

MÁSTER EN HEPATOLOGÍA

**EHMET. TRATAMIENTO. MODIFICACION DEL ESTILO
DE VIDA
DIETA Y EJERCICIO FÍSICO.**



Universidad
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L.E. A Digestivo. HCUV

TRATAMIENTO EHmet

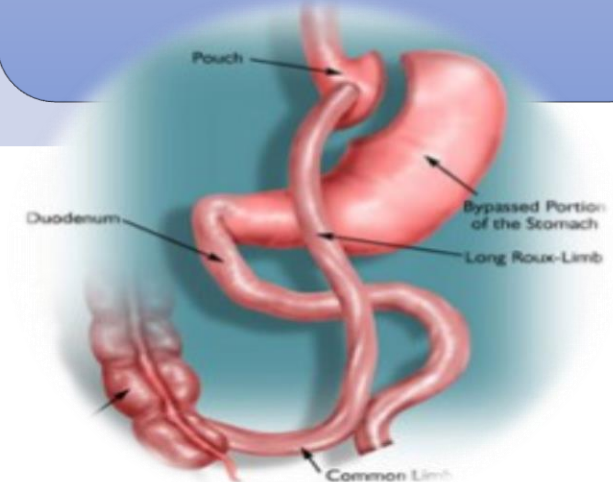


**CAMBIOS EN EL
ESTILO DE VIDA.**

**INTERVENCION
FARMACOLOGICA.**

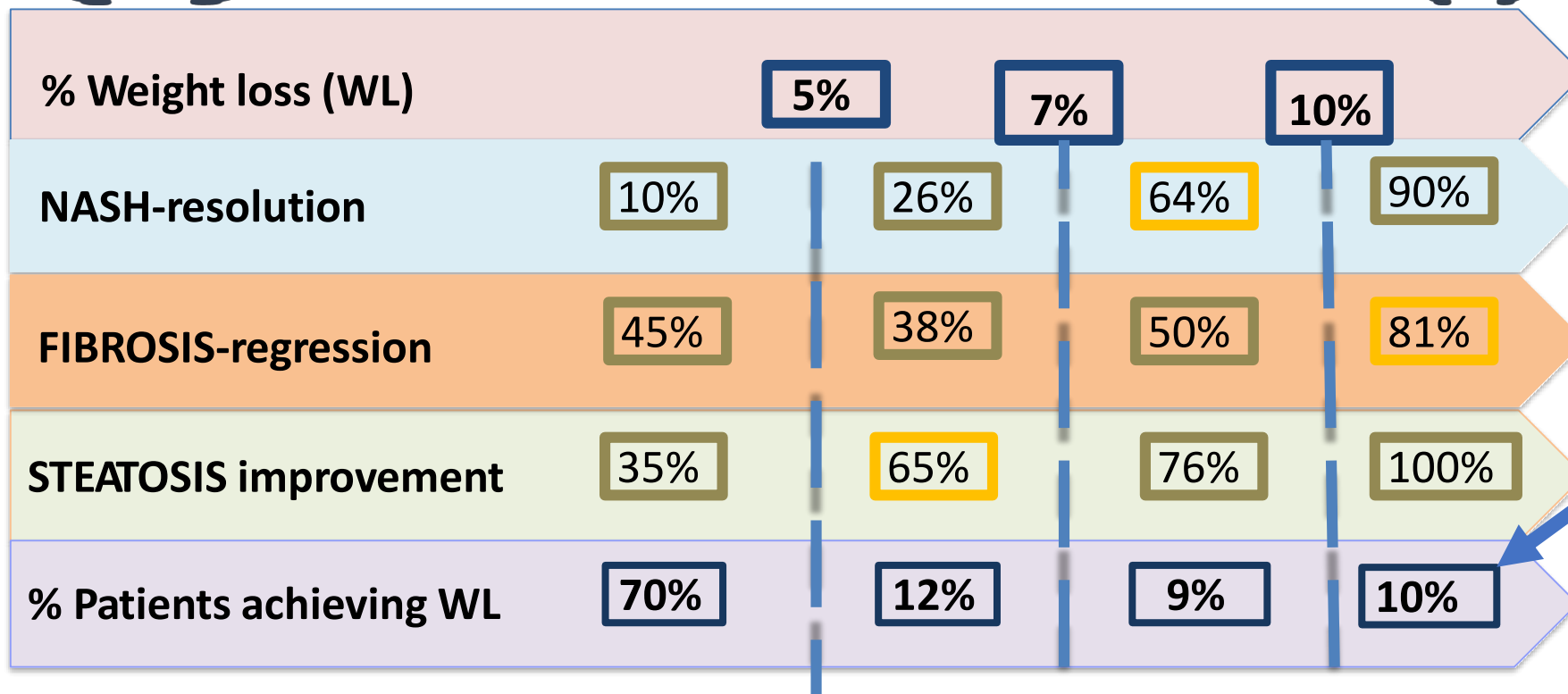


**ENDOSCOPIA Y
CIRUGÍA BARIÁTICA.**

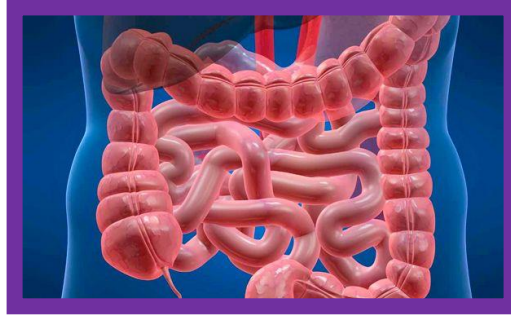
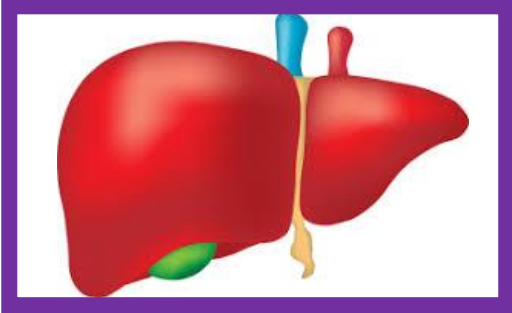




52 weeks of lifestyle intervention



INGREDIENTES



Previene la traslocación bacteriana y controla la inmunidad local

Disbiosis

Captación de ácidos grasos por el hígado



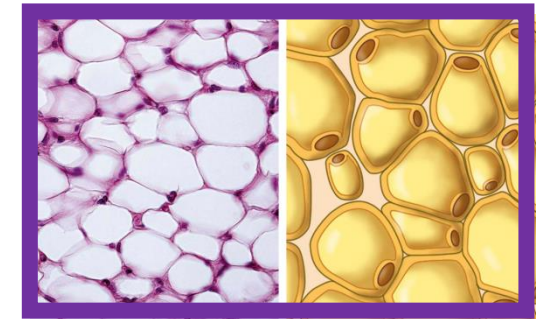
Grasas saturadas y proteínas animales

Lipogénesis de novo

lipolisis



Fructosa

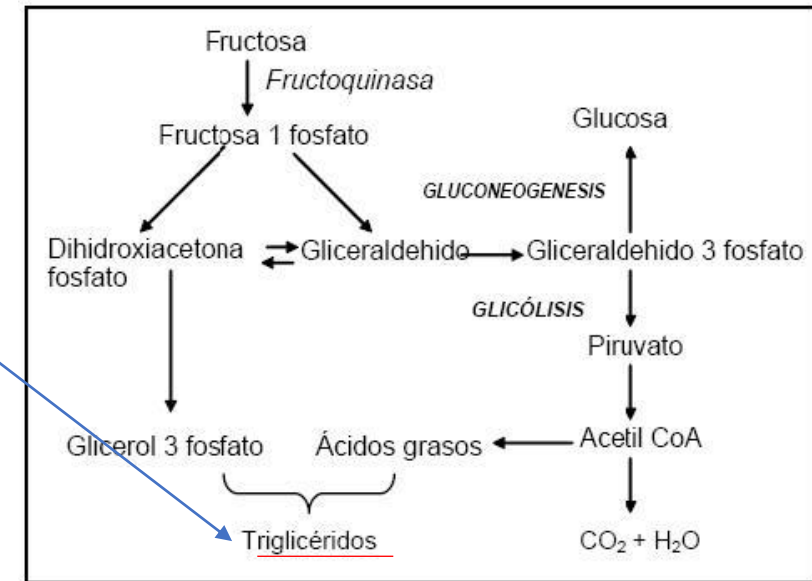
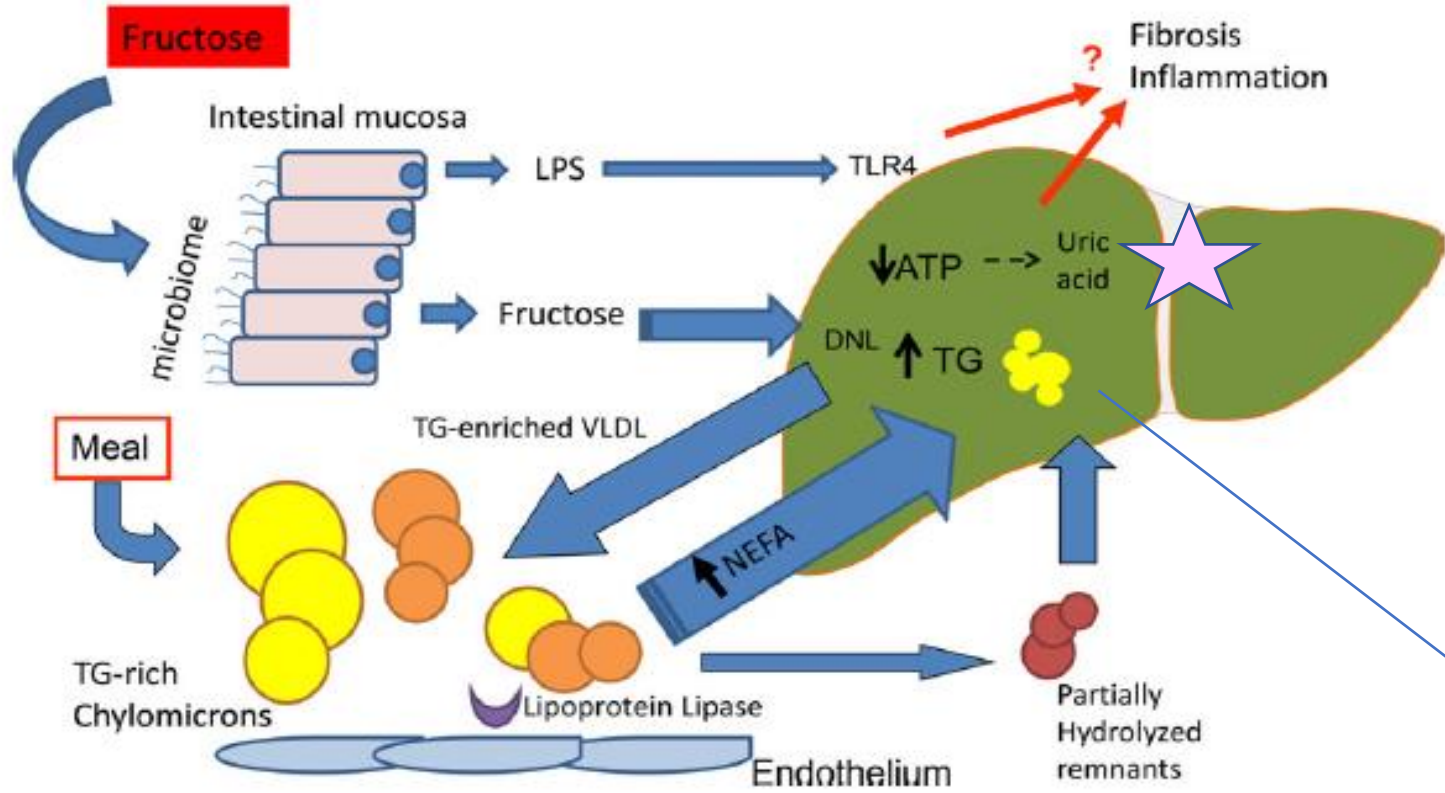


Resistencia a la insulina.

