA-IR e QUICKI**

→ È un utile strumento per individuare alterazioni del metabolism glucidico in bambini ed adolescenti con sovrappeso o obesità

$$600 \times HDL^{0.185} / Trigliceridi^{0.2} \times BMI^{1.338}$$

Terapia dell’obesità

Terapia Dietetico-comportamentale

Terapia Farmacologica

Terapia Chirurgica

Terapia Dietetico-comportamentale

SANA E CORRETTA ALIMENTAZIONE COSTITUITA DA 3 PASTI PRINCIPALI (COLAZIONE, PRANZO E CENA) E MASSIMO DUE SPUNTINI AL GIORNO (ATTENZIONE ALLA COLAZIONE!!!!)

EVITARE BIBITE E BEVANDE ZUCCHERATE

EFFETTUARE ALMENO 60 MINUTI DI ATTIVITÀ FISICA QUOTIDIANA ANCHE NON CONTINUATIVA (RIDURRE SEDENTARIETÀ)

ATTIVITÀ FISICA INTENSA E STRUTTURATA ALMENO TRE VOLTE A SETTIMANA (DANZA, CORSA, NUOTO) PER MIGLIORARE LA COMPOSIZIONE CORPOREA E RIDURRE I FATTORI DI RISCHIO CARDIO-METABOLICO

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Terapia Dietetico-comportamentale

APPROCCIO

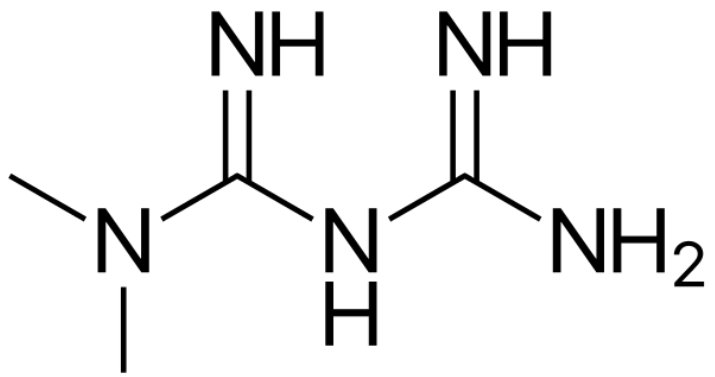
5	porzioni di frutta e verdura al giorno
2	ore davanti agli schermi
1	Ore di attività fisica moderata-vigorosa
0	Bibite zuccherate

Terapia Farmacologica

Metformina:

riduce i livelli di glicemia (ipoglicemizzante orale), riducendo la produzione glucidica epatica, riducendo l'assorbimento intestinale di glucosio e aumentando la sensibilità insulinica dei tessuti periferici.

Dosaggio: **500 mg alla sera per una settimana**, poi 500 mg per due volte al giorno(mattino e sera) per una settimana, poi 500 mg al mattino e 1000 mg alla sera per un'altra settimana fino ad arrivare a 1000 mg per due volte al giorno



Terapia Farmacologica

Liraglutide:

analogo del recettore GLP-1. Riduce senso della fame rallentando lo svuotamento gastrico ed agendo a livello ipotalamico sui centri della fame riducendo l'appetito.

Dosaggio: 0.6 mg per via s.c al giorno per una settimana, poi si aumenta di 0.6 mg al giorno per una settimana fino ad un max di 3 mg al giorno

