

TERAPIE INNOVATIVE E MEDICINA DI PRECISIONE:

VERSO LA "DECRONICIZZAZIONE" DEL DIABETE

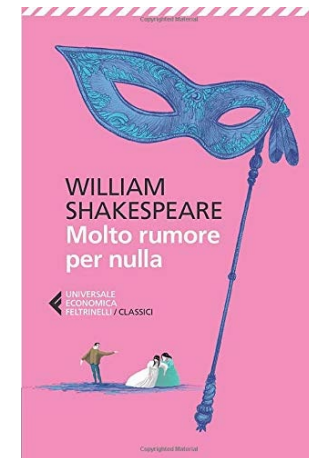
Approcci personalizzati nell'obesità

Moderatori: Raffaella Di Luzio, Michele Riva

Diete chetogeniche: molto rumore per....?

Flavia Prodam

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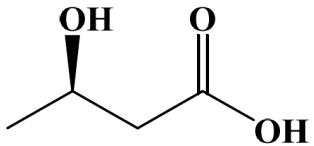
DISCLOSURES

Abiogen; Amryt; Astra Zeneca; Boheringer; Difass International; Caelus Health; ; Menarini; Novo Nordisk; Probiotical , Sanofi; Therascience

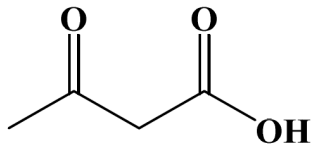
Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi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

DIETA CHETOGENICA

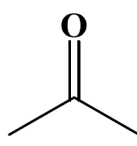
Any nutritional intervention with the purpose of inducing ketosis



(*R*)- β -hydroxybutyric acid



acetoacetic acid



acetone

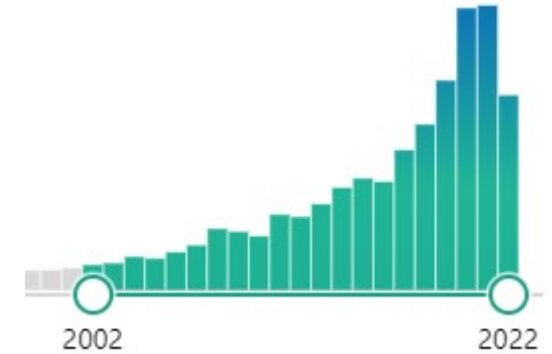


Table 1 Proposed descriptions and abbreviations for ketogenic diets

Diet description	Abbreviation	Carbohydrates	Calories	Lipids
Very-low-calorie ketogenic diet	VLCKD	<30–50 g/day	<700–800 kcal/day	<30–40 g/day
Low-calorie ketogenic diet	LCKD	<30–50 g/day	>700–800 kcal/day and < TEE	>30–40 g/day
Isocaloric ketogenic diet	ICKD	<30–50 g/day	In line with TEE	70–80% of daily calorie intake
Intermittent fasting	IF	40-55%	> BMR and < TEE	20-35% of daily calorie intake
Time-restricted eating	TRE	40-55%	> BMR and < TEE	20-35% of daily calorie intake
Fasting mimicking diet	FMD	40-50%	700-1100 kcal/day	40-50% of daily calorie intake
rProtein-sparing modified fast	rPSMF	>40 and <100g/day	1200-1800 kcal/day < TEE	30-50% of daily calorie intake

VLCKD

Energia complessiva:
600-800 Kcal/die

4-12 SETTIMANE

Apporto proteico = 1.2-1.5 g/kg (su peso ideale; 40-43%)

Apporto glicidico = < 30-50 g/die (13-20% energia)

Apporto lipidico = 25-30 g/die (40-44% energia)



APPROCCIO
DIETOLOGICO MIRATO

ATTIVITÀ FISICA
PERSONALIZZATA

GESTIONE COGNITIVO-
COMPORTAMENTALE ADATTATA

Il dimagrimento
in chetogenesi

La reintroduzione glucidica e l'attività fisica

L'alimentazione
equilibrata



INTEGRAZIONE VITAMINE E MINERALI

VERDURA CONSIGLIATA

Lista 1

A volontà ma senza esagerazione
e diversificandola il più possibile.

Asparagi
Melanzane
Bietole
Broccoli
Sedano
Funghi
Cavolfiore
Ravanelli
Crescione
Cetrioli
Insalata verde
Indivia o insalata belga

Spinaci
Finocchi
Radicchio
Germogli di soia
Cardi
Peperoni verdi
Rucola
Verza
Zucchine

Lista 2

Massimo 100 g a pasto.

Carciofi
Cavoli
Cavoletti di Bruxelles
Fagiolini
Rape
Porri
Peperoni rossi e gialli
Pomodori

Tutto quello che
non è indicato
nelle due liste
non è consentito



STEP VLCKD

Very low-carbohydrate (< 10% carbohydrates) or 20-50 g/day

Low-carbohydrate (<26% carbohydrates) or less than < 130 g/day

Moderate-carbohydrate (26%-44%)

High-carbohydrate (45% or greater)



20% WEIGHT-LOSS



2019

M. Caprio^{1,2} · M. Infante³ · E. Moriconi^{1,4} · A. Armani¹ · A. Fabbri³ · G. Mantovani⁵ · S. Mariani⁴ · C. Lubrano⁴ · E. Poggiogalle⁴ · S. Migliaccio⁶ · L. M. Donini⁴ · S. Basciani⁴ · A. Cignarelli⁷ · E. Conte⁷ · G. Ceccarini⁸ · F. Bogazzi⁹ · L. Cimino¹⁰ · R. A. Condorelli¹⁰ · S. La Vignera¹⁰ · A. E. Calogero¹⁰ · A. Gambineri¹¹ · L. Vignozzi¹² · F. Prodam¹³ · G. Aimaretti¹³ · G. Linsalata¹⁴ · S. Buralli¹⁴ · F. Monzani¹⁴ · A. Aversa¹⁵ · R. Vettor¹⁶ · F. Santini⁸ · P. Vitti⁹ · L. Gnessi⁴ · U. Pagotto¹¹ · F. Giorgino⁷ · A. Colao¹⁷ · A. Lenzi⁴ on behalf of the Cardiovascular Endocrinology Club of the Italian Society of Endocrinology

Obesity Facts

Guidelines

Obes Facts 2021;14:222–245
DOI: 10.1159/000515381

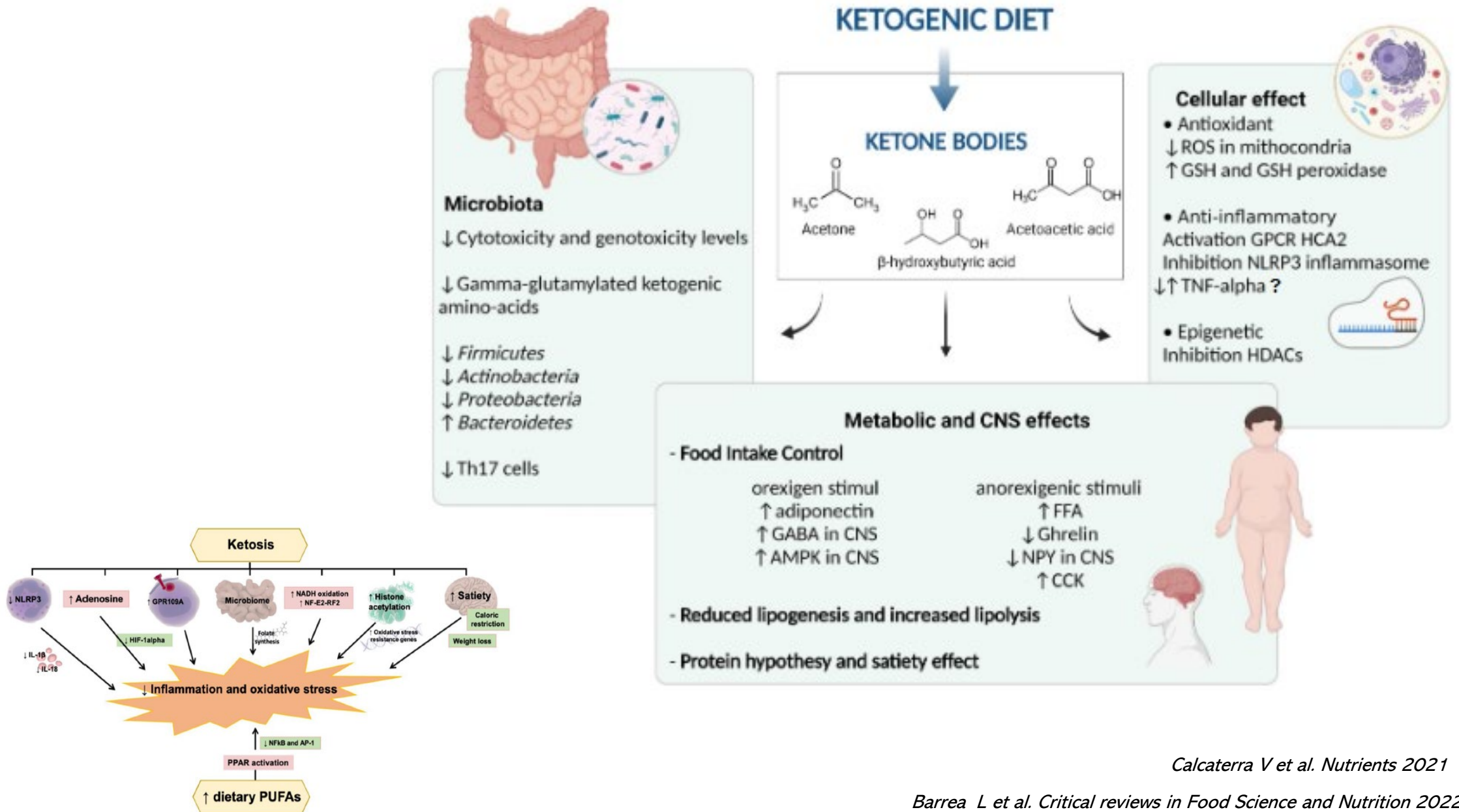
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2021

European Guidelines for Obesity Management in Adults with a Very Low-Calorie Ketogenic Diet: A Systematic Review and Meta-Analysis

Giovanna Muscogiuri^{a,b} · Marwan El Ghoch^c · Annamaria Colao^{a,b} · Maria Hassapidou^d · Volkan Yumuk^e · Luca Busetto^f · Obesity Management Task Force (OMTF) of the European Association for the Study of Obesity (EASO)

MECCANISMI KD





Mini-Review

New Horizons. A New Paradigm for Treating to Target with Second-Generation Obesity Medications