El exceso de lípidos: stress oxidativo, disfunción mitocondrial,
Sustancias lipotóxicas: apoptosis
Estimulo de células estrelladas: fibrosis

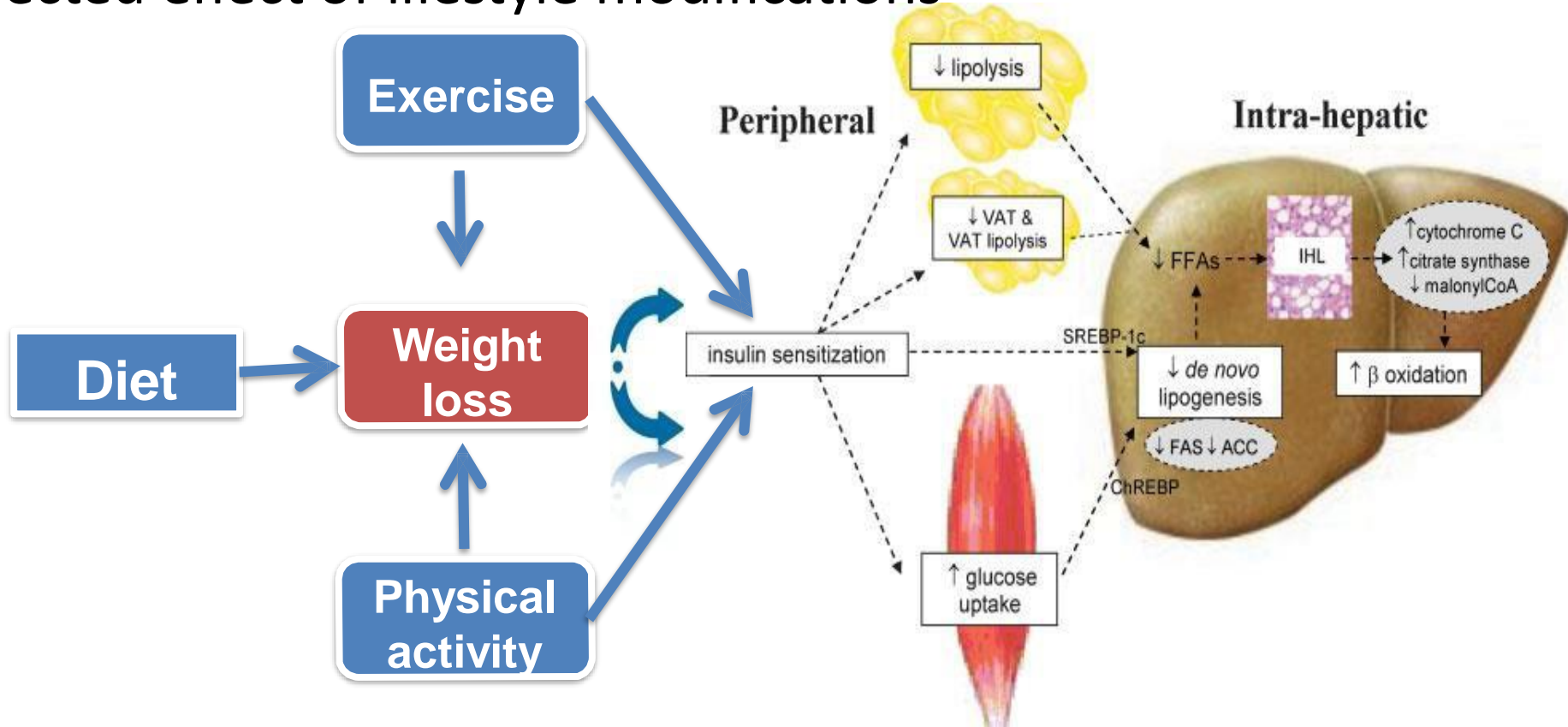
Fructosa

Postulated Role of Fructose in Mediating NAFLD



ANTÍDOTOS

Expected effect of lifestyle modifications



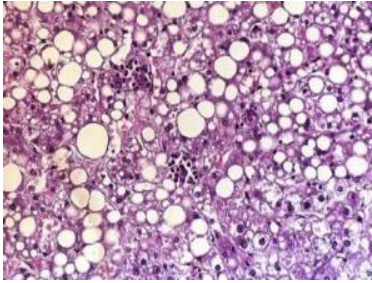
Patrón dietético de los pacientes con EHMET

- Alto en grasas saturadas y colesterol
- Bajo en grasas poliinsaturadas, fibra y antioxidantes
- Alto en fructosa
- PRIMER PASO PARA EL TTO PERSONALIZADO:
ENCUESTA NUTRICIONAL



RECOMENDACIONES DIETÉTICAS GENERALES EN LA EHMET, DUDAS!!

- ↓ Hidratos de carbono?
- ↓ Grasas?



Nutritional Modulation of Non-Alcoholic Fatty Liver Disease and Insulin Resistance

Hannele Yki-Järvinen

Baja grasa-alta HC
Alta grasa-baja HC

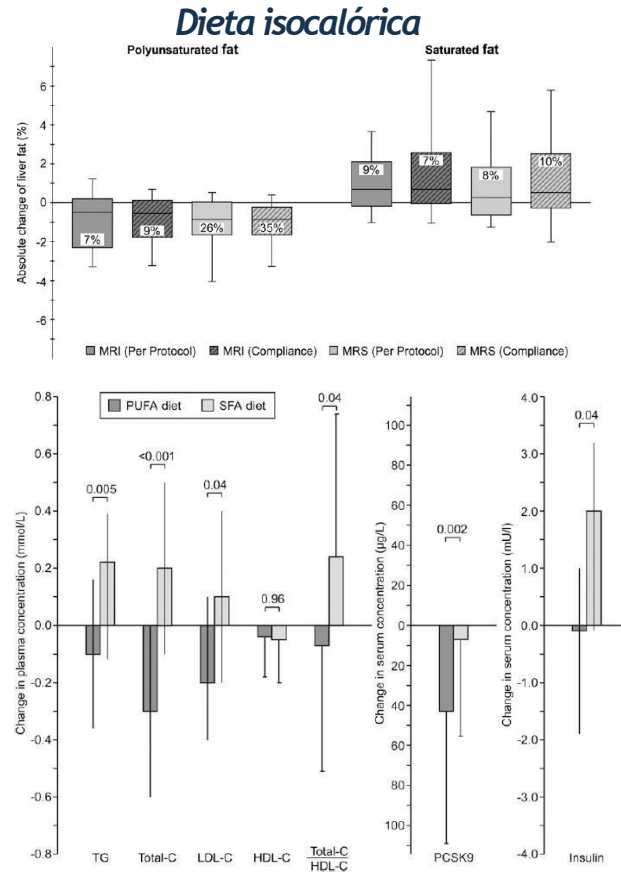
Table 1. Studies comparing effects of low fat-high carbohydrate and high fat-low carbohydrate on liver fat and insulin sensitivity.

N	BMI (kg/m ²)	Age (Years)	Duration	Design	Cal	% Fat % Carb	Liver Fat (%)	Insulin Sensitivity Method Change	Year of Reference
							Before-After		
10	33	43	2 weeks	C	ISO	16% 61% 56% 31%	10-8* 10-13	fS-Ins Improved Worsened	2005 [25]
20	29	34	3 weeks	P	ISO	20% 65% 55% 30%	4.0-3.5* 2.2-2.6	Clamp NS NS	2011 [26]
61	31	30-65	10 weeks	P	ISO	40% ^a 39% 43% ^b 40%	3.2-2.3* 3.2-3.5	fS-Ins NS Worsened	2012 [27]
45	30	35-70	8 weeks	P	ISO	28% 53% 42% ^c 40%	17.7-16.1 7.4-5.2↓*	fS-Ins NS NS	2012 [28]
35	27	69	4 weeks	P	ISO	23% 57% 43% 38%	2.2-1.7↓ 1.2-1.6	fS-Ins NS NS	2013 [29]

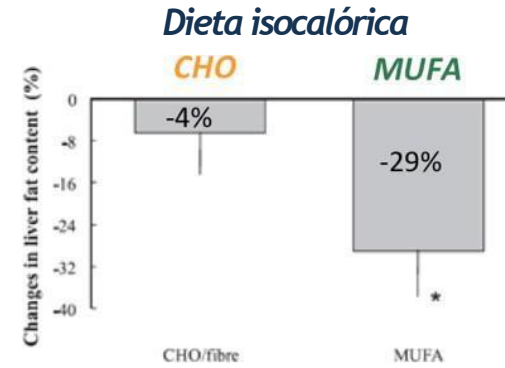
Table 1. Cont.

12	32	55	6 weeks	C	ISO	21% ^d 49% 44% ^e 34%	11.2-10.0 14.2-8.6↓*	Clamp NS* Improved	2013 [30]
22	37	44	11 weeks	P	HYPO	20% 65% 75% 10%	11.2-6.2↓ 12.4-7.7↓	fS-Ins Improved* Improved	2009 [31]
18	35	45	2 weeks	P	HYPO	34% 50% 59% 8%	19-8.6↓* 22-15.8↓	fS-Ins NS NS	2011 [32]
102	32	45	6 months	P	HYPO	"reduced fat" "reduced carb"	9.6-5.6↓ 7.6-4.0↓	fS-Ins Improved Improved	2011 [33]
39	23	25	7 days	P	HYPER	+fructose +fat	12-14 ^h ↑ 11-21 ^h ↑	fS-Ins NS NS	2010 [34]
39	18-27	20-38	7 weeks	P	HYPER	40% ⁱ 43% 36% ^g 48%	0.75-0.79 0.96-1.5*	fS-Ins NS NS	2014 [35]

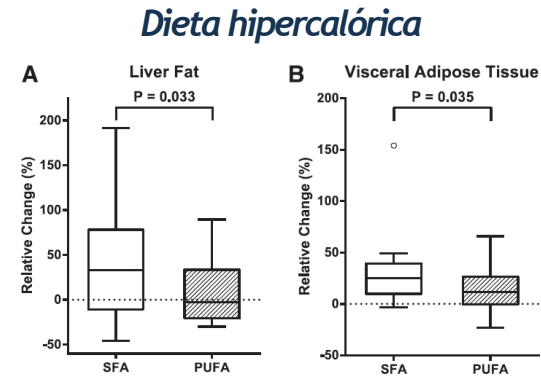
¿No será más importante la calidad de las grasas?