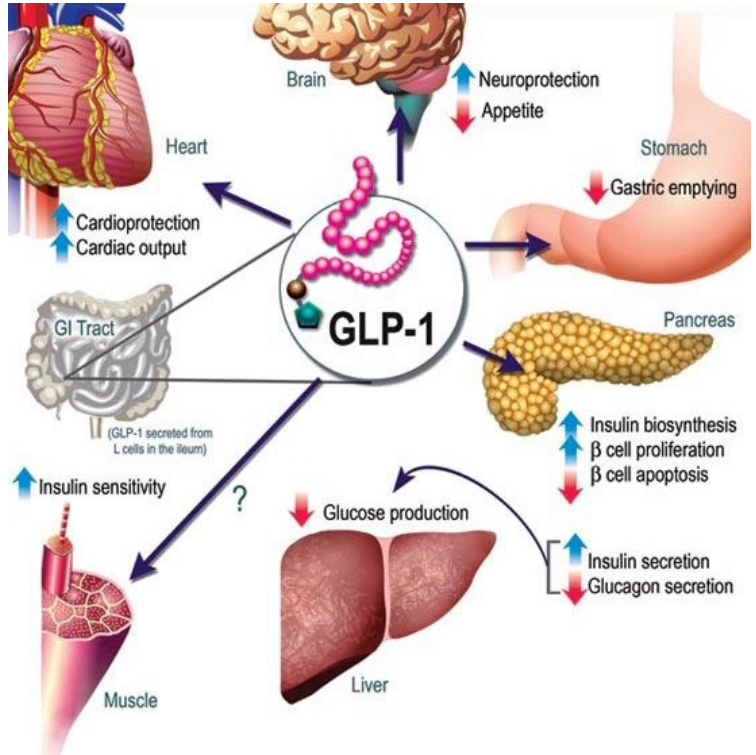


Table 1 | Summary of three large adolescent AOM clinical trials published since 2020

Medication	Study design	Participants and eligibility criteria	Efficacy outcomes	Safety outcomes
Liraglutide 3 mg (ref. 26)	Randomized (1:1), placebo-controlled trial; 56 weeks of treatment with 12-week lifestyle modification therapy run-in period	251 adolescents (12 to <18 years old); BMI corresponding to adult BMI of ≥30 kg/m^2 and BMI ≥95th percentile; excluded Tanner stage I[a]	BMI standard deviation score difference of −0.22 (P=0.002) favouring liraglutide; percentage change in BMI difference of −4.6% favouring liraglutide; no significant changes in cardiometabolic risk factors or weight-related quality of life	Overall adverse events were similar (88.8% liraglutide vs 84.9% placebo); gastrointestinal issues were the most commonly reported adverse events and were more frequent with liraglutide (64.8%) vs placebo (36.5%)
Phentermine–topiramate[39]	Randomized (1:1:2 placebo, mid-dose, top-dose) placebo-controlled trial; 56 weeks of treatment	227 adolescents (12 to <17 years old); BMI ≥95th percentile; excluded Tanner stage I[a]	Percentage change in BMI difference of −8.1% (P<0.001) for mid-dose and −10.4% (P<0.001) for top-dose favouring phentermine–topiramate; ~20% reduction in blood levels of triglycerides and ~10% increase in blood levels of HDL-cholesterol with both doses of phentermine–topiramate	Overall adverse events were similar (51.8% placebo, 37.0% mid-dose, 52.2% top-dose); no differences across groups for measures of mental health, cognition, drug abuse, dependence or withdrawal
Semaglutide 2.4 mg (ref. 33)	Randomized (1:2 placebo, semaglutide), placebo-controlled trial; 68 weeks of treatment with 12-week lifestyle modification therapy run-in period	201 adolescents (12 to <18 years old); BMI ≥95th percentile or BMI ≥85th percentile with ≥1 weight-related comorbidity; excluded Tanner stage I[a]	Percentage change in BMI difference of −16.7% (P<0.001) favouring semaglutide; improved cardiometabolic risk factors (HbA_{1c}, lipid profile and blood levels of alanine aminotransferase) and weight-related quality of life	Overall adverse events were similar (78.9% semaglutide vs 82.1% placebo); gastrointestinal issues were the most commonly reported adverse events and were more frequent with semaglutide (61.7%) vs placebo (41.8%)

AOMs, anti-obesity medications. [a]Tanner stage I indicates pre-pubertal status.

Kelly, A.S. Current and future pharmacotherapies for obesity in children and adolescents. *Nat Rev Endocrinol* **19**, 534–541 (2023).