W. Timothy Garvey¹

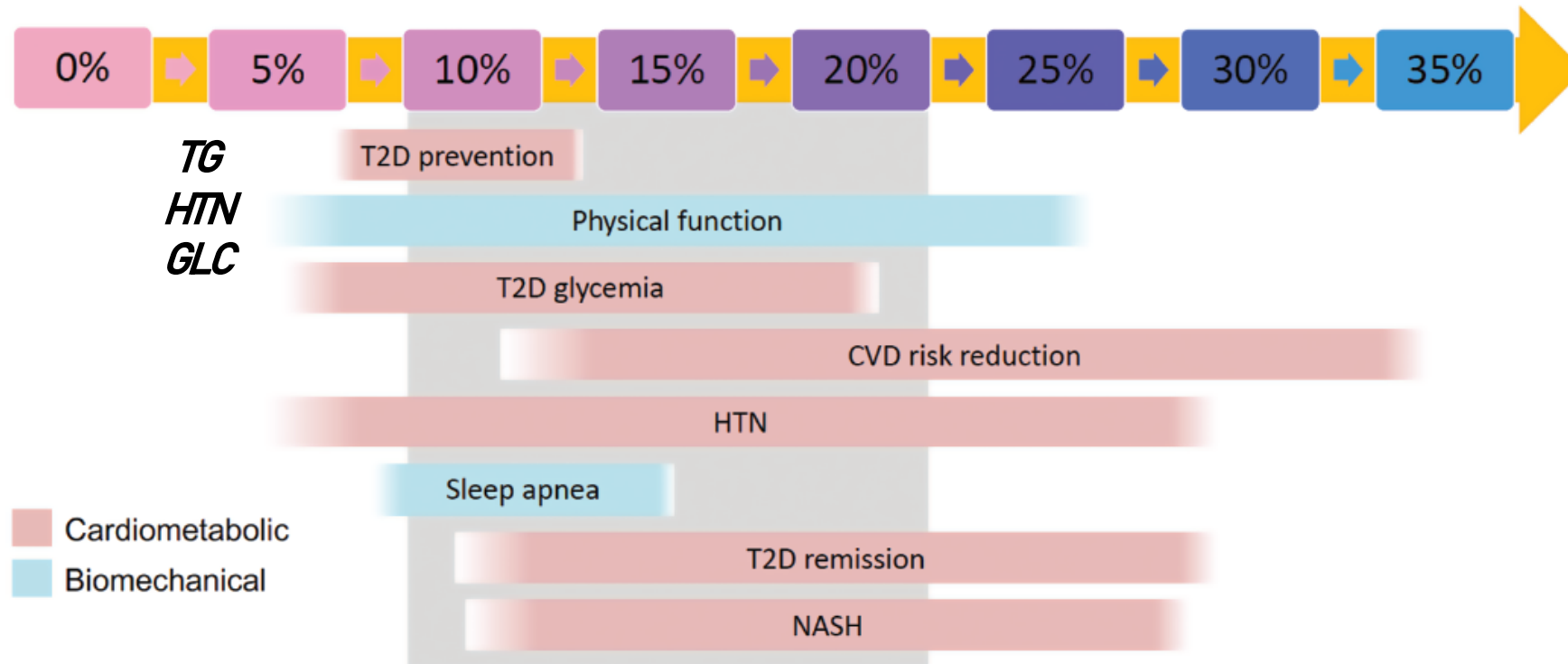


Figure 2. Treating ABCD/obesity to target for prevention and treatment of complications. Abbreviations: ABCD: adiposity-based chronic disease; CVD: cardiovascular disease; HTN: hypertension; NASH, nonalcoholic steatohepatitis; T2D, type 2 diabetes.



COMPARATORS

BARIATRIC SURGERY

Pooled mean TWL at 1-year follow-up: **31.9%** after LRYGB and **29.5%** after LSG

Pooled mean TWL at 5-year follow-up: **28.1%** after LRYGB and **27.0%** after LSG

DRUGS

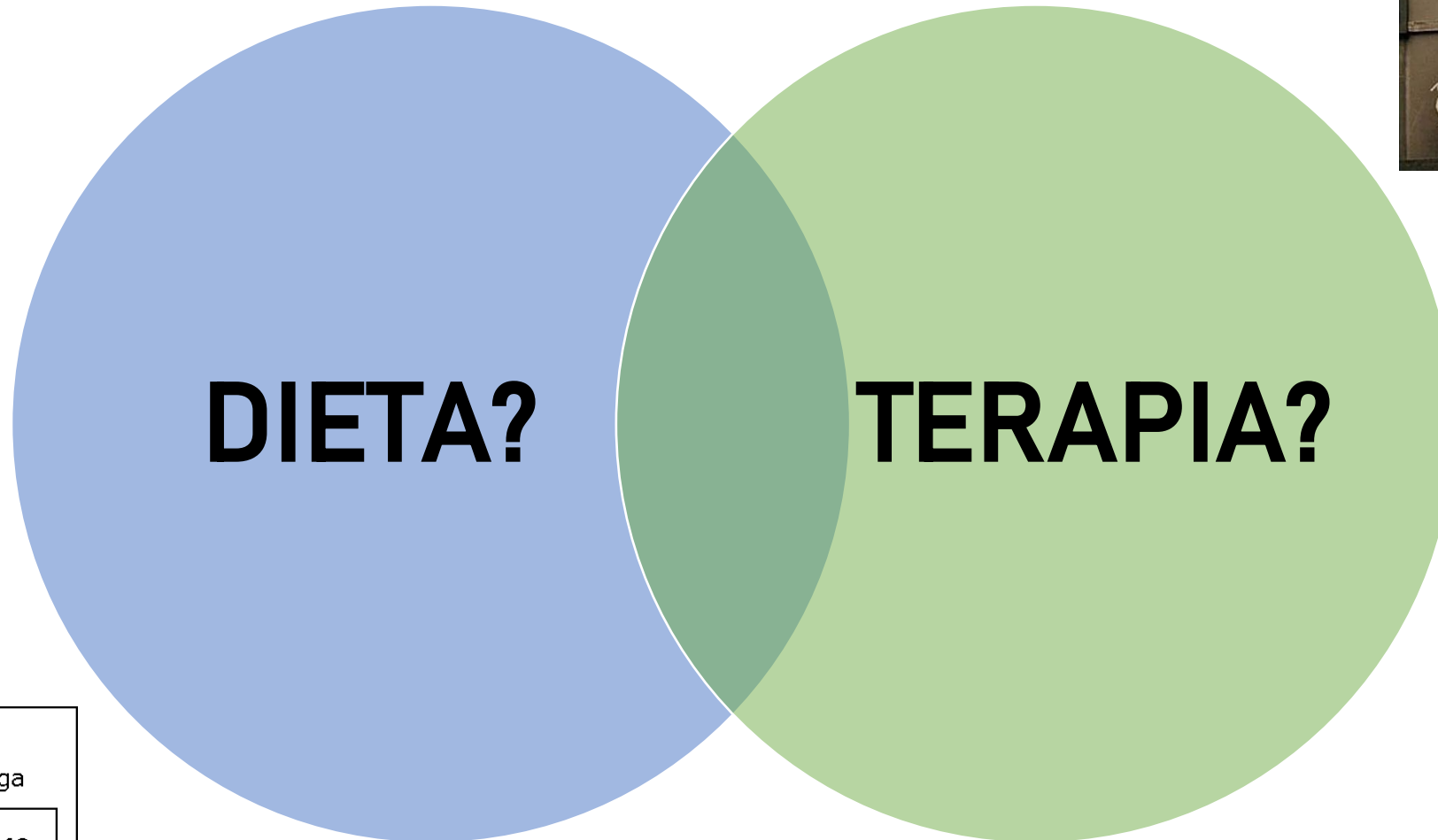
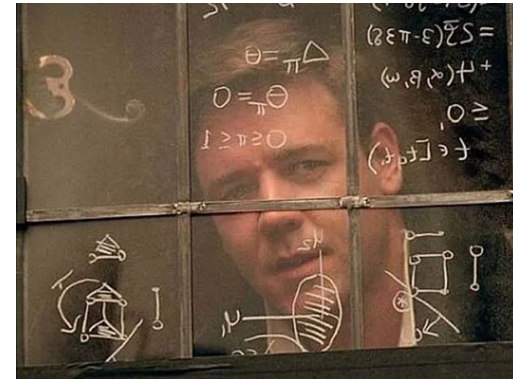
From **5% to 21%** TWL depending on the drug
(Orlistat, Naltrexone-Ibuproprione, Phentermine-Topimaratate, Liraglutide, Semaglutide, Tirzepatide)

From **9.6% to 13%** TWL in T2DM with OW/OB
(Semaglutide and Tirzepatide)





DILEMMA DEL PRIGIONIERO



		Clyde:	
		confessa	nega
Bonnie:	confessa	-5, -5	0, -10
	nega	-10, 0	-1, -1



For VLCKD?