Bjermo et al, Am J Clin Nutr 2012



Bozeto et al, Diabetes Care 2012

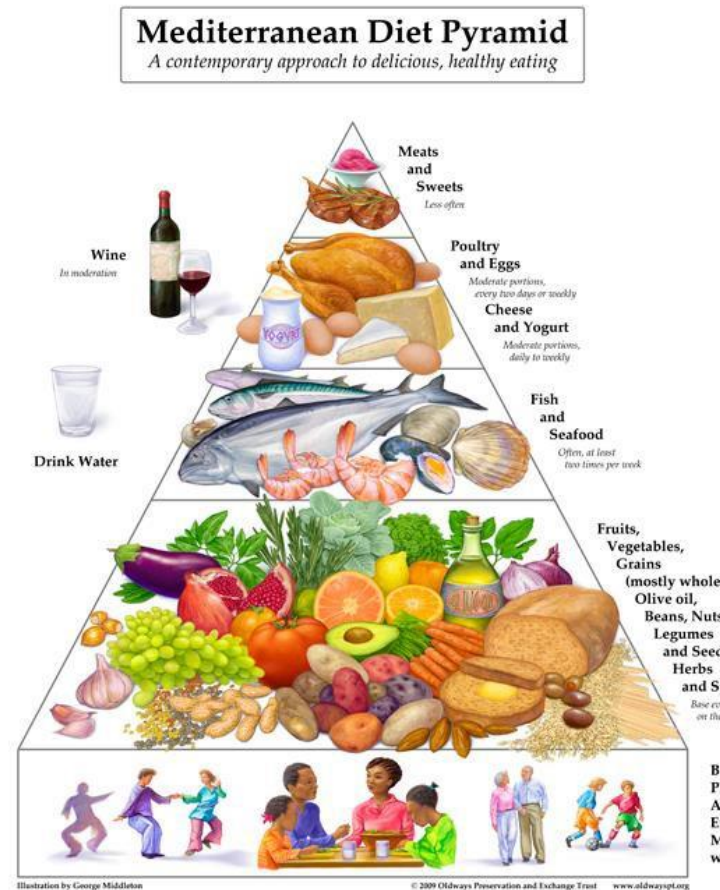


Rosqvist et al, Diabetes 2014

The Mediterranean diet is superior to low fat diet in RCTs

High in

- Olive oil ≥ 4 tbsp/day
- nuts handful/day
- Fish ≥ 3 /wk
- Legumes ≥ 3 /wk
- Fruits & Vegetables
- Fat - 40% /kcal, mostly MUFA and $\omega 3$ PUFA



Low in

- Soda drinks
- Sweets
- Red and processed meats
- Carbohydrate- 40% /kcal

Salas-Salvadó J., Ann Intern Med 2014
Ryan MC., Journal of Hepatology 2013

Nordmann AJ., The American Journal of Medicine 2011
Estruch R., N Engl J Med 2013

DIETA MEDITERRANEANA vs LF/HCD

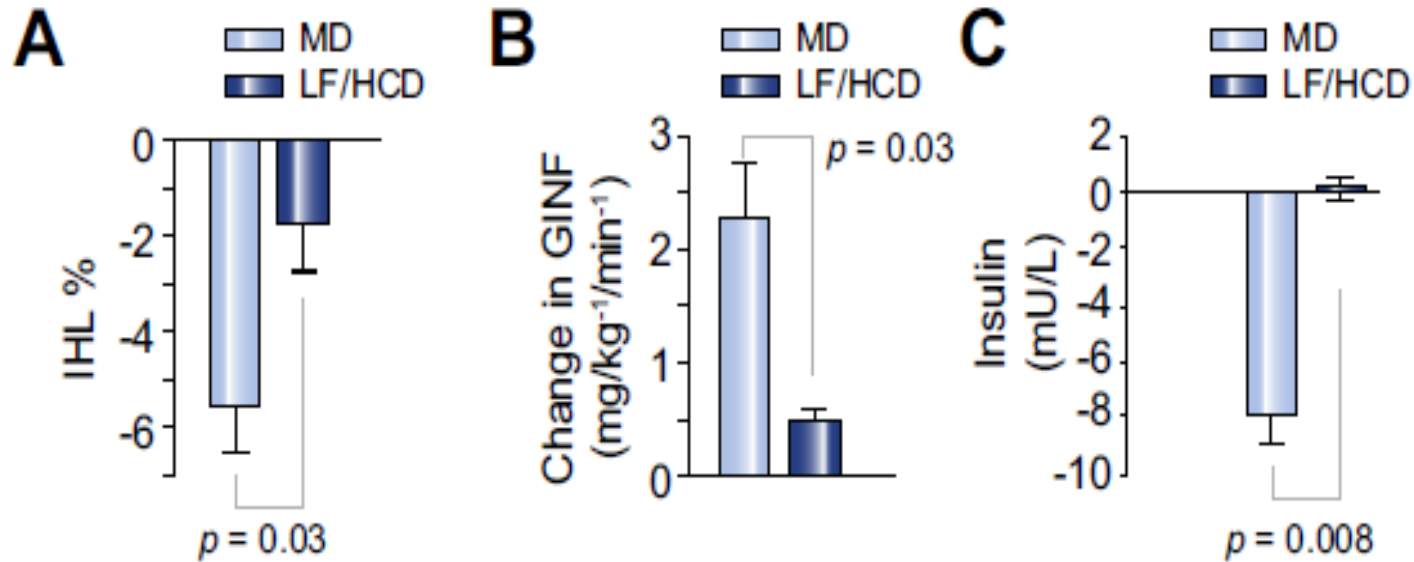


Table 4. Multivariable logistic regression analysis exploring factors associated with insulin resistance (75th percentile of HOMA-IR, ≥ 3.8) in 334 non-diabetic patients with NAFLD

	<i>P</i>	Odd ratio	95% Confidence intervals	
Female sex	0.855	1.060	0.567	1.982
Age (continuous)	0.025	1.035	1.004	1.067
High waist circumference (>102 for men and >88cm for women)	<0.001	7.855	2.809	21.964
Hypertriglyceridemia (triglycerides ≥ 150 mg/dl)	0.011	2.152	1.196	3.872
Arterial hypertension	0.535	0.818	0.434	1.542
Statin use	0.167	0.629	0.326	1.214
Log (ALT)	0.002	2.549	1.397	4.649
Previous MACCE	0.394	1.705	0.500	5.814
Med-Diet score (for each point)	0.018	0.801	0.667	0.962



PPAR- α

PPRE

Nrf2

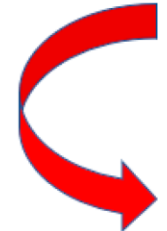
ARE

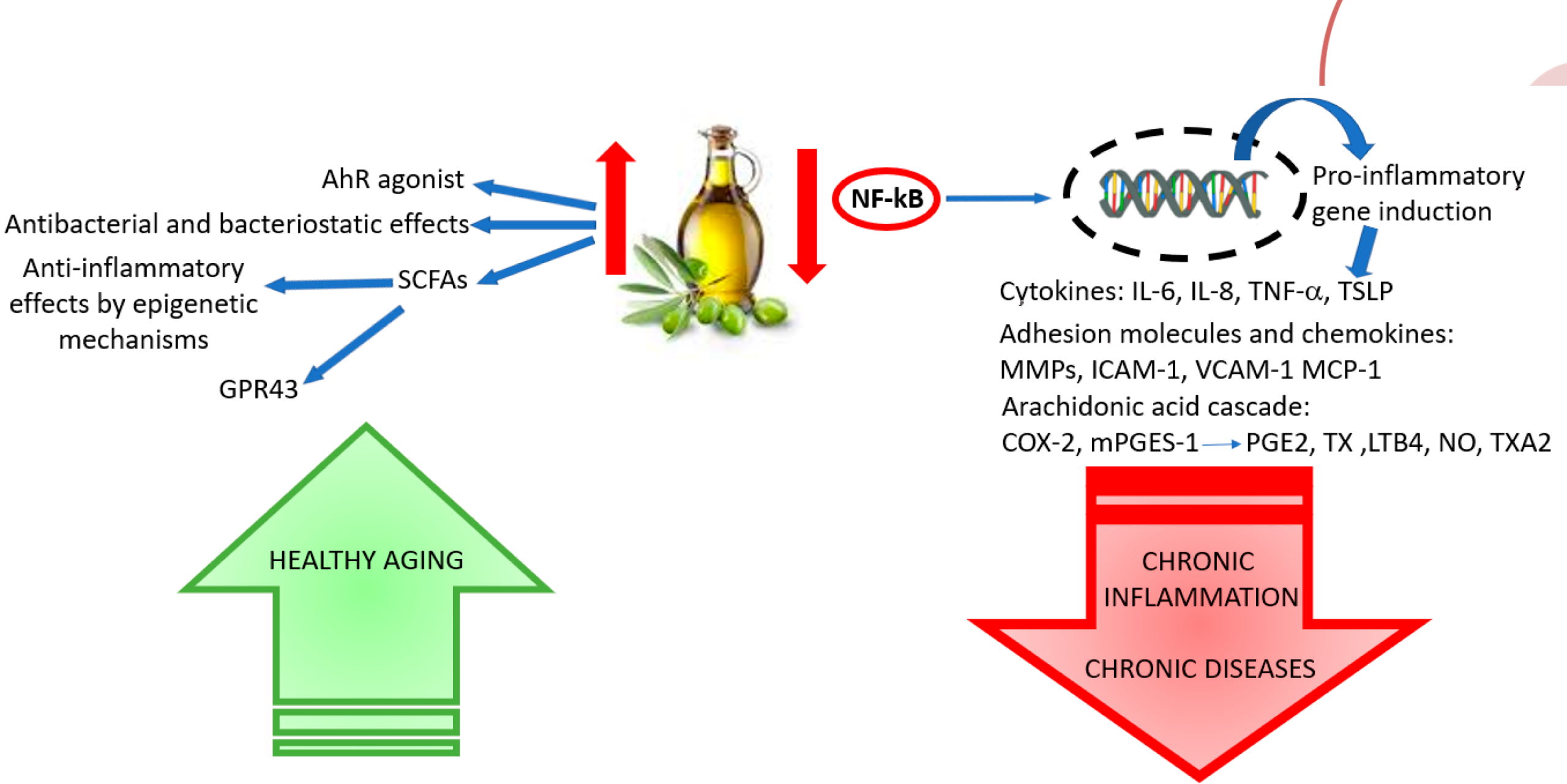
AMPK

FoxO1

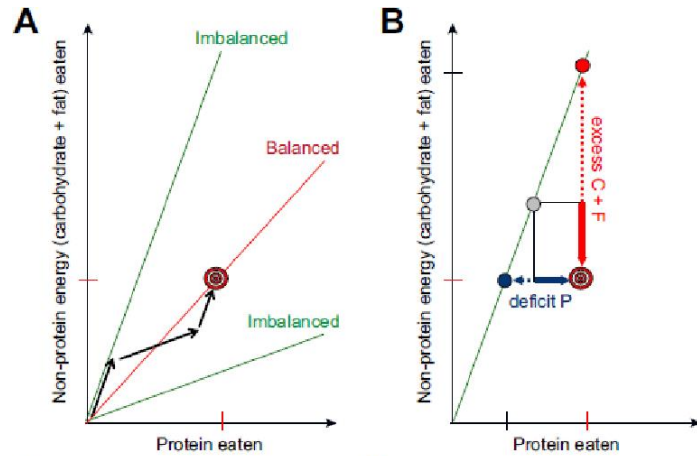
Antioxidant gene expression
Antioxidant enzymes