Terapia Chirurgica

TABLE 20 Criteria for Pediatric Metabolic and Bariatric Surgery[733]

Weight Criteria	Criteria for Comorbid Conditions
Class 2 obesity, BMI ≥ 35 kg/m^2 or 120% of the 95th percentile for age and sex, whichever is lower	Clinically significant disease; examples include but are not limited to T2DM, IIH, NASH, Blount disease, SCFE, GERD, obstructive sleep apnea (AHI >5), cardiovascular disease risks (HTN, hyperlipidemia, insulin resistance), depressed health-related quality of life.
Class 3 obesity, BMI ≥ 40 kg/m^2 or 140% of the 95th percentile for age and sex, whichever is lower	Not required but commonly present.

AHI, apnea-hypopnea index.

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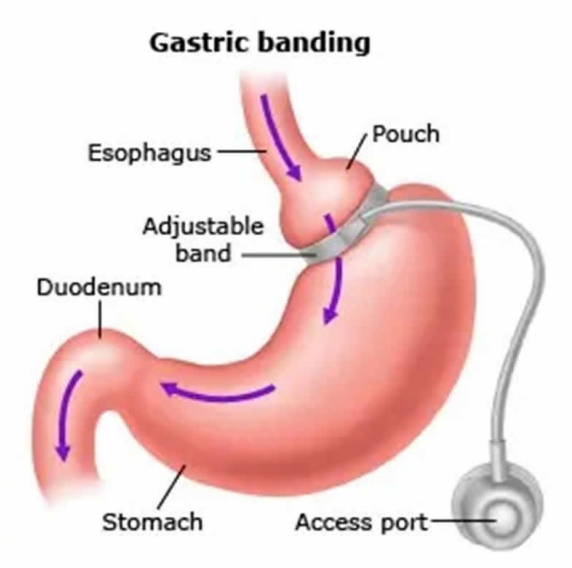
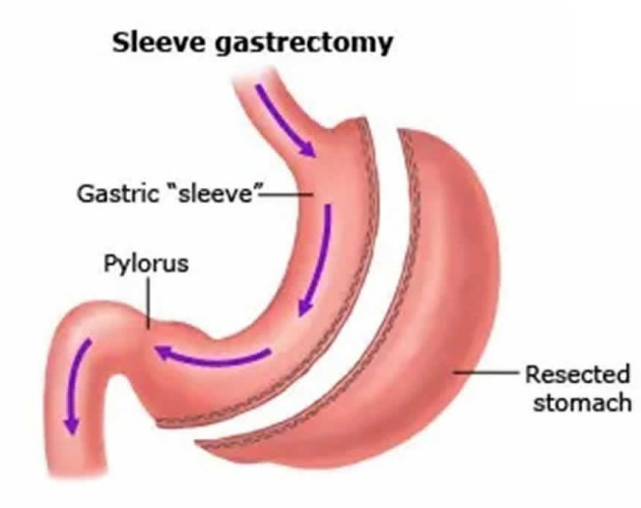
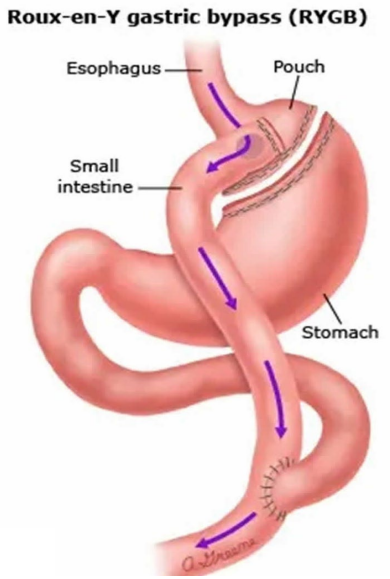