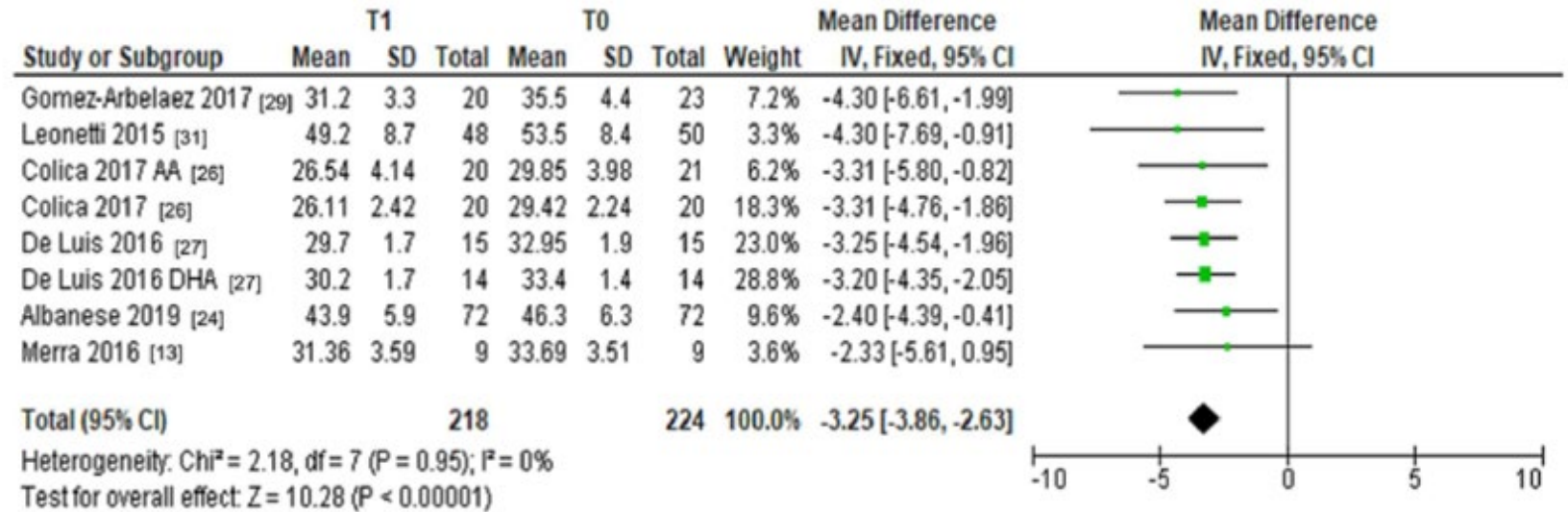
8 week intervention →

BMI

reduced by 3.25 kg/m²

BW by 7.5kg

1 month of VLCKD

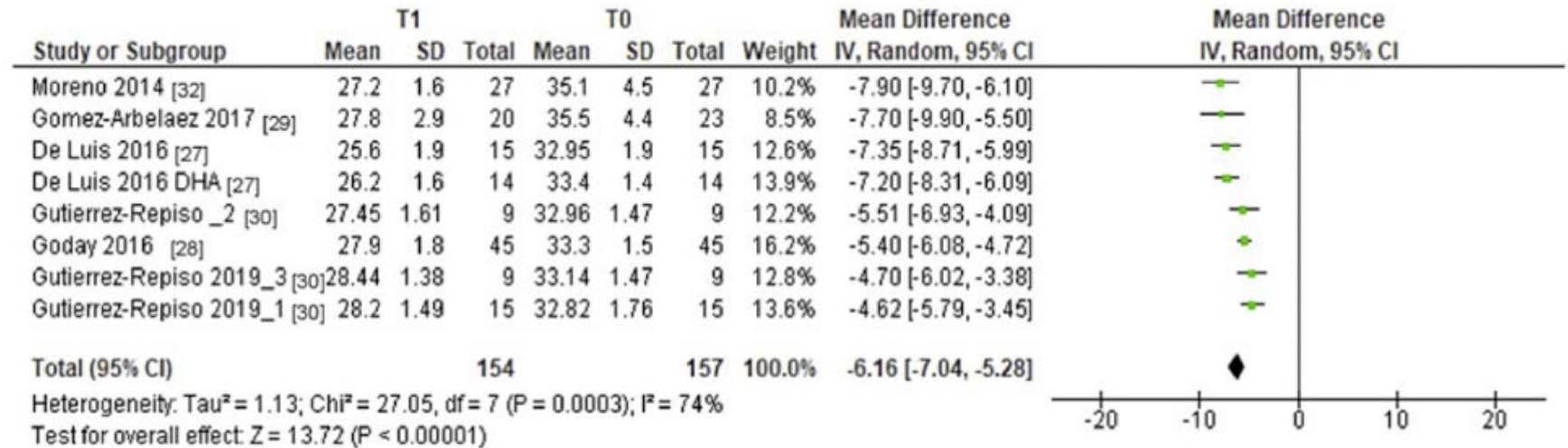


BMI

reduced by 6.16 kg/m²

BW by 16.8kg

6 months after VLCKD



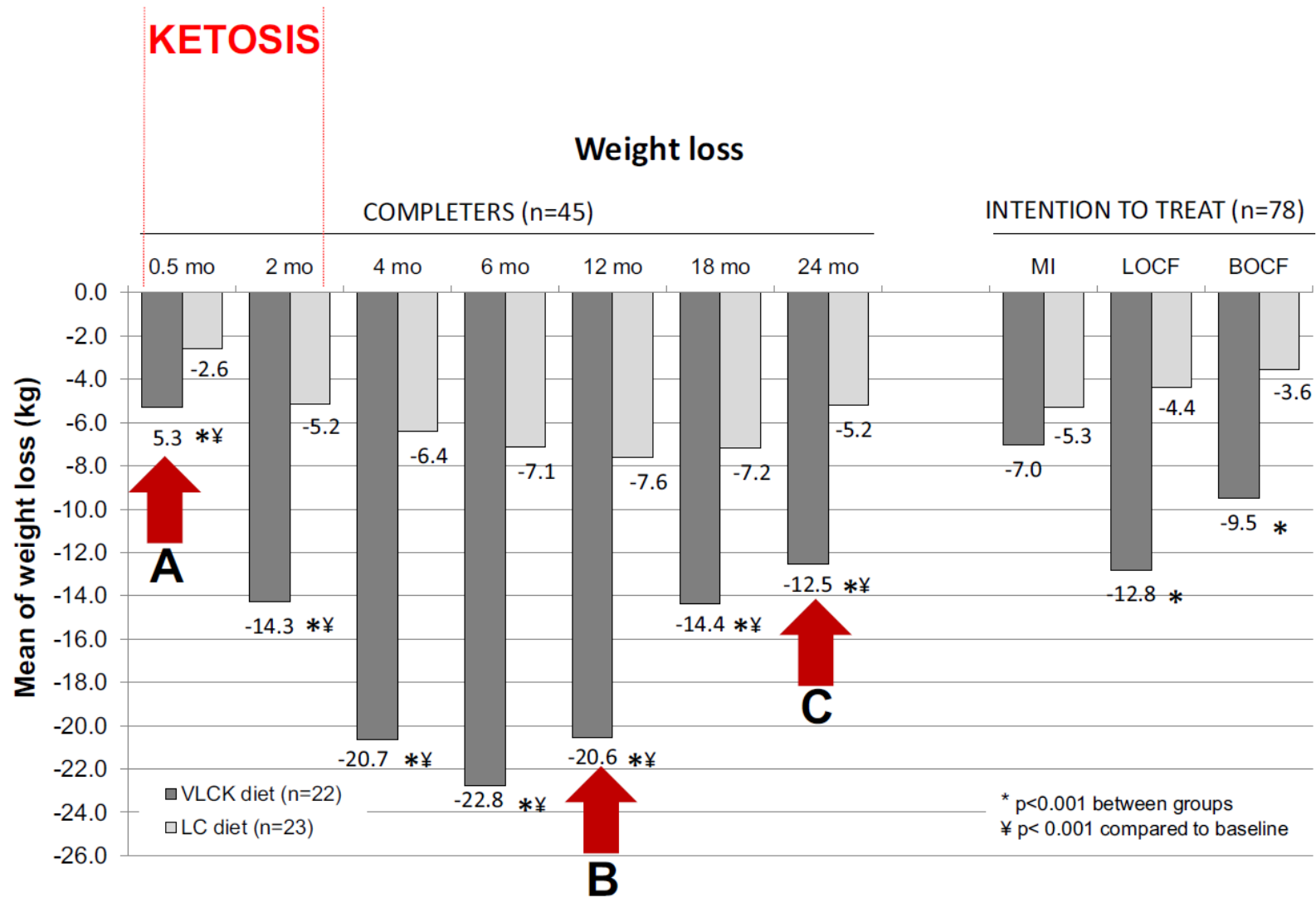
VISCERAL FAT

reduced by 16.5%

4 months after VLCKD

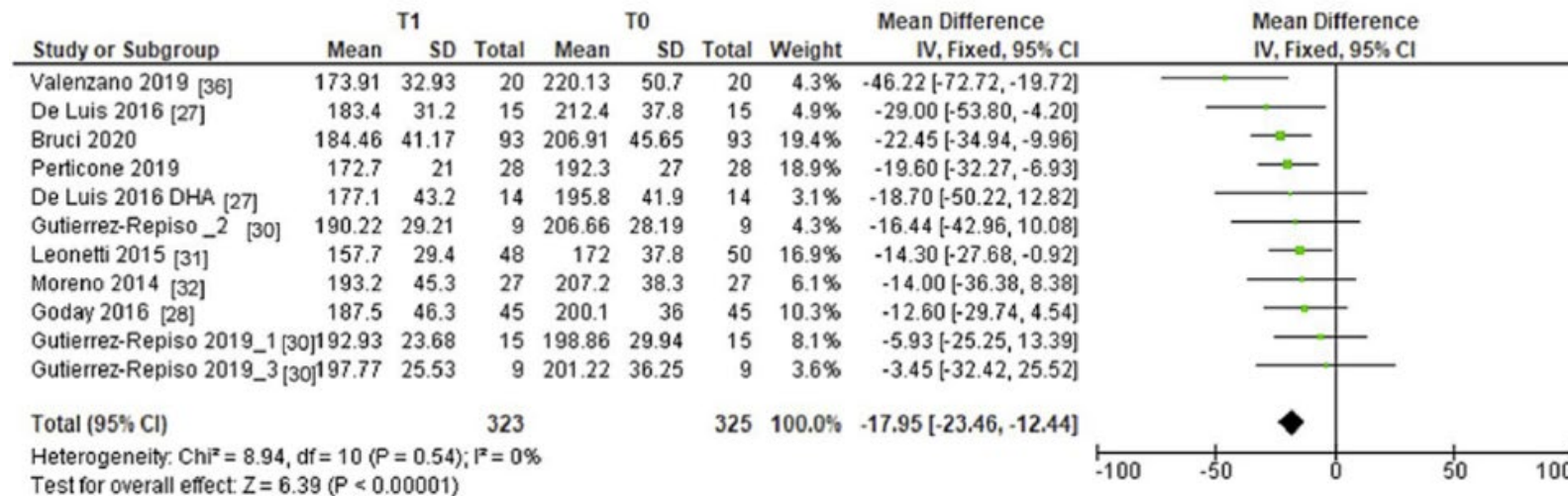
TWL: around 8% in 1 month and 15% in 6 months