(Cu-ZnSOD, Mn-SOD, c-GCS, GST, NQO1, PON2, γ -GCL, CAT)





Geometric Framework for Nutrition in liver diseases



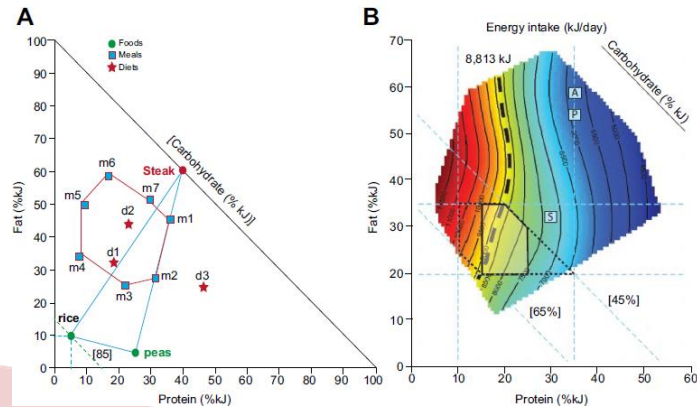
- Fructose
- Glucose
- AGE

CARBO-HYDRATES



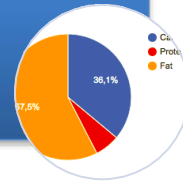
- Hypercaloric
- Isocaloric
- Hypocaloric

CALORIES



- Micronutrients:
- Vitamins
- Choline
- Coffee
- Selenium
- Carotenoids

Nutrients



- MUFA
- SFA
- PUFA

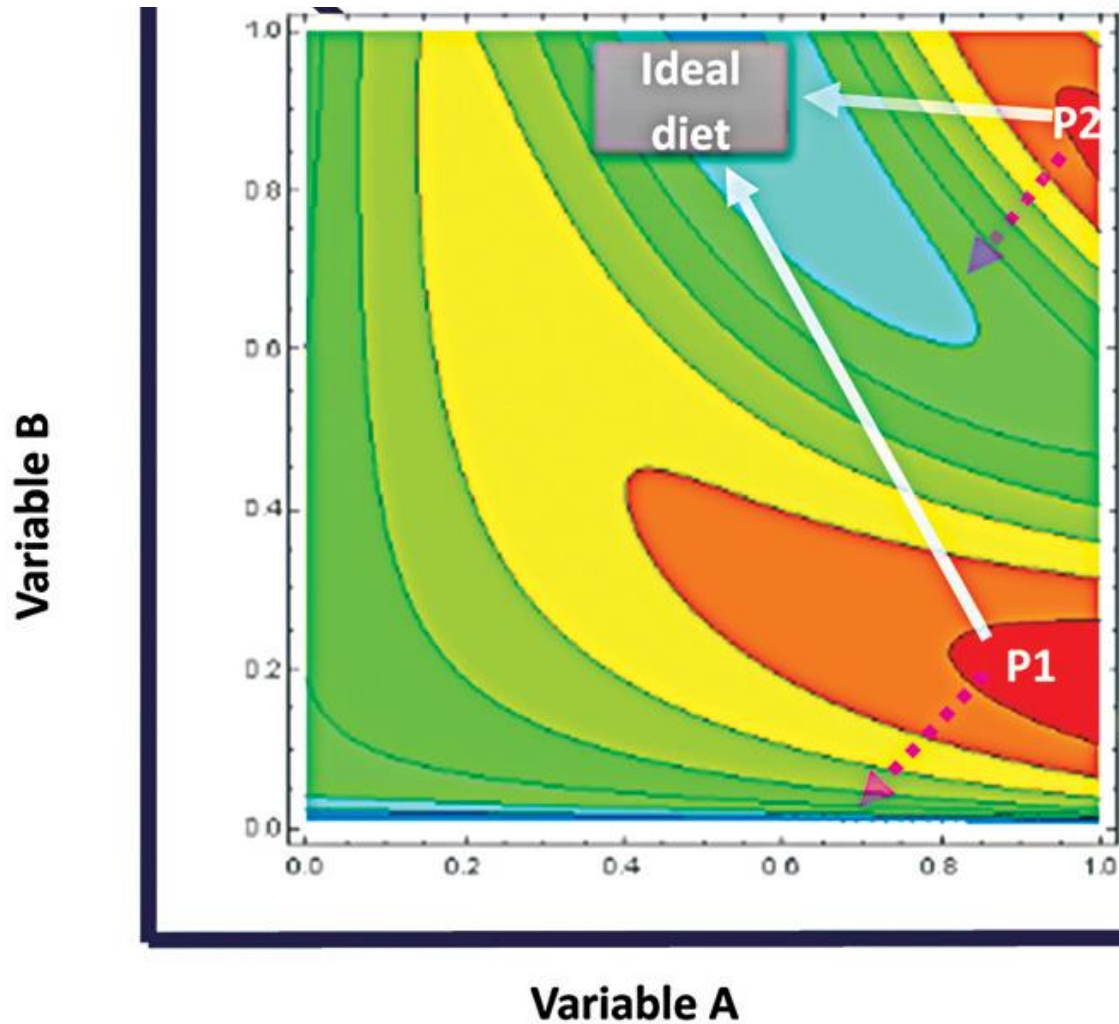
FAT



Dietary Recommendations for the Management of Non-alcoholic Fatty Liver Disease (NAFLD): A Nutritional Geometry Perspective

Manuel Romero-Gómez , Rocío Aller , Franz Martín-Bermudo

Sem Liv Dis 2022



Dietary Recommendations for the Management of Non-alcoholic Fatty Liver Disease (NAFLD): A Nutritional Geometry Perspective

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NAFLD's recommended menu

A. Breakfast: Oatmeal; semi-skimmed milk; blueberries, raspberries, rolled almonds, coffee



B. Morning snack: 1 fruit.

C. Lunch: Salmon salad: broiled salmon, toasted bread croutons, arugula, red onion, cherry tomatoes, cucumber, garlic powder, avocado and pine nuts, seasoned with extra virgin olive oil and apple cider vinegar. Apple.



D. Dinner: Grilled chicken breast with pumpkin puree, beetroot salad with boiled carrot, corn, celery, and parsley and seasoned with lemon juice and extra virgin olive oil. Whole yogurt with walnuts and kiwi.



NASH resolution and fibrosis regression in INAMET trial

Nutritional intervention	NASH resolution		P<0.05
	No	Yes	
LFD	20 (76%)	7 (24%)	
MD	14 (43%)	18 (57%)	

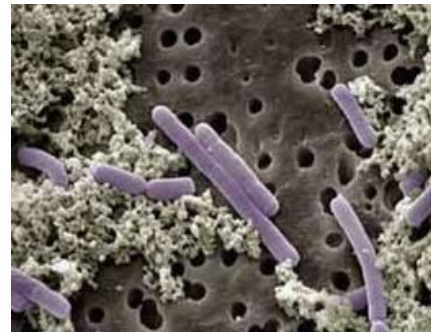


Nutritional intervention	Fibrosis TE (kPa)		
	Progression (%)	Stable (%)	Improvement (%)
LFD	19	19	62
MD	22	20	58

Nutritional intervention	Fibrosis (Hepamet fibrosis score)		
	Progression	Stable (%)	Improvement (%)
LFD	15	73	12
MD	10	80	10

PERDIDA DE PESO 2,5%

PROBIOTICOS



Gut microbiome-targeted therapies in nonalcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression

Suzanne R Sharpton,¹ Bharat Maraj,¹ Emily Harding-Theobald,¹ Eric Vittinghoff,² and Norah A Terrault³

Department of ¹Medicine and ²Biostatistics and Epidemiology, University of California San Francisco, San Francisco, CA; and ³Keck Medicine at University of Southern California, Los Angeles, CA

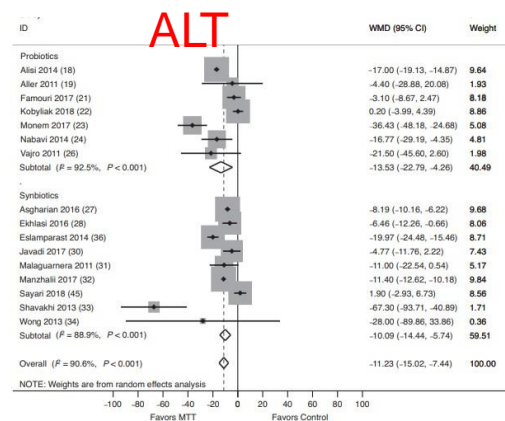


FIGURE 2 Forest plot of the effect of MTT on serum ALT, stratified by probiotics and synbiotics, and measured by the WMD. Probiotics/synbiotics were associated with a significant reduction in ALT compared with control. ALT, alanine aminotransferase; MTT, microbiome-targeted therapy; WMD, weighted mean difference.

ELASTOGRAFIA

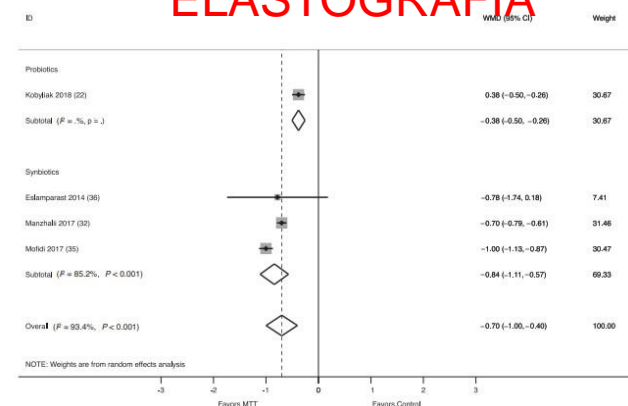


FIGURE 3 Forest plot of the effect of MTT on LSM, as measured by elastography, stratified by probiotics and synbiotics, and measured by the WMD. Probiotics/synbiotics were associated with a significant reduction in LSM compared with control. LSM, liver stiffness measurement; MTT, microbiome-targeted therapy; WMD, weighted mean difference.

Esteatosis ECO

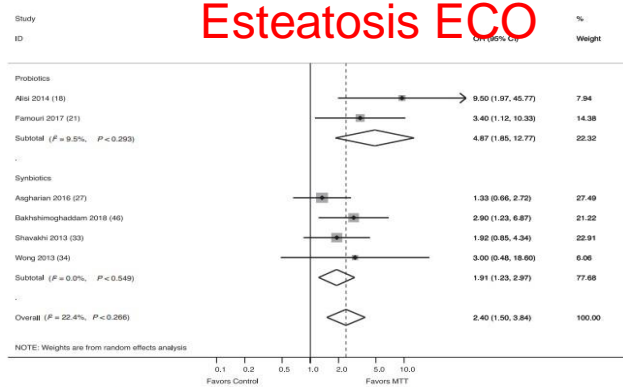


FIGURE 4 Forest plot of the effect of MTT on improvement in hepatic steatosis, as graded by ultrasound, stratified by probiotics and synbiotics. Probiotics/synbiotics were associated with increased odds of having improvement from moderate/severe hepatic steatosis compared with control. MTT, microbiome-targeted therapy.