	Change in BMI after 3 years (kg /m²)	Effects on type 2 diabetes remission	Mortality at less than 30 days	Mortality at more than 30 days	Re-operation rate	Complications
Adjustable gastric banding	−11·43 (−18·14 to −4·72)	67·58% (49·51 to 82·83)	0·07% (0·02 to 0·12)	0·21% (0·08 to 0·37)	7·01% (3·99 to 11·24)	7·80% (3·90 to 13·00)
Sleeve gastrectomy	−16·78 (−20·57 to −12·99)	85·53% (72·69 to 94·07)	0·29% (0·11 to 0·63)	0·34% (0·14 to 0·60)	2·96 (1·70 to 4·71)	8·90 (5·60 to 13·00)
Roux-en-Y gastric bypass	−21·88 (−27·96 to −15·79)	92·83% (85·29 to 97·21)	0·38% (0·22 to 0·59)	0·39% (0·01 to 0·86)	5·34 (4·48 to 6·48)	12·00 (7·30 to 17·00)

Data are n or n% (95% CI). Data in table are from Chang (2014).[102] For this analysis, surgical procedures were grouped: adjustable gastric banding included laparoscopic gastric banding and swedish band; sleeve gastrectomy included sleeve gastrectomy and vertical banded gastroplasty; and Roux-en-Y gastric bypass included laparoscopic and open procedures and biliopancreatic diversion with or without duodenal switch. BMI=body-mass index.

Table 3: **Surgical procedures for treatment of obesity**

Bray GA, Frühbeck G, Ryan DH, Wilding JP. Management of obesity. Lancet. 2016

	Affected gene	Specific clinical features
Monogenic obesity		
LEP	LEP, LEPR, POMC, PCSK1, MC4R genes: Autosomal recessive transmission: severe, early-onset obesity and eating disorders with related signs (see beside). Milder phenotype in heterozygous patients without related signs and more metabolic obesity complications.	Endocrine abnormalities (gonadotropic and thyrotropic insufficiency).
LEPR		Endocrine abnormalities (gonadotropic, somatotropic and thyrotropic insufficiency).
POMC		Endocrine abnormalities (corticotropic, gonadotropic, somatotropic and mild thyrotropic insufficiency), red hair.
PCSK1		Severe neonatal diarrhea, endocrine abnormalities (corticotropic, gonadotropic, somatotropic and thyrotropic insufficiency), hypoglycemia.
MC4R		Increased height growth in childhood.