LONG-TERM

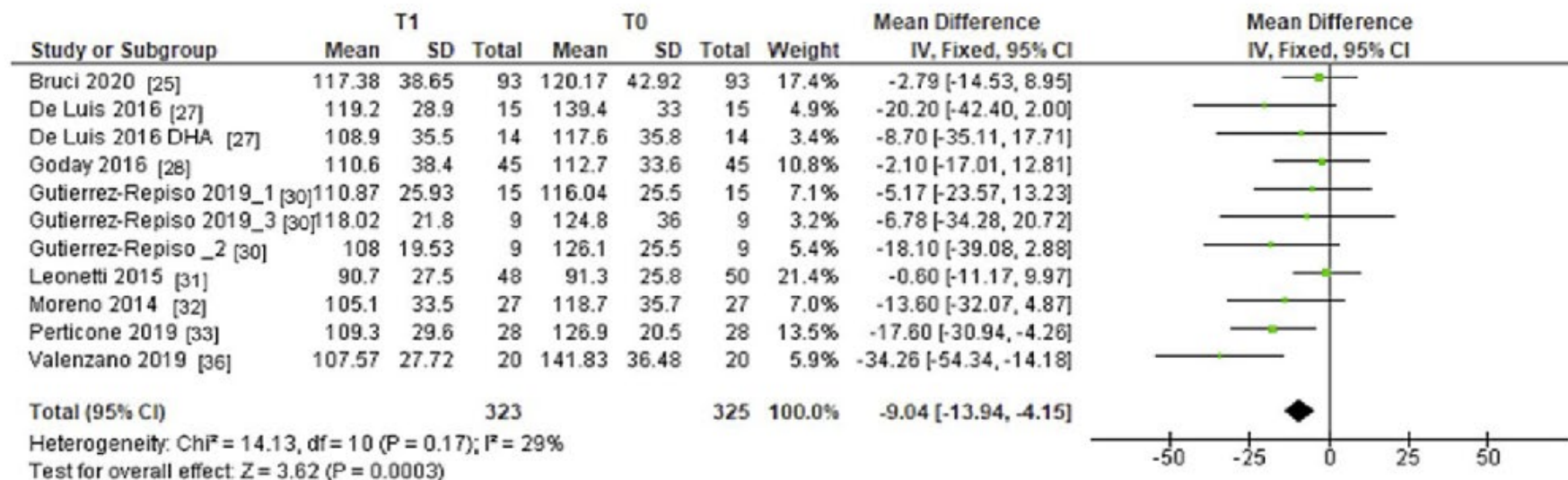


LIPIDS

TOTAL CHOLESTEROL
- 17.9 mg/dL

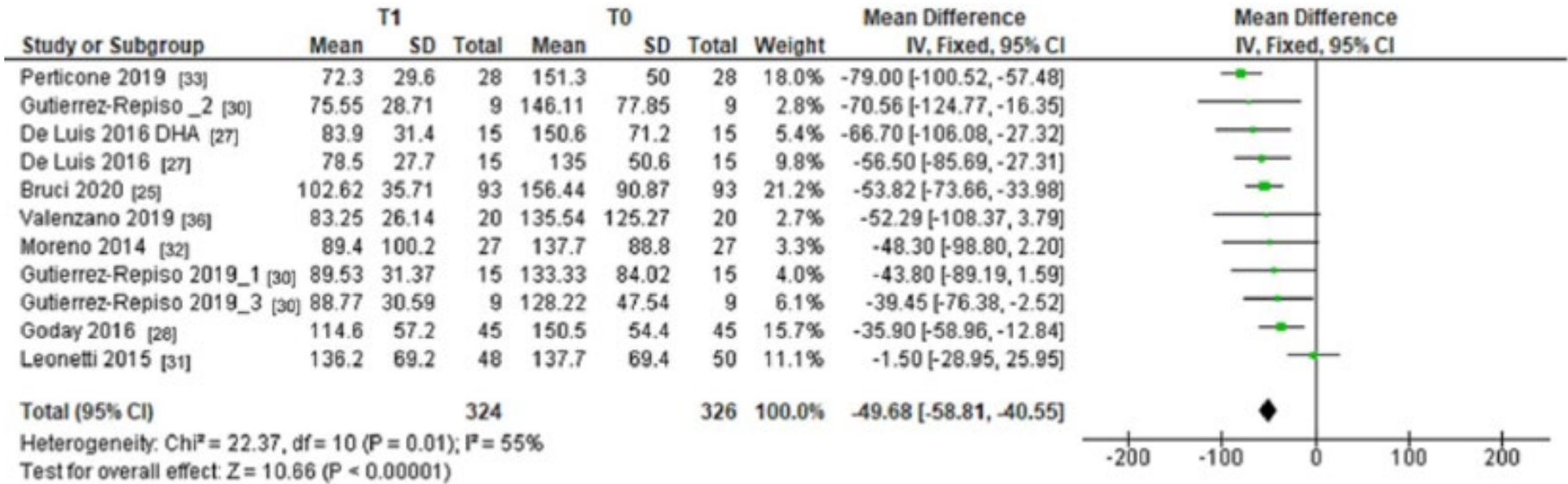


LDL-c
- 9 mg/dL

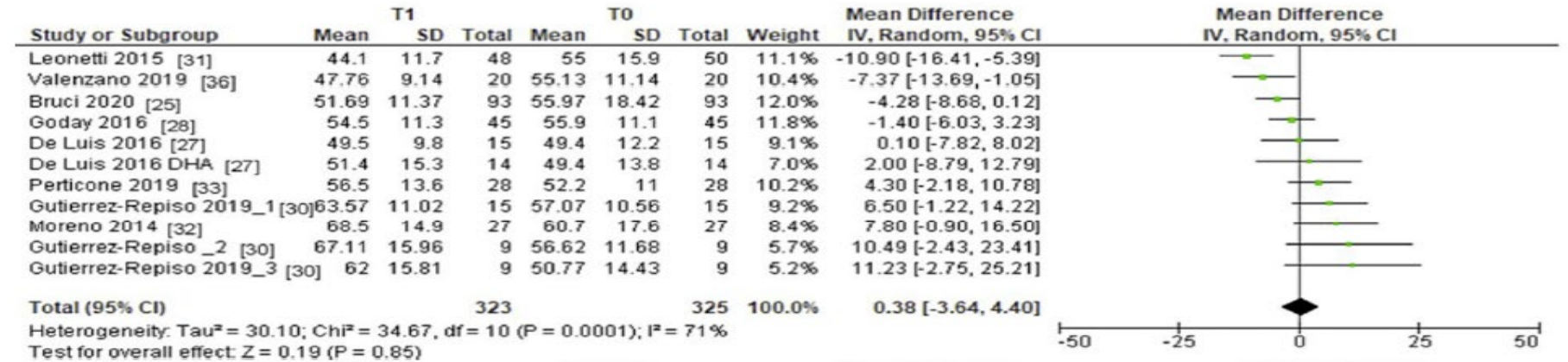


LIPIDS

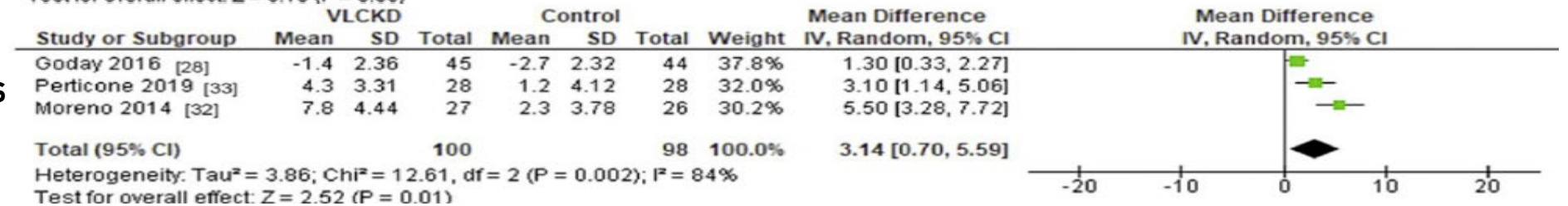
TRIGLYCERIDES
- 49.7 mg/dL



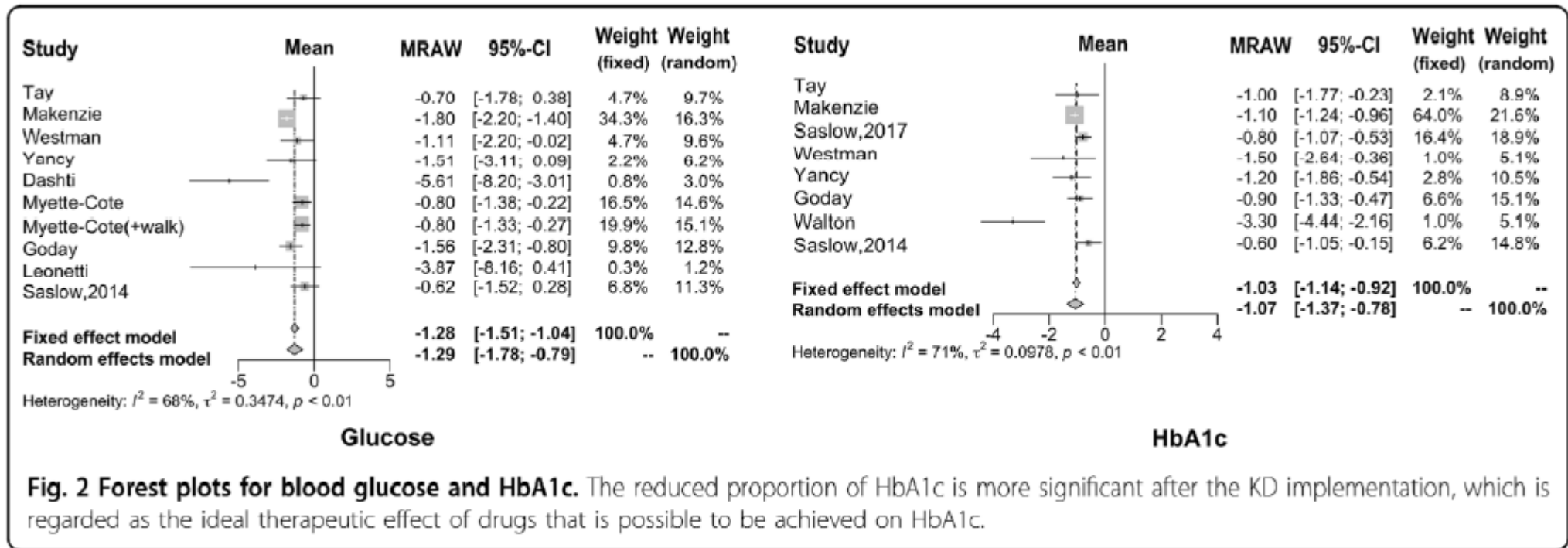
HDL-c
+ 0.38 mg/dL (ns)



+ 3.14 mg/dL
compared to
other weight loss diets



OBESITY AND T2DM



AT THE END KETOSIS → FASTING GLUCOSE
- 1.29 mmol/L (-23 mg/dL)

HbA1c
- 1.07 %L



LONG-TERM

Table 4. Mean differences ($\pm$ SD) between baseline (T0), 3 months (T1) and 12 months (T2) in VLCKD and LCD groups.