IMC

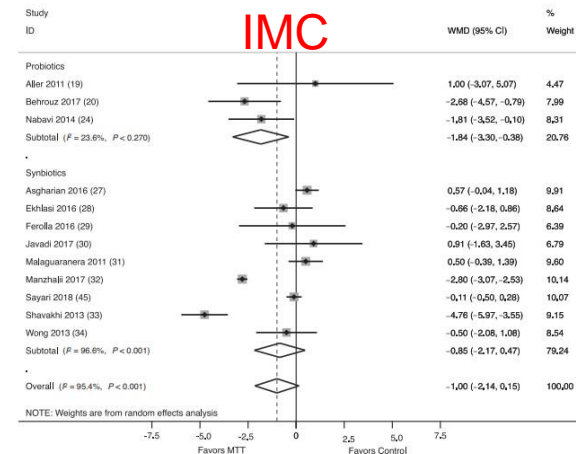


FIGURE 5 Forest plot of the effect of MTT on BMI, stratified by probiotics and synbiotics, and measured by the WMD. Probiotics/synbiotics were associated with a significant reduction in BMI compared with control. MTT, microbiome-targeted therapy; WMD, weighted mean difference.

Development and validation of a noninvasive model “NASH resolution model” -- NASHRES

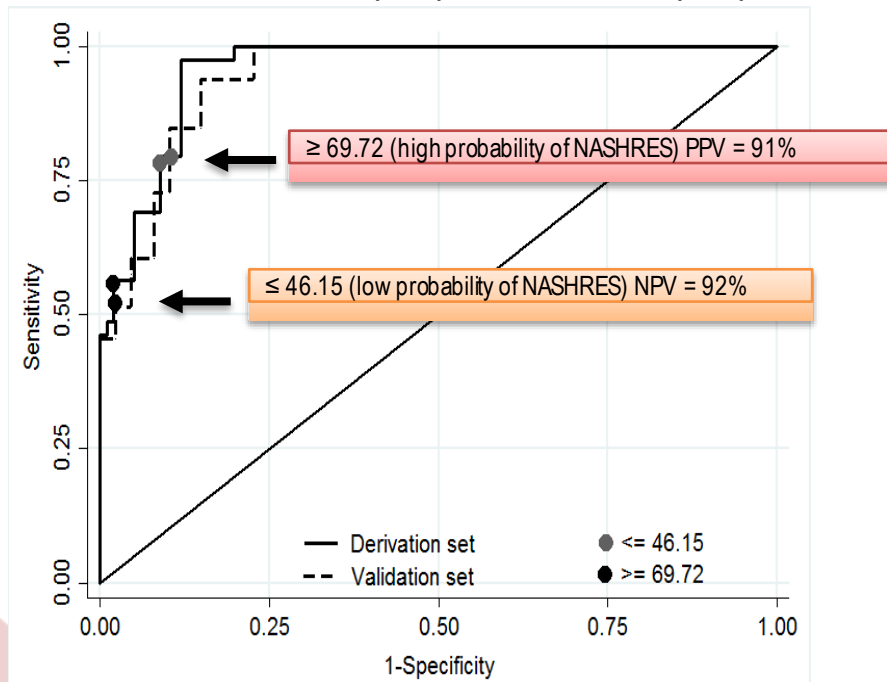
261 patients treated with lifestyle intervention and paired liver biopsies (140 in derivation set / 121 in temporary validation set)

Non-invasive prediction of histological NASH resolution



NASHRES formula for calculating NASH resolution probability: $EXP(0.047 + 0.972 \times \text{weight loss} + 2.194 \times \text{normal levels of ALT (EOT)} - 3.076 \times \text{type 2 diabetes} - 2.376 \times \text{NAS} \geq 5 - 0.102 \times \text{age}) / (1 + EXP(0.047 + 0.972 \times \text{weight loss} + 2.194 \times \text{normal levels of ALT (EOT)} - 3.076 \times \text{type 2 diabetes} - 2.376 \times \text{NAS} \geq 5 - 0.102 \times \text{age})) \times 100.$

AUC in derivation (0.96) and validation (0.95) sets



NASHRES - NASH Resolution Score

Weight loss percent: 5 Calculate

Age: 40 full years

NAS ≥ 5 : Yes No

Type 2 diabetes: Present Absent

ALT at end of treatment: Normal Elevated

Result: High probability of NASH resolution

NASHRES: 95,35

Clear Data About

A cutoff ≥ 69.72 accurately predict NASH resolution (0.96) and reversal of fibrosis (0.86)

EJERCICIO FISICO



How to assess activity?

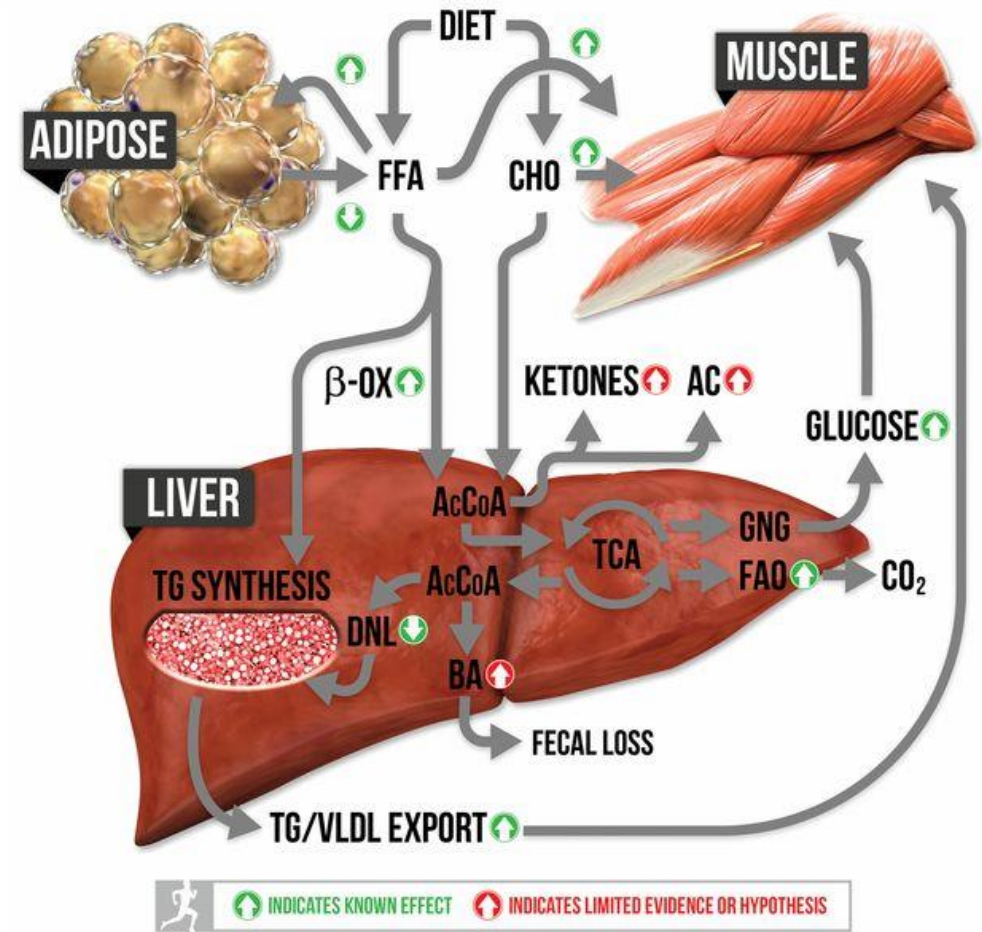
- Sedentary behaviour:
 - Total amount of time sitting
 - Number of breaks
- Physical activity:
 - Inactive
 - Minimally active
 - Health-enhancing physically active
- Exercise:
 - Aerobic exercise
 - Resistance exercise
 - High intensity intermittent exercise
 - Vigorous aerobic exercise

- How to prescribe exercise?



EFECTOS DEL EJERCICIO A NIVEL HEPATICO

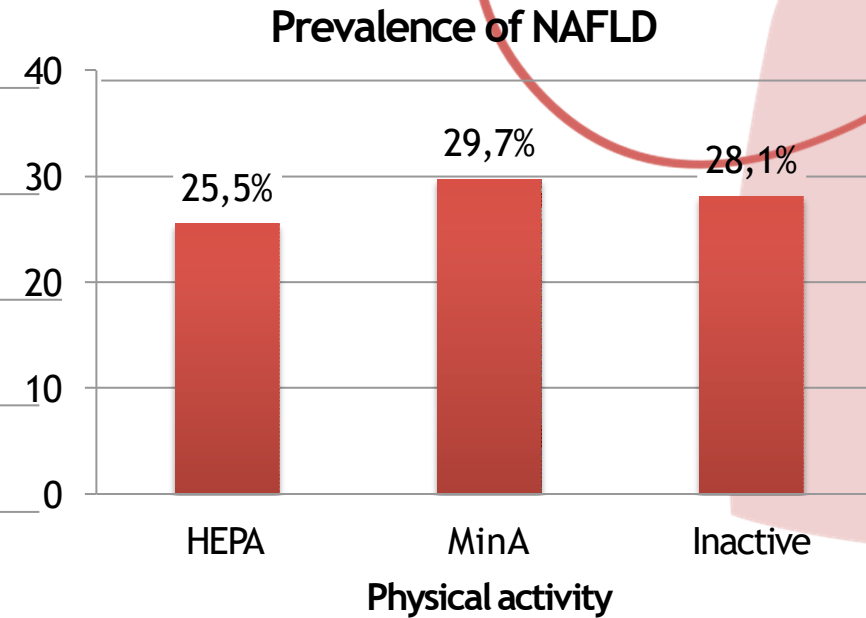
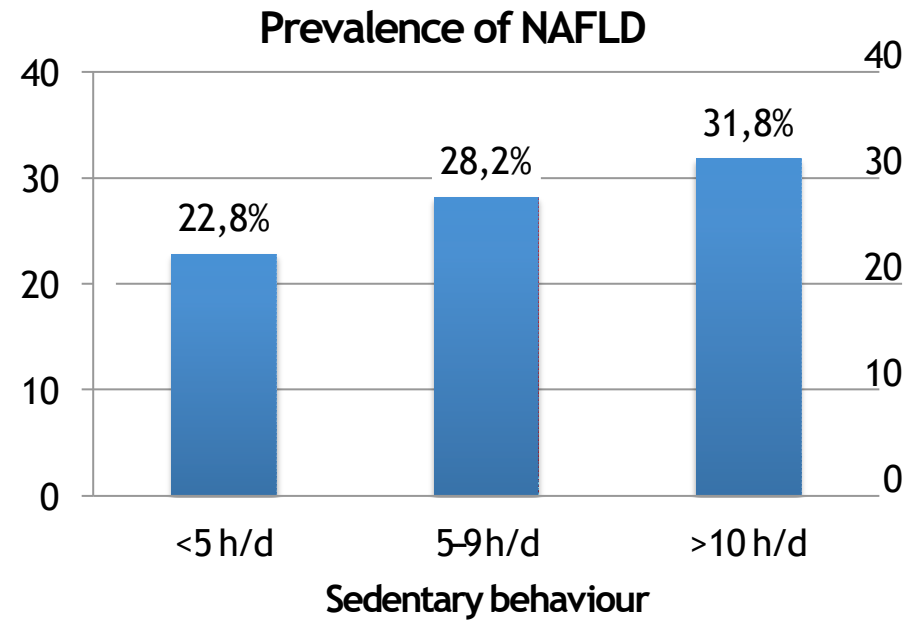
- Promover la regulación a la baja de los genes y las proteínas en la vía del **LDN**
- Mejorar respiración **mitocondrial**
- Aumentar la capacidad **gluconeogénica**
- Descomposición de los **lípidos** intrahepáticos
- Exportar de sustratos fuera del hígado mediante la cetogénesis, las acilcarnitinas, el colesterol y los ácidos biliares.