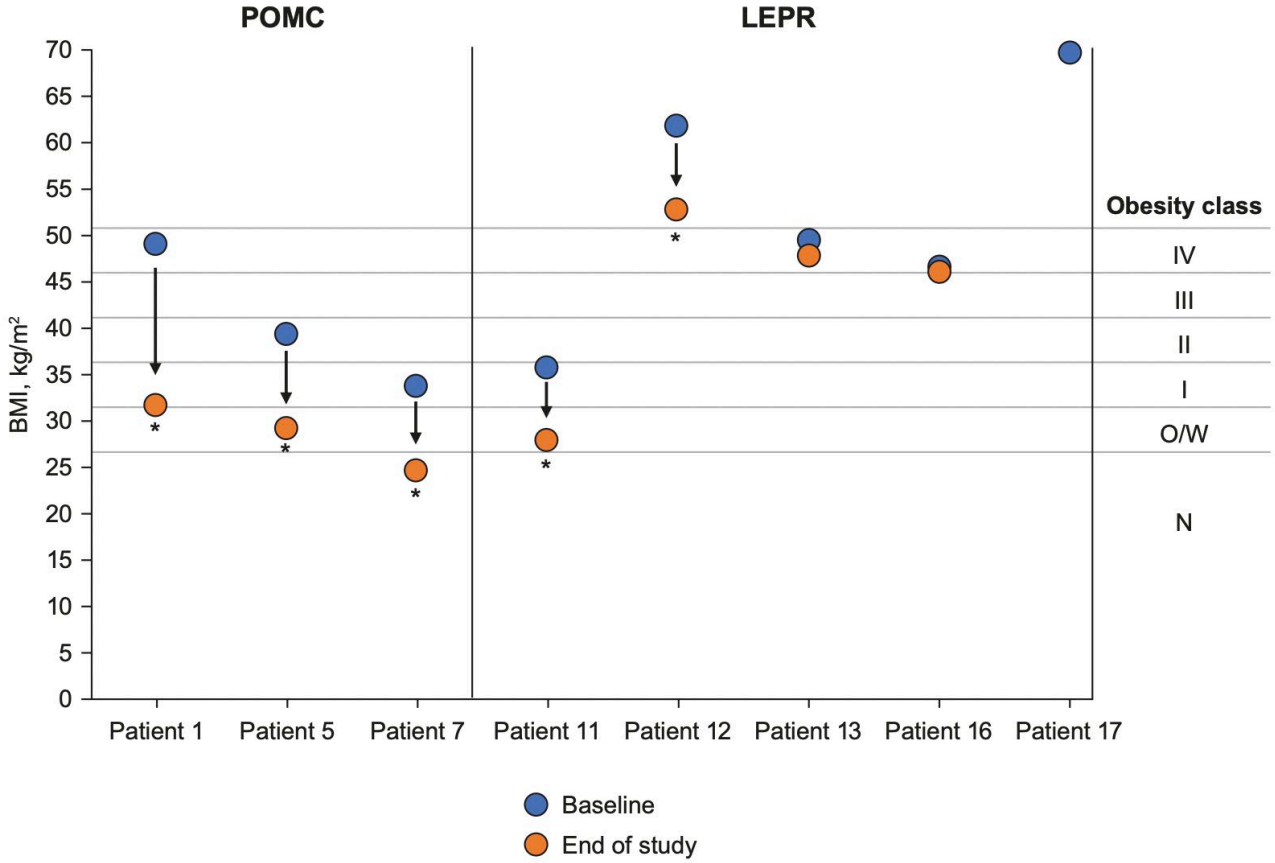
- **Più del 90% delle obesità pediatriche sono idiopatiche** (predisposizione genetica, fattori fisiologici, socioeconomic e ambientali)

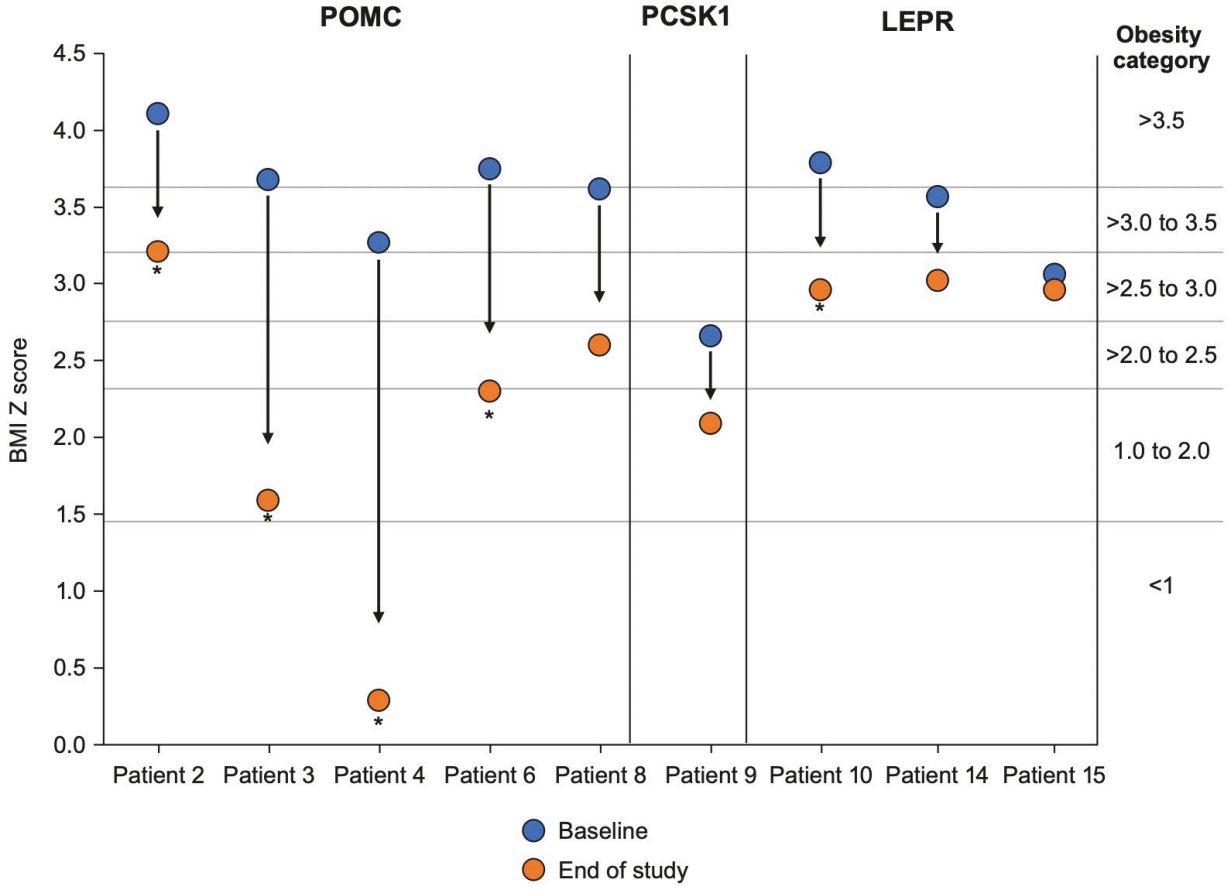
- Meno del 10% sono secondarie ad altre condizioni:
  - *Obesità sindromiche e forme mongeniche*
  - *Disturbi endocrini*
  - *Farmaci*
  - *Oncologiche*
  - *Malattie psichiatriche*