Parameters	Δ T0-T1 (Mean $\pm$ SD)		<i>p</i> -Value	Δ T0-T2 (Mean $\pm$ SD)		<i>p</i> -Value
	VLCKD	LCD		VLCKD	LCD	
Weight	9.51 $\pm$ 7.13	0.31 $\pm$ 3.08	0.000	12.93 $\pm$ 8.84	0.58 $\pm$ 4.18	0.000
BMI	3.57 $\pm$ 2.16	0.41 $\pm$ 1.38	0.000	4.76 $\pm$ 2.78	0.19 $\pm$ 1.53	0.000
WHR	0.01 $\pm$ 0.03	0.00 $\pm$ 0.01	0.609	0.01 $\pm$ 0.04	0.00 $\pm$ 0.02	0.638
BPsys	8.53 $\pm$ 7.62	−2.20 $\pm$ 16.81	0.032	13.73 $\pm$ 14.34	−2.40 $\pm$ 10.44	0.005
BPdias	9.33 $\pm$ 11.54	2.87 $\pm$ 9.49	0.104	9.33 $\pm$ 11.54	−3.80 $\pm$ 14.25	0.018
HbA1c (%)	0.69 $\pm$ 0.65	0.42 $\pm$ 1.01	0.533	0.61 $\pm$ 0.54	0.13 $\pm$ 0.76	0.070

Significant *p* values are highlighted in bold. HbA1c plasma levels are expressed as a percentage of total hemoglobin.

Pharmacological Treatment		VLCKD	LCD
Diet	1	4	0
Metformin + Diet	5	11	8
Metformin + Sulphonylurea	2	0	0
Metformin + GLP-1 agonists	2	0	6
Metformin + SGLT2 inhibitors	3	0	1
Metformin + DPP4 inhibitors	2	0	0





CONTROINDICAZIONI-EFFETTI COLLATERALI-MONITORAGGIO

Table 3 Absolute contraindications to the use of VLCKD

Absolute contraindications
Type 1 diabetes mellitus, latent autoimmune diabetes in adults, β -cell failure in type 2 diabetes mellitus, use of sodium/glucose cotransporter 2 (SGLT2) inhibitors (risk for euglycemic diabetic ketoacidosis)
Pregnancy and breastfeeding
Kidney failure and moderate-to-severe chronic kidney disease, liver failure, hearth failure (NYHA III-IV), respiratory failure
Unstable angina, recent stroke or myocardial infarction (< 12 months), cardiac arrhythmias
Eating disorders and other severe mental illnesses, alcohol and substance abuse
Active/severe infections
Frail elderly patients
48 h prior to elective surgery or invasive procedures and perioperative period
Rare disorders: porphyria, carnitine deficiency, carnitine palmitoyltransferase deficiency, carnitine-acylcarnitine translocase deficiency, mitochondrial fatty acid β -oxidation disorders, pyruvate carboxylase deficiency

The most common side effects that were reported were lethargy (46.2%), halitosis (46.2%), headache (45.3%), dry mouth (43.5%), constipation (28%), hypotension (17.9%), dizziness (16%), vomiting/nausea (15.1%), hair loss (15.1%), diarrhoea (12.3%), hyperuricemia (10.4%) and visual disturbances (4.7%).

Table 1 Parameters that need to be monitored before, during and at the end of a VLCKD regimen

Parameters	Frequency of monitoring	Rationale of monitoring
Complete blood count	At baseline and at the end of the VLCKD program	To exclude patients with severe alterations of blood count
Creatinine, BUN, uric acid (serum)	At baseline and during the ketogenic phase	Monitoring of kidney function and potential increase in uric acid
Glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (serum)	At baseline and at the end of the VLCKD program	Excluding patients with uncontrolled diabetes, monitoring of lipid profile
ALT, AST, γ -GT, total and direct bilirubin (serum)	At baseline, during the ketogenic phase and at the end of the VLCKD program	Monitoring of liver function and cholestatic parameters
Sodium, potassium, calcium, magnesium, inorganic phosphate (serum)	At baseline, during the ketogenic phase and at the end of the VLCKD program	Monitoring for potential dehydration and electrolyte abnormalities
β -Hydroxybutyrate (capillary blood or urine)	During the ketogenic phase	Monitoring of ketosis
TSH, FT4 (serum)	At baseline	To exclude thyroid function abnormalities
25-Hydroxyvitamin D (serum)	At baseline	To treat vitamin D deficiency, if present
Complete urinalysis and microalbuminuria (urine)	At baseline, during the ketogenic phase and at the end of the VLCKD program	To exclude any potential kidney damage
Body composition and hydration status (by bioelectrical impedance analysis)	At baseline, during the ketogenic phase and at the end of the VLCKD program	Monitoring of body composition (fat mass, fat-free mass, body cell mass, total body water, extracellular water)



Quando è indicata la VLCKD?

La VLCKD può essere considerata se:

- ✓ **Insuccesso delle diete precedenti**
- ✓ **Insuccesso della terapia farmacologica → valutare compliance**
- ✓ **Intervento chirurgico programmato (bariatrico o non bariatrico)**
- ✓ **Ritorno ad un peso forma post- allattamento**
- ✓ **Bisogno di un effetto starter/prosecuzione motivante**
- ✓ **Incremento ponderale dopo un arresto del fumo**
- ✓ **Aumento ponderale con terapie farmacologiche**
- ✓ **Incremento ponderale dopo chirurgia bariatrica**

La VLCKD trova la sua massima evidenza di efficacia in:

- ✓ **Obesità + Diabete mellito tipo 2 o Sindrome Metabolica**
- ✓ **Obesità + epilessia resistente (pediatrici e non)**
- ✓ **Riduzione immediata del rischio cardiovascolare**
- ✓ **Obesità + Ipogonadismo maschile**
- ✓ **Obesità Sarcopenica**

Journal of Endocrinological Investigation
<https://doi.org/10.1007/s40618-019-01061-2>

CONSENSUS STATEMENT



Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE)

M. Caprio^{1,2} · M. Infante³ · E. Moriconi^{1,4} · A. Armani¹ · A. Fabbri³ · G. Mantovani⁵ · S. Mariani⁴ · C. Lubrano⁴ · E. Poggiogalle⁴ · S. Migliaccio⁶ · L. M. Donini⁴ · S. Basciani⁴ · A. Cignarelli⁷ · E. Conte⁷ · G. Ceccarini⁸ · F. Bogazzi⁹ · L. Cimino¹⁰ · R. A. Condorelli¹⁰ · S. La Vignera¹⁰ · A. E. Calogero¹⁰ · A. Gambineri¹¹ · L. Vignozzi¹² · F. Prodham¹³ · G. Aimaretti¹³ · G. Linsalata¹⁴ · S. Buralli¹⁴ · F. Monzani¹⁴ · A. Aversa¹⁵ · R. Vettor¹⁶ · F. Santini⁸ · P. Vitti⁹ · L. Gnessi⁴ · U. Pagotto¹¹ · F. Giorgino⁷ · A. Colao¹⁷ · A. Lenzi⁴ on behalf of the Cardiovascular Endocrinology Club of the Italian Society of Endocrinology



ALTRO?????



Effects of a Personalized VLCKD on Body Composition and Resting Energy Expenditure in the Reversal of Diabetes to Prevent Complications

Parameters	Basal Mean $\pm$ SD	Four Weeks Mean $\pm$ SD	Eight Weeks Mean $\pm$ SD	Δ Base–Four Weeks	Δ Four Weeks–Eight Weeks	Δ Base–Eight Weeks
DXA						
Arm FM (kg)	4.74 $\pm$ 1.30	4.36 $\pm$ 1.14	4.16 $\pm$ 1.17	–7.58	–7.39	–10.26
Leg FM (kg)	11.6 $\pm$ 4.18	10.97 $\pm$ 4.16	10.05 $\pm$ 3.75	–4.52	–8.21	–12.37
Trunk FM (kg)	28.35 $\pm$ 9.47	24.33 $\pm$ 6.68	21.33 $\pm$ 6.04	–9.64	–12.28	–20.72
Android FM (kg)	5.12 $\pm$ 1.87	4.28 $\pm$ 1.29	3.66 $\pm$ 1.23	–11.46	–14.96	–24.80
Gynoid FM (kg)	6.53 $\pm$ 2.05	5.97 $\pm$ 1.92	5.34 $\pm$ 1.63	–6.86	–10.13	–16.33
Whole FM (kg)	46.15 $\pm$ 13.22	42.35 $\pm$ 11.96	38.04 $\pm$ 11.18	–8.20	–10.36	–17.75
Arm FM (%)	43.26 $\pm$ 9.9	42.55 $\pm$ 9.24	42.22 $\pm$ 9.11	–2.41	–3.74	–6.36
Leg FM (%)	36.39 $\pm$ 9.56	36.64 $\pm$ 10.22	35.94 $\pm$ 10.41	–0.34	–4.87	–4.98
Trunk FM (%)	49.92 $\pm$ 6.6	48.32 $\pm$ 6.68	46.3 $\pm$ 7.18	–2.52	–6.13	–8.31
Android FM (%)	53.15 $\pm$ 6.34	51.48 $\pm$ 6.66	49.29 $\pm$ 7.52	–2.57	–6.10	–8.22
Gynoid FM (%)	42.51 $\pm$ 8.69	42.27 $\pm$ 9.24	41.19 $\pm$ 9.09	–1.13	–5.33	–6.38
Whole FM (%)	43.87 $\pm$ 7.38	42.89 $\pm$ 7.42	40.67 $\pm$ 7.59	–2.29	–6.13	–8.10
Arm LM (kg)	5.96 $\pm$ 1.84	5.74 $\pm$ 1.49	5.74 $\pm$ 1.69	–5.77	–1.78	–1.71
Leg LM (kg)	18.95 $\pm$ 4.26	17.97 $\pm$ 4.22	17.79 $\pm$ 4.46	–5.17	–1.37	–6.53
Trunk LM (kg)	26.56 $\pm$ 4.81	24.85 $\pm$ 4.69	24.54 $\pm$ 4.90	–5.30	–0.54	–6.09
Android LM (kg)	4.28 $\pm$ 0.89	3.91 $\pm$ 0.83	3.84 $\pm$ 0.85	–6.76	–1.59	–8.36
Gynoid LM (kg)	8.37 $\pm$ 1.63	7.85 $\pm$ 1.63	7.72 $\pm$ 1.71	–5.70	–1.54	–7.28
Whole LM (kg)	55.39 $\pm$ 10.52	52.9 $\pm$ 10.37	52.94 $\pm$ 10.46	–4.58	0.25	–4.49
Bone Mass (kg)	2.78 $\pm$ 0.59	2.80 $\pm$ 0.58	2.77 $\pm$ 0.59	–0.45	–1.02	–1.45

Effects of a Personalized VLCKD on Body Composition and Resting Energy Expenditure in the Reversal of Diabetes to Prevent Complications

Parameters	Basal Mean $\pm$ SD	Four Weeks Mean $\pm$ SD	Eight Weeks Mean $\pm$ SD	Δ Base–Four Weeks	Δ Four Weeks–Eight Weeks	Δ Base–Eight Weeks
CALORIMETRY						
VO ₂ (mL/min)	251.88 $\pm$ 42.7	214.92 $\pm$ 33.56	235.03 $\pm$ 88.42	–14.85	0.56	–6.27
VCO ₂ (mL/min)	208.88 $\pm$ 36.52	160.67 $\pm$ 34.26	160.81 $\pm$ 35.50	–20.49	–2.08	–23.80
RQ	0.83 $\pm$ 0.03	0.73 $\pm$ 0.04	0.73 $\pm$ 0.04	–12.37	0.07	–12.01
REE (kcal)	1784.50 $\pm$ 313.18	1435.33 $\pm$ 223.71	1498.00 $\pm$ 316.65	–16.83	1.94	–16.59