INDICATES KNOWN EFFECT INDICATES LIMITED EVIDENCE OR HYPOTHESIS

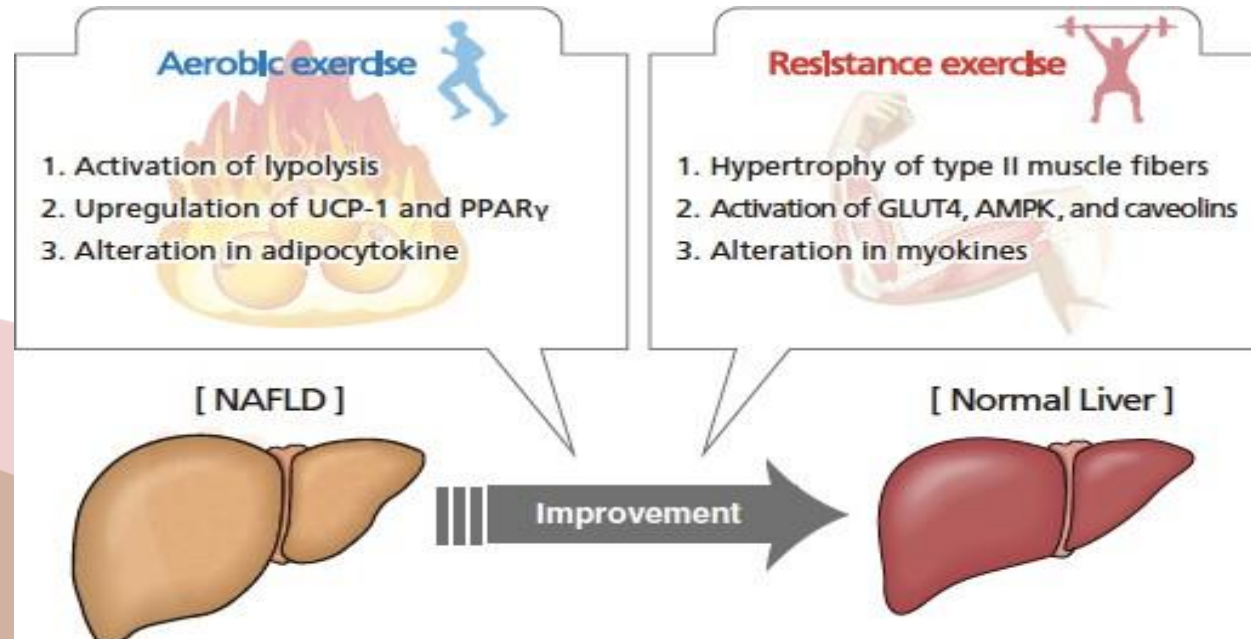
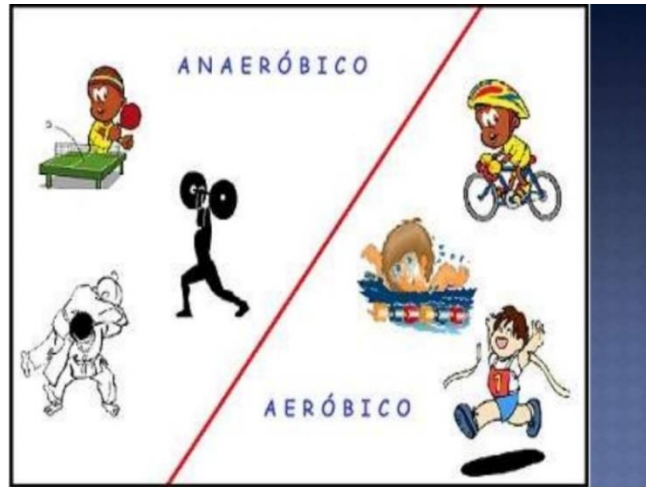
John P. Thyfault, and R. Scott Rector Diabetes 2020;69:517-524

SEDENTARISMO/ACTIVIDAD FISICA EJERCICIO FISICO



	Number	Cases	Age-sex-adjusted PR ^a (95% CI)
Sitting time			
<5 h/day	33,892	7724	1.00 (reference)
5-9 h/day	53,618	15,133	1.05 (1.02-1.07)
≥10 h/day	51,546	16,400	1.12 (1.09-1.14)
<i>p</i> value for trend			<0.001
Physical activity level			
Inactive	62,313	17,473	1.00 (reference)
Minimally active	52,536	15,619	0.94 (0.92-0.95)
HEPA	24,207	6165	0.81 (0.79-0.83)
<i>p</i> value for trend			<0.001

TIPO DE EJERCICIO FISICO



EVITAR SARCOPENIA

Ejercicio Aeróbico

1. Metabolismos implicados en el mantenimiento de la resíntesis de la tasa de ATP: **Glucolisis aeróbico y Lipólisis (B-oxidación)**.
2. Condiciones teóricas para maximizar este metabolismo: 50-55 % FCT y/o 42-47 % **VO2max**.

• Adaptaciones:

1. ↑ Densidad mitocondrial.
2. Angiogénesis a nivel vascular.

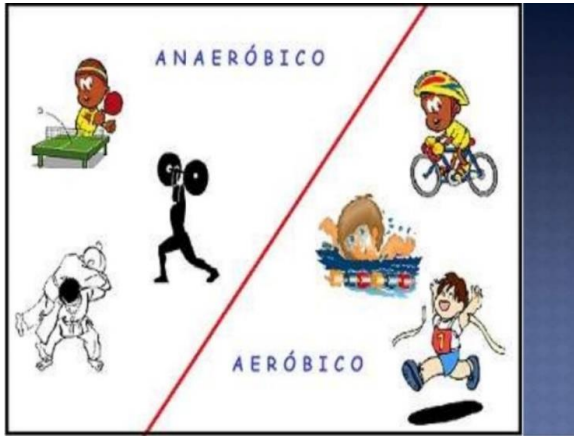


Ejercicio anaeróbico

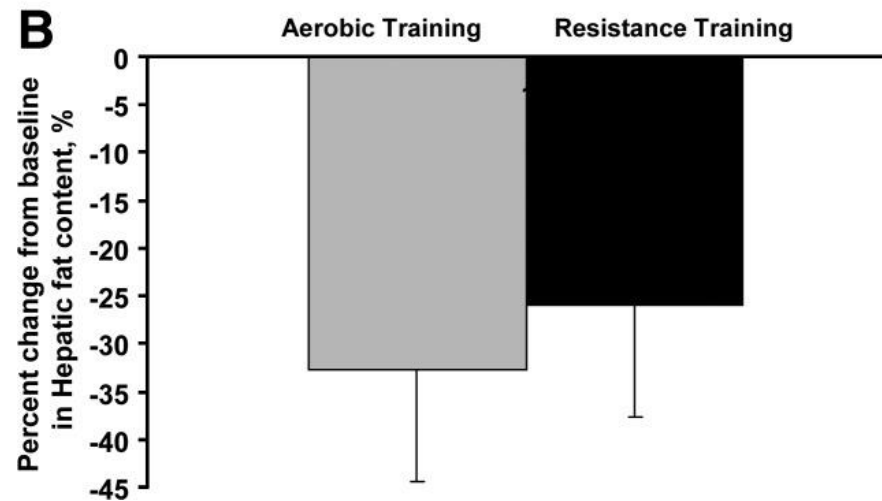
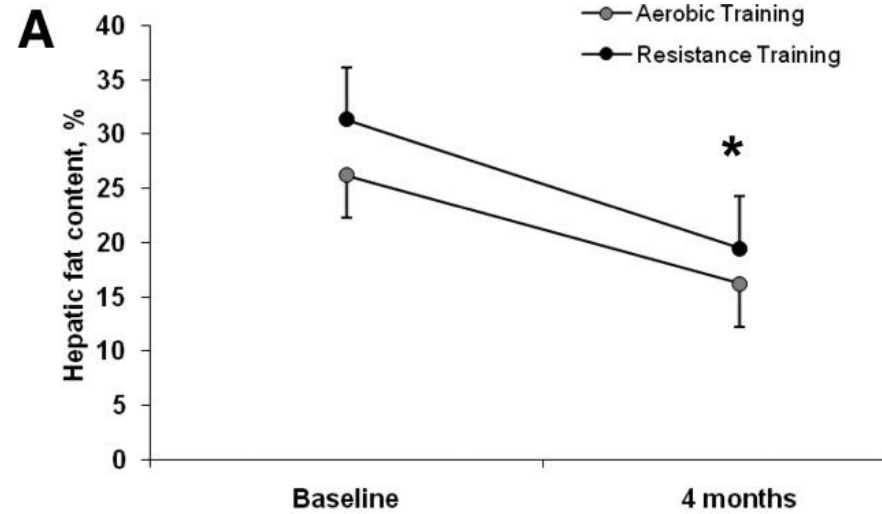


- Adaptaciones:

1. Mejoras a nivel hormonal (↑ concentraciones de GH, IGF-1 y Testosterona).
2. Mejora la **sensibilidad a la Insulina** y por ende la homeostasis del metabolismo de la glucosa.
3. Masa magra: ↑ de la sección transversal de la fibra. El trabajo de fuerza induce hipertrofia e hiperplasia celular por células satélite y un mayor engrosamiento de tendones.
4. Aumenta la **tasa metabólica basal**
5. Mejora la **oxidación de ácidos grasos..**
6. Mejora la **lipotoxicidad.**
7. Mejora la sensibilidad a la **leptina y a la adiponectina** ya que se regula al alza la transcripción de los genes correspondientes.
8. Este trabajo ↓ la grasa visceral.