	Affected gene	Specific clinical features
Syndromic obesity		
Prader Willi syndrome	Abnormal parental genomic imprinting of paternal 15q11-q13 region.	Neonatal hypotonia, suckling disorders in the first months, hyperphagia and food impulsivity around 4 years, moderate intellectual disability, social interaction and behavioral disorders, endocrine abnormalities (growth hormone deficiency, hypogonadism), dysmorphia, scoliosis.
16p11.2 microdeletion syndrome	Autosomal dominant transmission, small region of chromosome 16.	Developmental delay, intellectual disability.
Fragile X syndrome	X-linked dominant transmission, CGG trinucleotide expansion of FMR1 promotor leading to a lack of transcription.	Intellectual deficiency and dysmorphic features of varying degree, more severe and frequent in males. 40% of obesity with some PWS-like phenotypes.
Bardet-Biedl syndrome	Autosomal recessive transmission, 22 genes known.	Retinal dystrophy, polydactyly, renal abnormalities, hypogonadism, hepatic fibrosis, learning disabilities.
Alström syndrome	Autosomal recessive transmission, ALMS1 gene.	Retinal dystrophy, dysmorphic features, short stature, central deafness, endocrine abnormalities (central or peripheral hypogonadism and hypothyroidism, polycystic ovary syndrome) dilated cardiomyopathy, liver and renal fibrosis and no intellectual disability.
Pseudohypoparathyroidism	Autosomal dominant transmission, GNAS gene.	Dysmorphia, shot bones, short stature, subcutaneous ossifications, variable developmental delay, hypocalcemia, hypothyroidism, pubertal delay, epilepsy.
MYT1L	Autosomal dominant transmission, MYT1L gene.	Developmental and language delay, intellectual disability, behavioral disorders and dysmorphic features.

Natural History of Obesity Due to POMC, PCSK1, and LEPR Deficiency and the Impact of Setmelanotide

Martin Wabitsch,[1] Sadaf Farooqi,[2] Christa E. Flück,[3] Natasa Bratina,[4] Usha G. Mallya,[5] Murray Stewart,[5] Jill Garrison,[5] Erica van den Akker,[6] and Peter Kühnen[7]





Grazie per l'attenzione

Dr. Giacomo Tantari