CARBOIDRATI

Quoziente respiratorio RQ = **1**

Calore di combustione Q= 15.64 kJ/g (4 kcal/g)

Resa energetica r= 20.95 kJ/L

LIPIDI

Quoziente respiratorio RQ = **0.71**

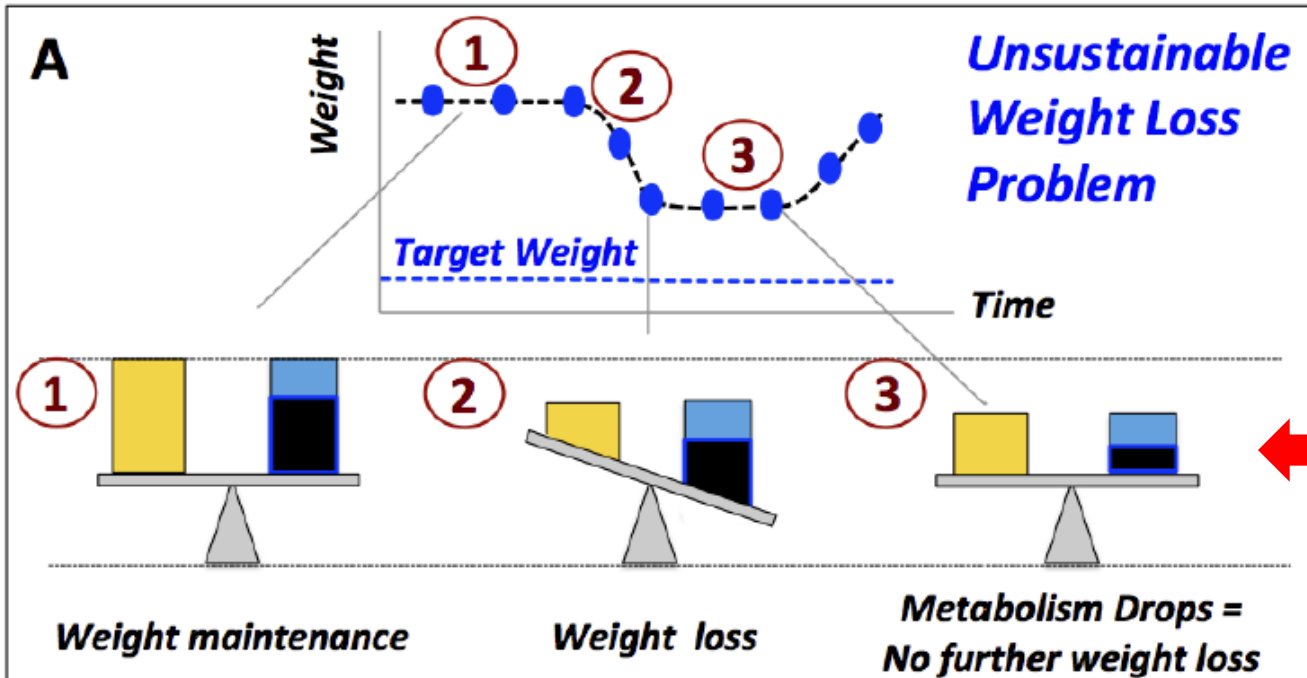
Calore di combustione Q= 39.22 kJ/g (9 kcal/g)

Resa energetica r= 19.75 kJ/L

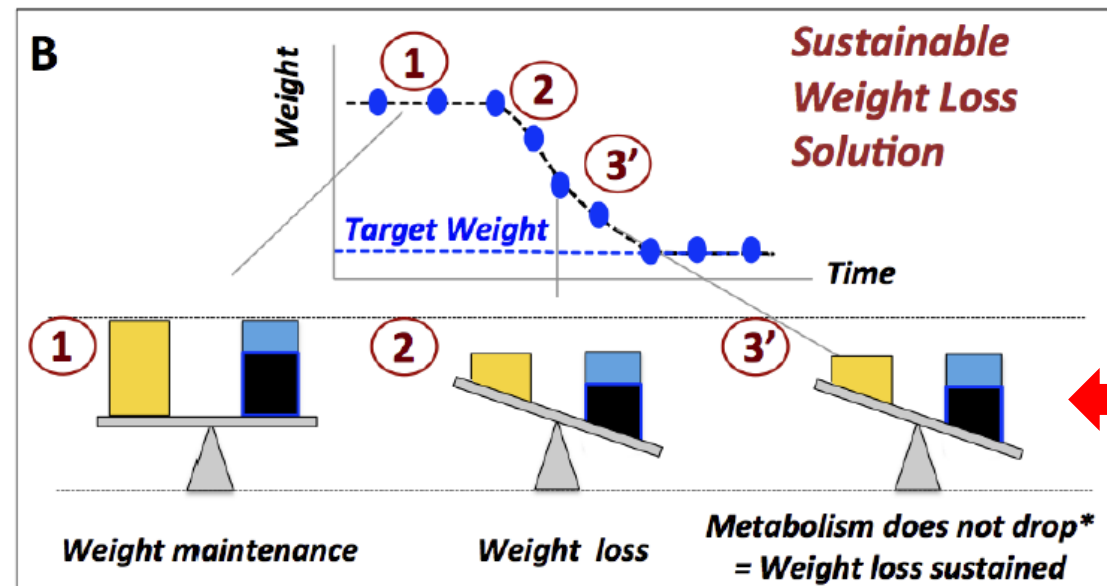
CALORIMETRIA INDIRECTA

Valori di QR < 0,707: gluconeogenesi e chetogenesi

Valori di QR > 1,000: lipogenesi



Giallo: intake calorico
Nero: REE
Blu: attività fisica



Metabolic Flexibility in Health and Disease

Pathophysiological role of metabolic flexibility on metabolic health

«the ability of an organism to respond or adapt according to changes in metabolic or energy demand as well as the prevailing conditions or activity»

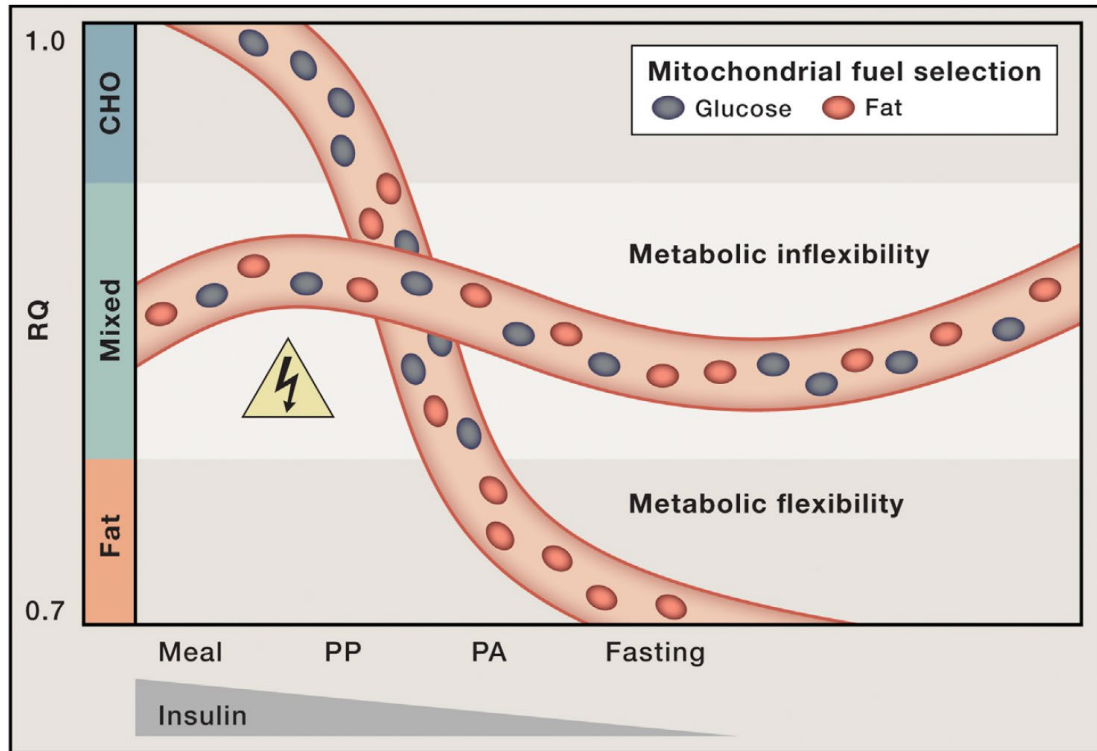
“an adaptive response of an organisms’ metabolism to maintain energy homeostasis by matching fuel availability and demand for periodic fasting, varying meal composition, physical activity and environmental fluctuations”

“the capacity for the organism to adapt fuel oxidation to fuel availability so ATP synthesis can match its demand”