Both resistance training and aerobic training reduce hepatic fat content in type 2 diabetic subjects with nonalcoholic fatty liver disease (the RAED2 randomized trial)



Grasa hepática

LEVE VS MODERADA INTENSIDAD

Non-invasive fibrosis scores of NAFLD and FLI before and after exercise

Score	Moderate intensity group			Low intensity group		
	Before exercise	After exercise	<i>p</i> value	Before exercise	After exercise	<i>p</i> value
NFS	-1.35	-1.59	0.278	0.66	0.75	0.621
FIB-4	0.84	0.81	0.722	0.88	0.86	0.772
APRI	0.41	0.27	0.005	0.43	0.40	0.285
FLI	62.84	50.55	<0.001	66.08	60.43	0.031

Nath P, J Clin Transl Hepatol. 2020

MODERADA VS INTENSA INTENSIDAD

JAMA Internal Medicine | Original Investigation

Effects of Moderate and Vigorous Exercise on Nonalcoholic Fatty Liver Disease A Randomized Clinical Trial

Hui-Jie Zhang, MD, PhD; Jiang He, MD, PhD; Ling-Ling Pan, MD, PhD; Zhi-Min Ma, MD, PhD; Cheng-Kun Han, MD; Chung-Shiuan Chen, MS; Zheng Chen, MD; Hai-Wei Han, MD; Shi Chen, MD; Qian Sun, MD; Jun-Feng Zhang, MD; Zhi-Bin Li, MD; Shu-Yu Yang, MD, PhD; Xue-Jun Li, MD, PhD; Xiao-Ying Li, MD, PhD

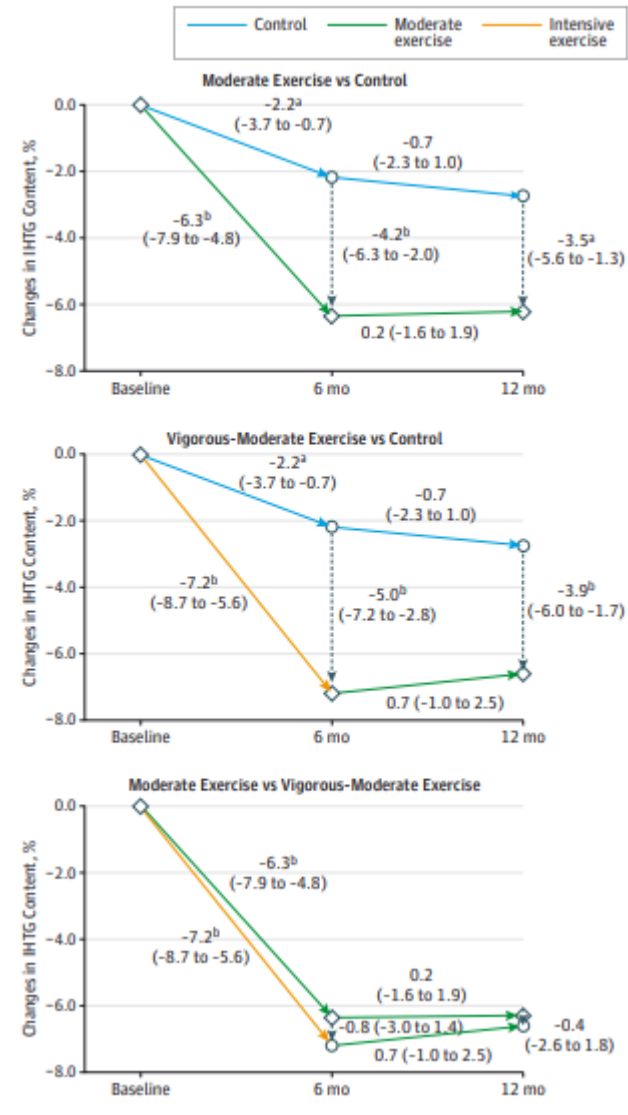
Key Points

Question Is vigorous exercise more effective in improving nonalcoholic fatty liver disease than moderate exercise?

Findings In this randomized clinical trial of 220 Chinese adults with abdominal obesity and nonalcoholic fatty liver disease, intrahepatic triglyceride content was significantly reduced by 5.0% in the vigorous exercise group and 4.2% in the moderate exercise group compared with a control group during 6 months. The change in intrahepatic triglyceride content was not significantly different between the vigorous and moderate exercise groups.

Meaning Vigorous and moderate exercise was equally effective in reducing intrahepatic triglyceride content among patients with nonalcoholic fatty liver disease.

Figure 2. Effects of Moderate and Vigorous Exercise on Intrahepatic Triglyceride Content (IHTG)