INSULIN-RESISTANCE

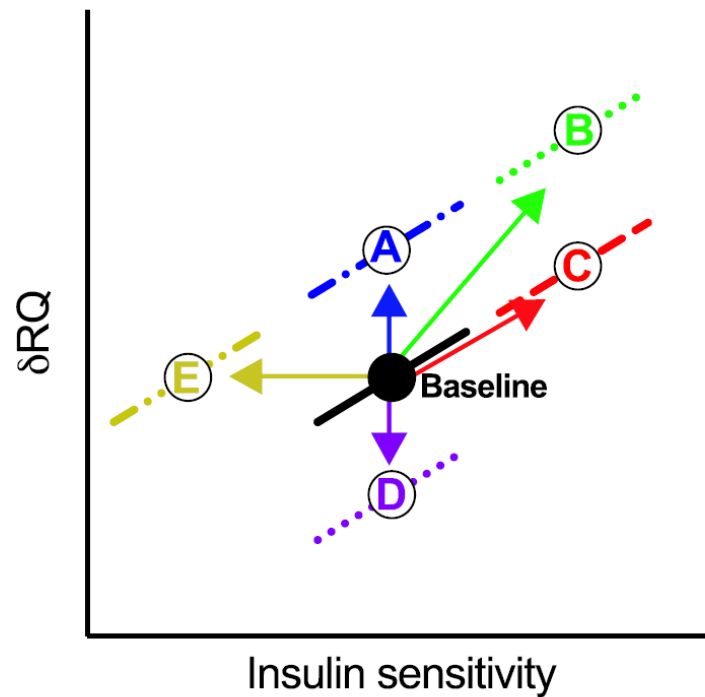
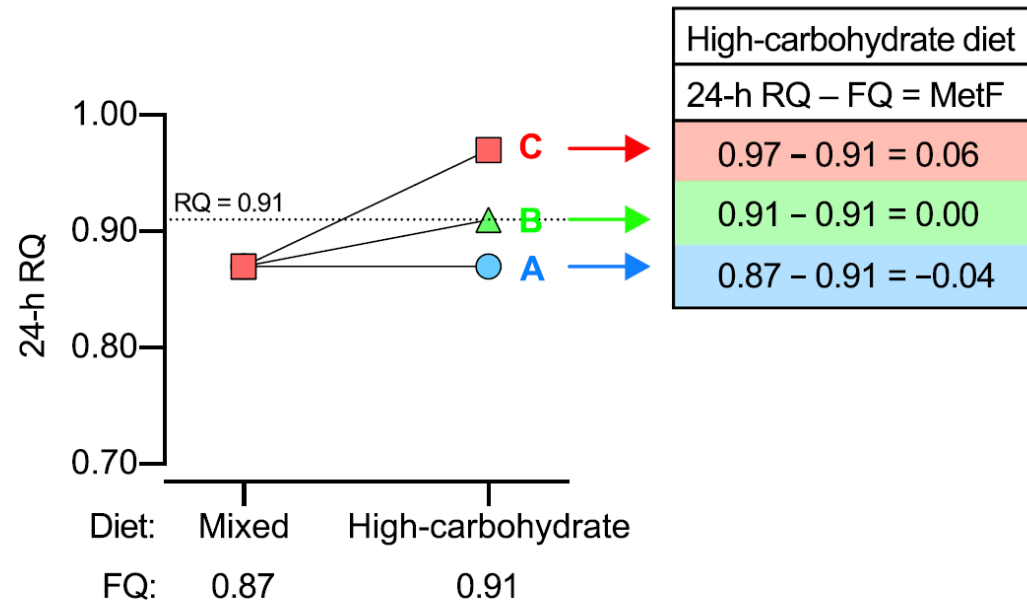


Metabolic Inflexibility: When Mitochondrial Indecision Leads to Metabolic Gridlock



In healthy, metabolically flexible states, consumption of a high-carbohydrate (CHO) meal together with a small rise in blood insulin levels elicit a surge in the respiratory quotient (RQ; $V\text{CO}_2/V\text{O}_2$), indicative of a robust shift from fatty acid to glucose oxidation. During the postprandial (PP) hours following a meal, mitochondria consume a mixture of fats and carbohydrate. Progression toward the postabsorptive (PA) state and prolonged fasting are accompanied by increased fat oxidation and a corresponding decline in the RQ.

Mitochondrial capacity to switch freely between oxidative fuels depending on the nutritional context is lost in obese, metabolically inflexible individuals. Persistent oxidation of a mixture of carbon fuels increases mitochondrial congestion and risk of metabolic hazard.



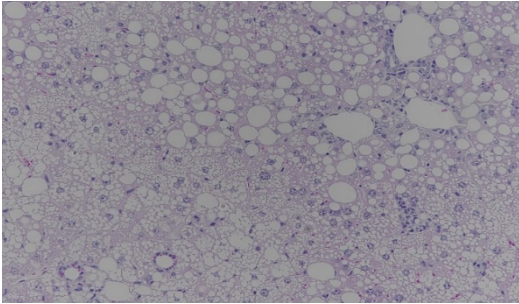
Intervention	Insulin sensitivity	Metabolic flexibility
A: caloric restriction in individuals with obesity	↔	↑
B: exercise in individuals with T2D	↑	↑
C: caloric restriction and exercise in individuals with T2D	↑	↔
D: eucaloric high-fat diet in healthy individuals	↔	↓
E: hypercaloric high-fat diet in healthy individuals	↓	↑



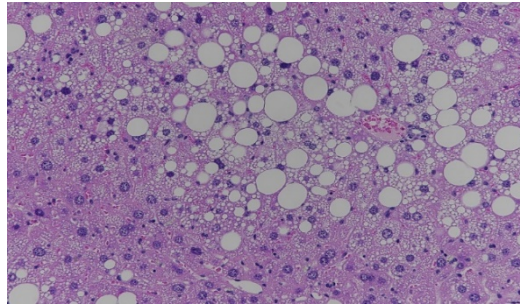


N(M)AFLD

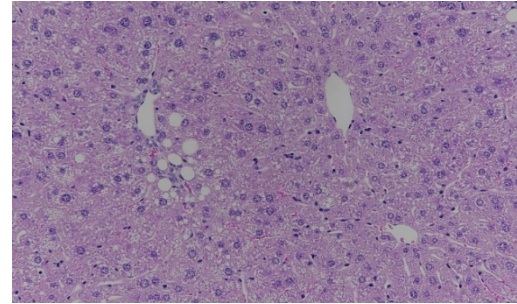
WD16w



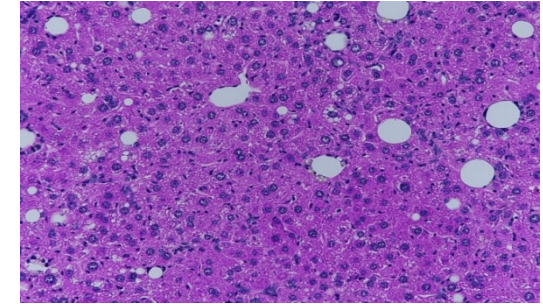
WD16w + KD2w



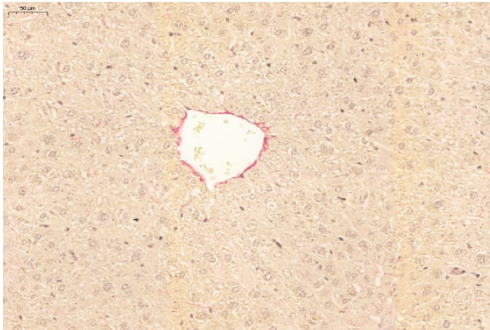
WD16w + KD4w



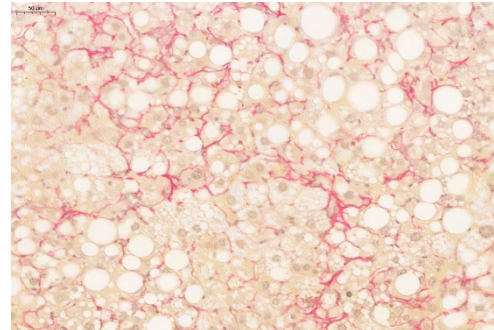
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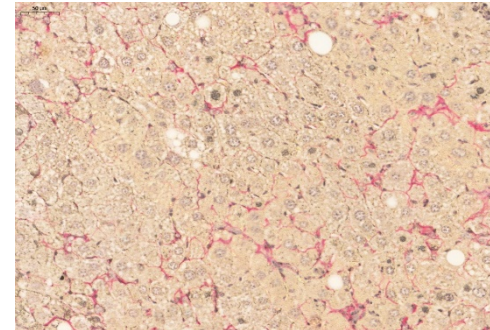
ND



WD16w

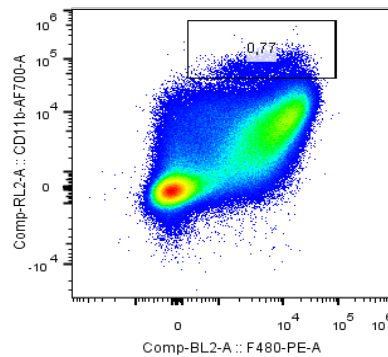


WD+KD

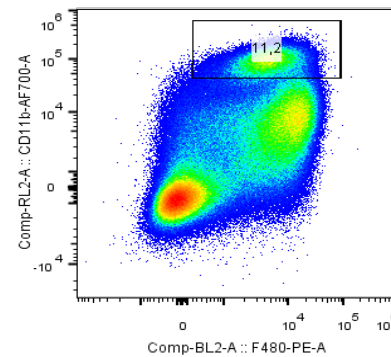


**TREM-2
Gal-3
OPN**

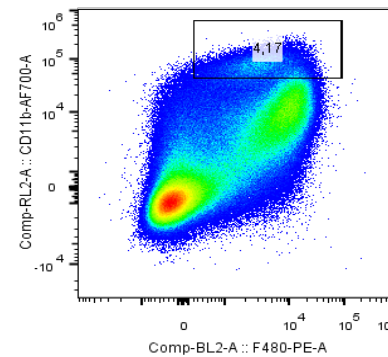
ND 16w



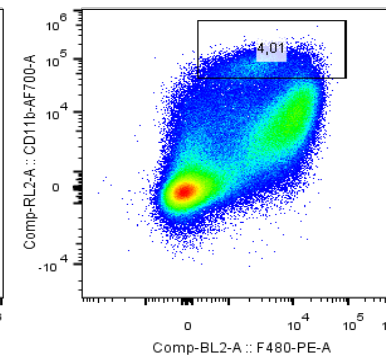
WD 16w



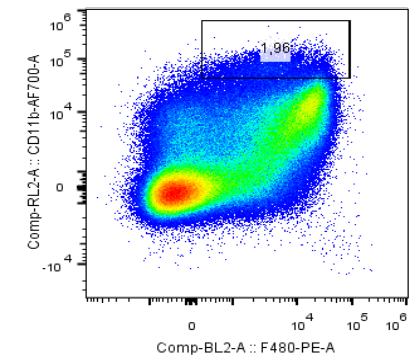
WD 16w +KD2w

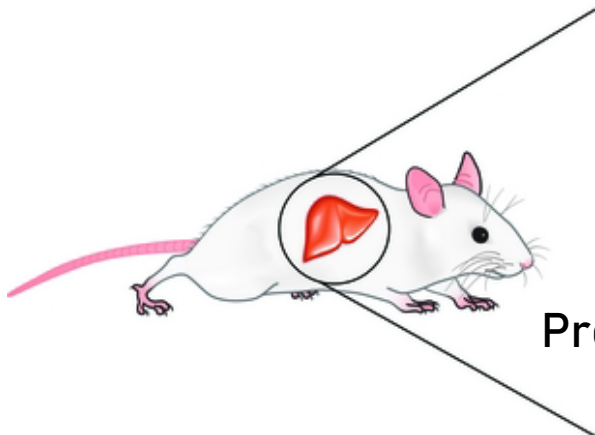


WD 16w +KD4w



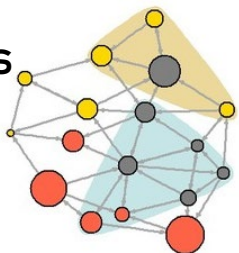
WD 16w +KD8w





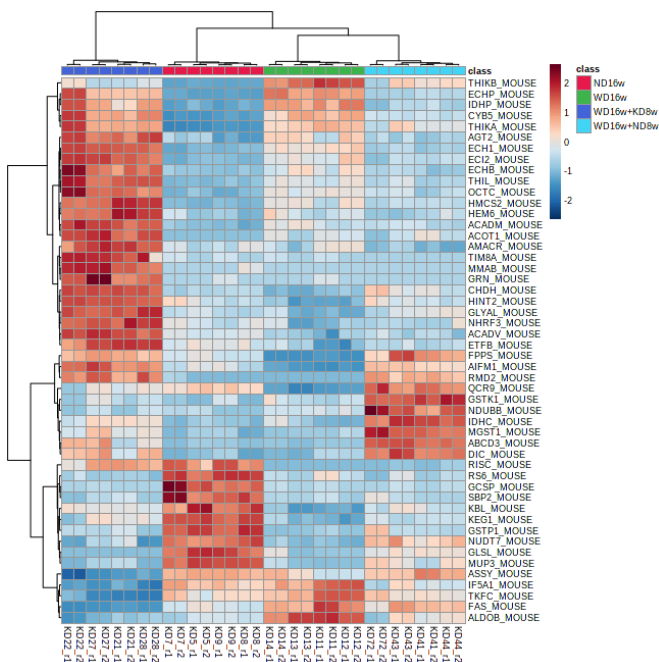
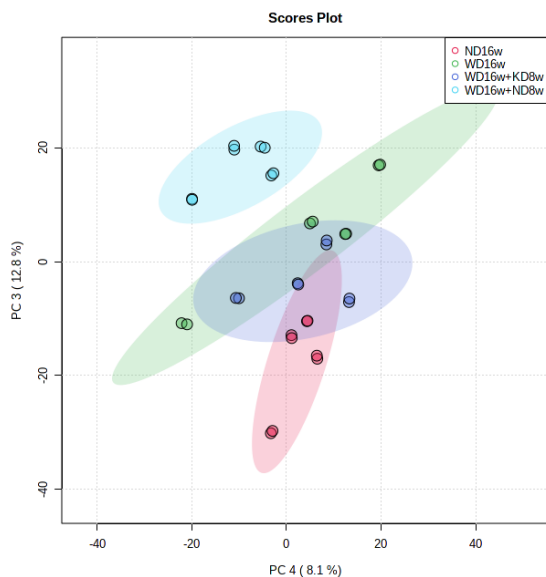
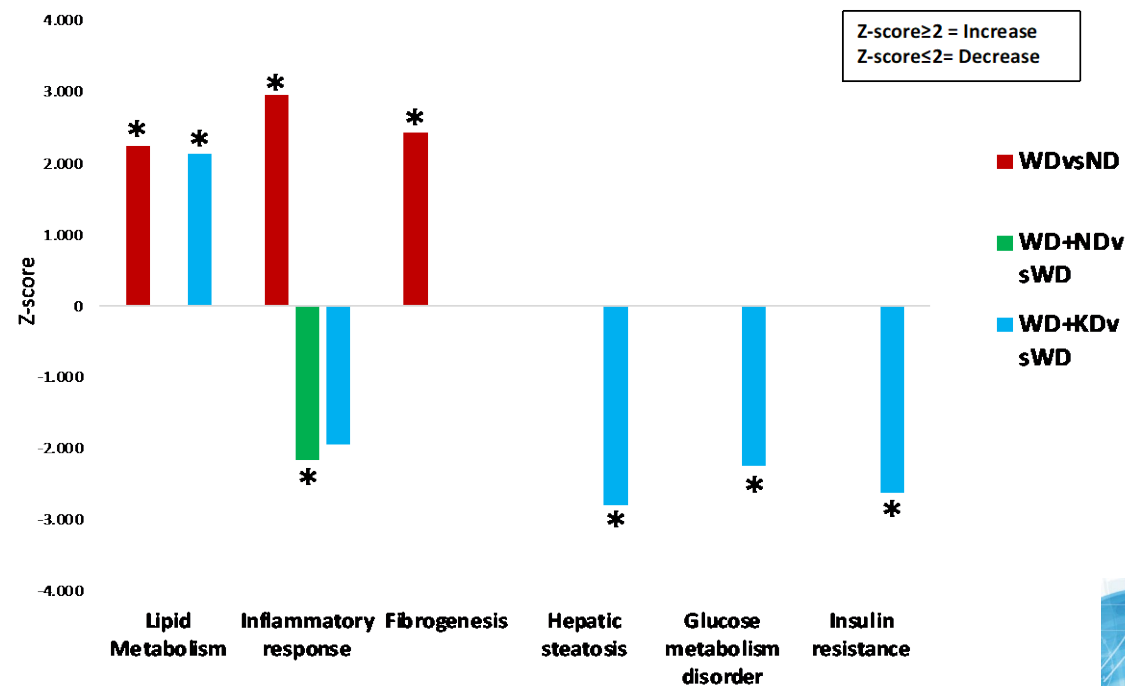
Proteomics

Bioinformatics



Liver proteomic analysis

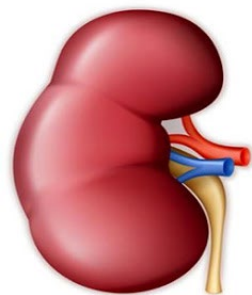
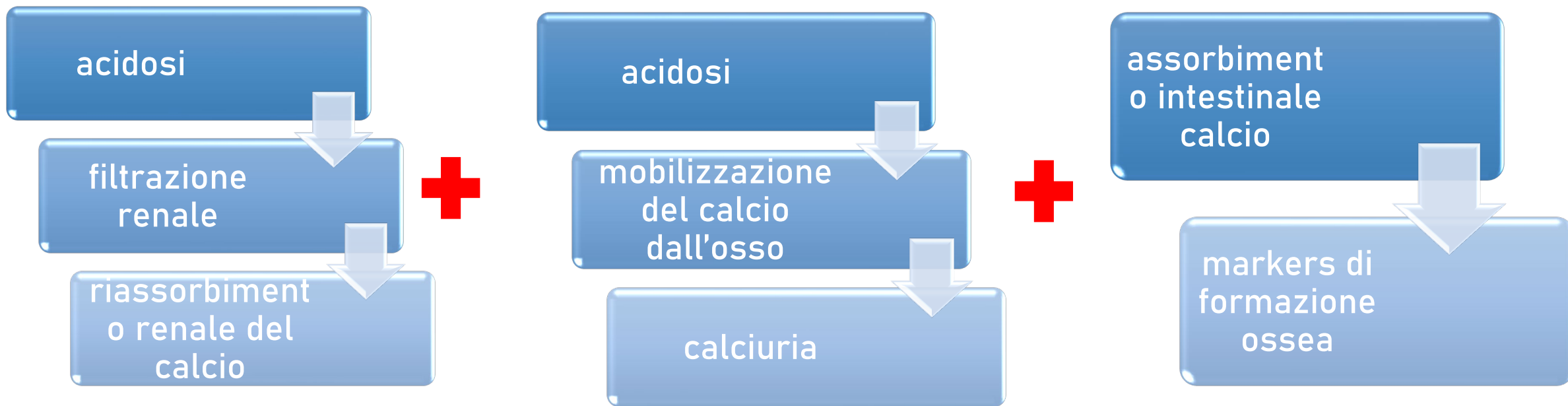
Diseases and functions comparison



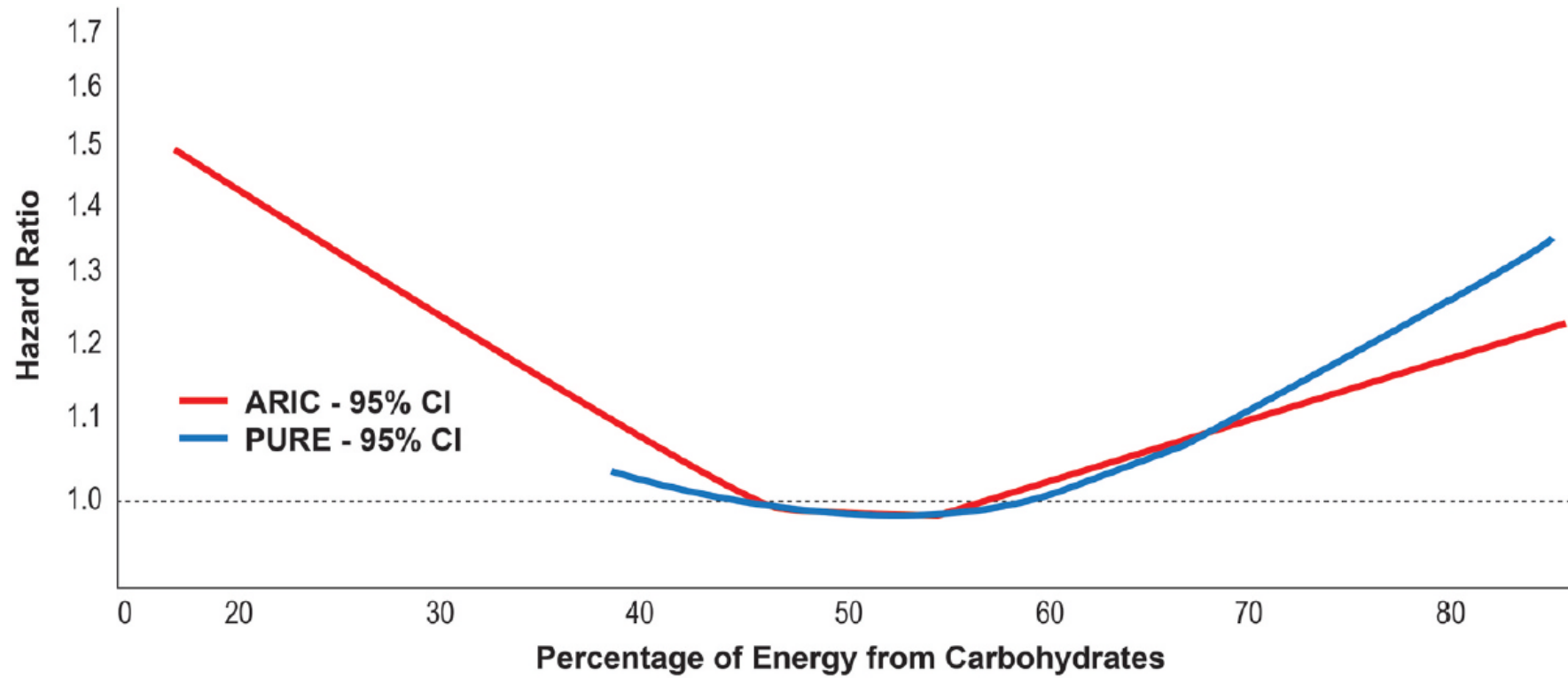
Significant reduction of pathways associated with NASH evolution



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