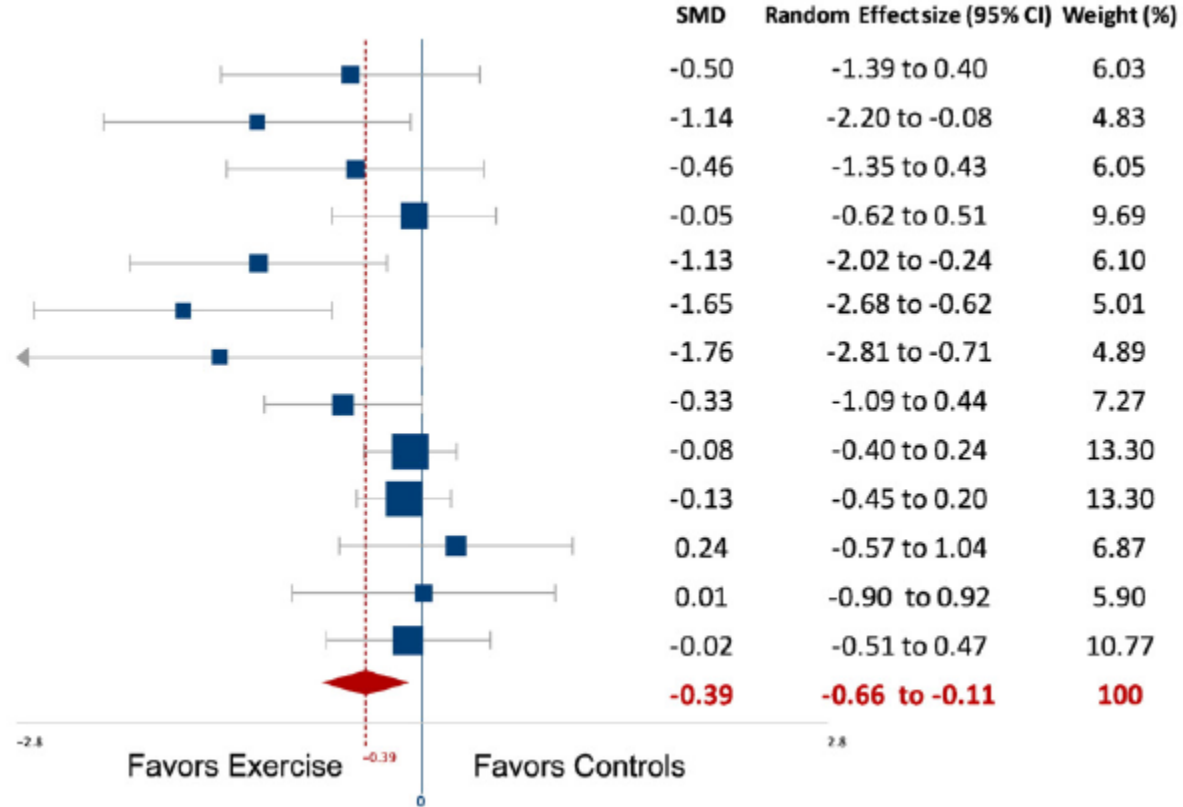


TG INTRAHEPATICOS

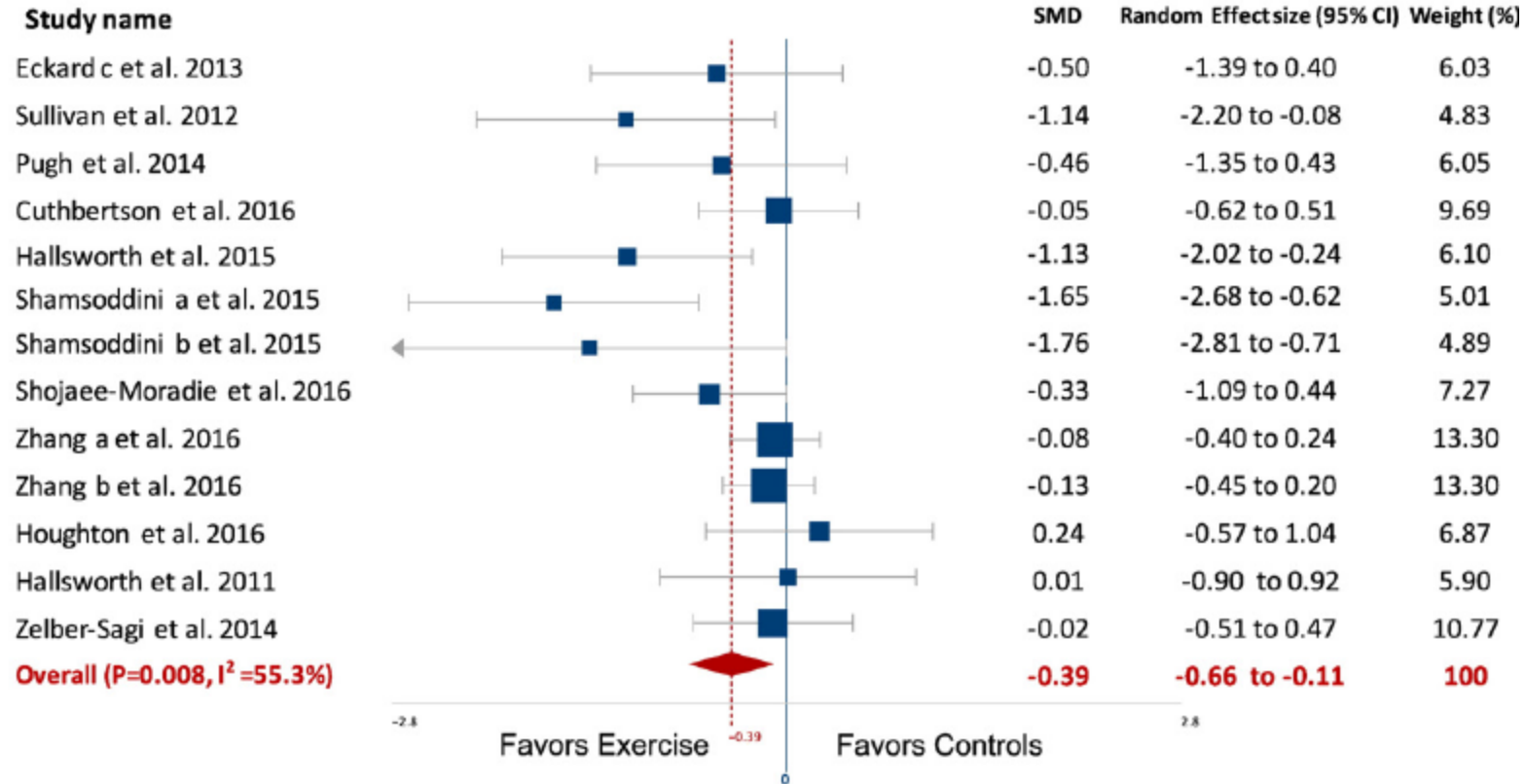
EJERCICIO FISICO Y NIVELES DE ALT

Study name

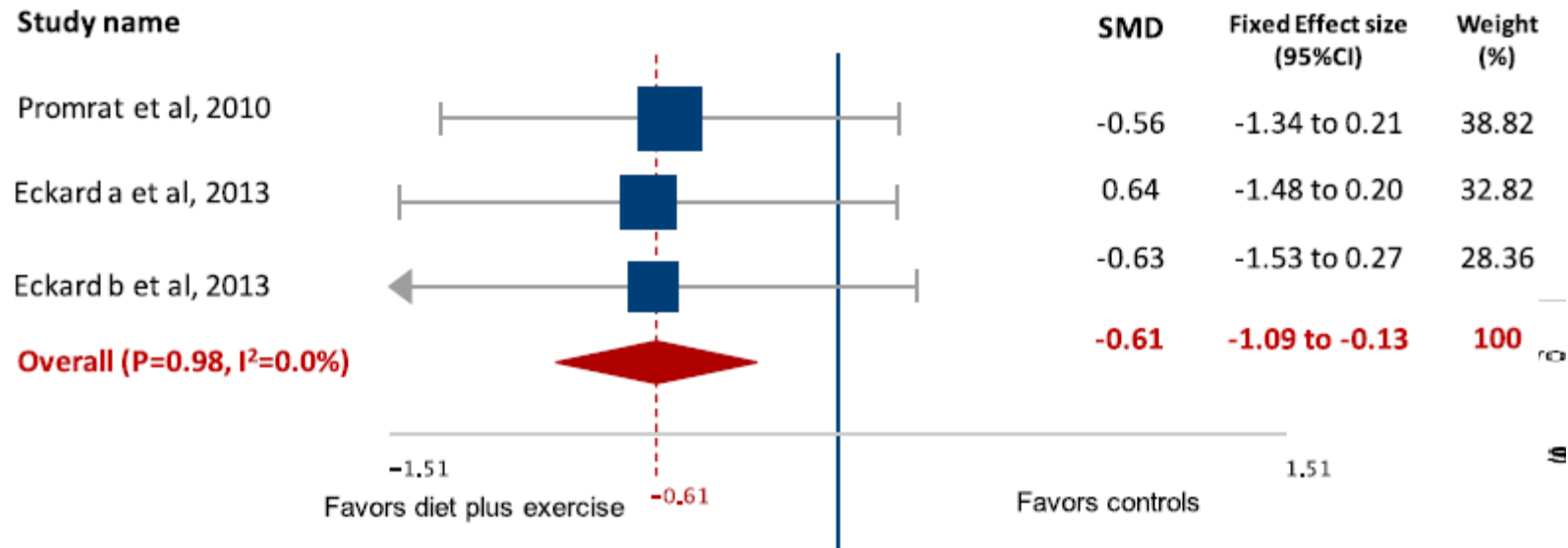
Eckard c et al. 2013
 Sullivan et al. 2012
 Pugh et al. 2014
 Cuthbertson et al. 2016
 Hallsworth et al. 2015
 Shamsoddini a et al. 2015
 Shamsoddini b et al. 2015
 Shojaee-Moradie et al. 2016
 Zhang a et al. 2016
 Zhang b et al. 2016
 Houghton et al. 2016
 Hallsworth et al. 2011
 Zelber-Sagi et al. 2014
Overall (P=0.008, I²=55.3%)



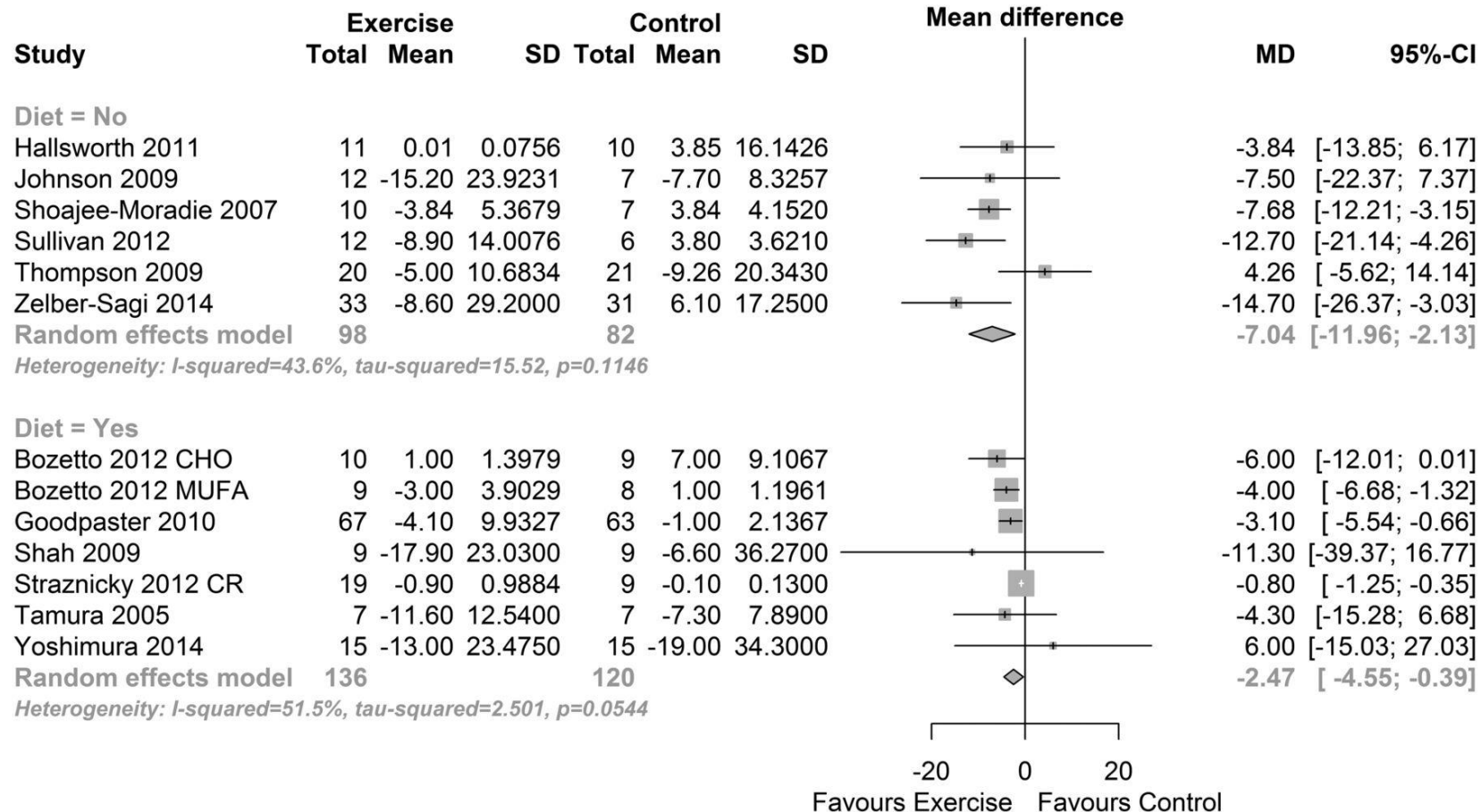
EJERCICIO FISICO Y TG INTRAHEPATICOS



NAS SCORE

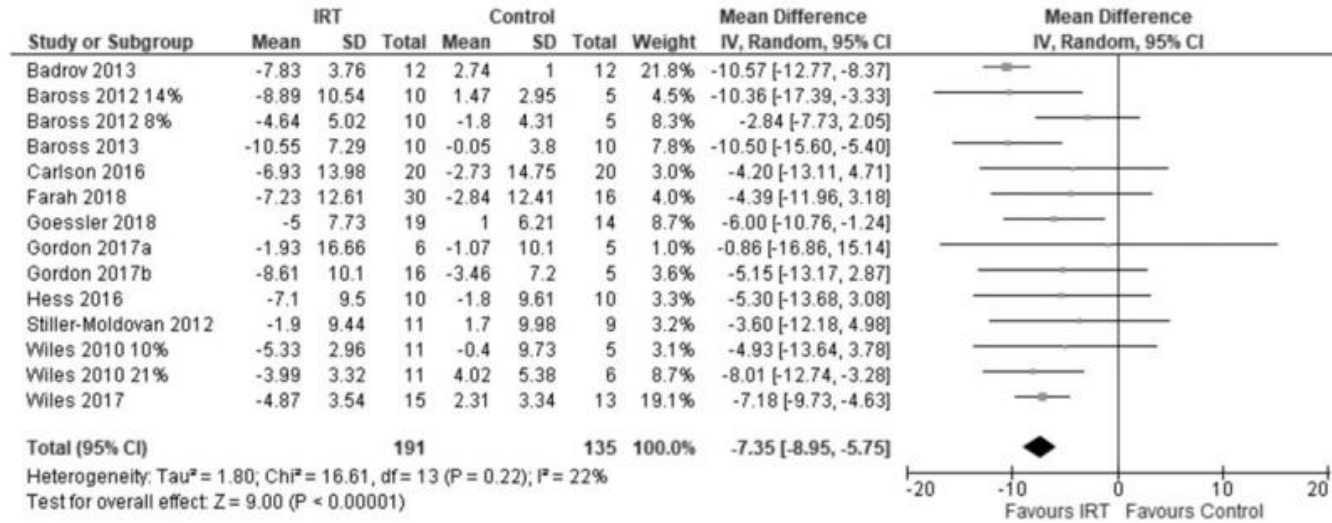


Change in total cholesterol: exercise interventions.

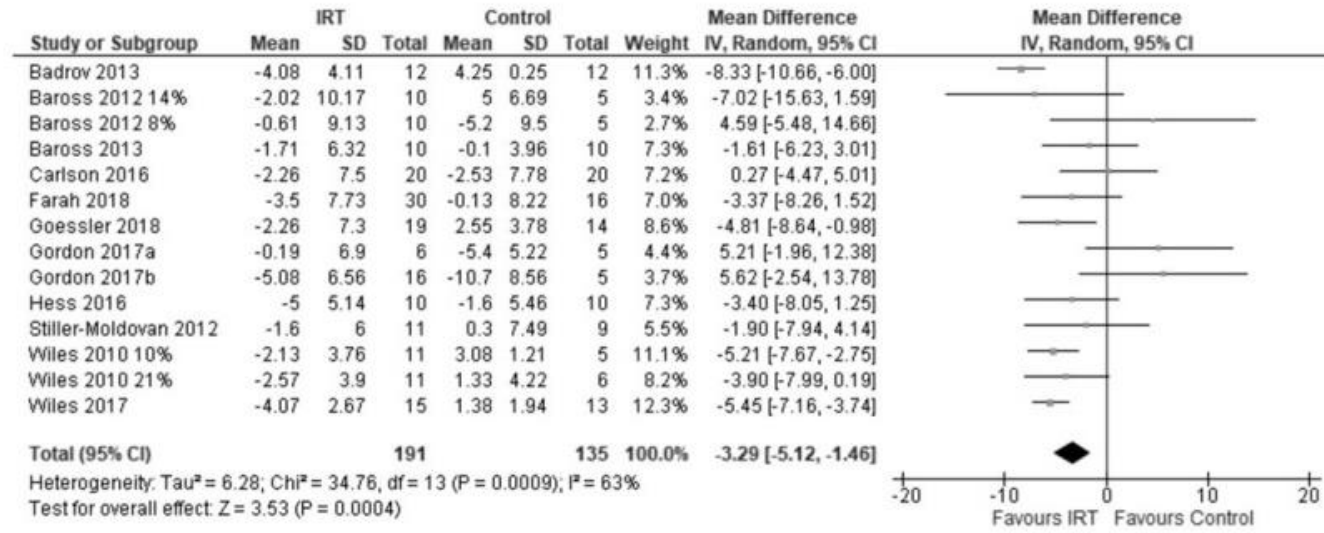


N A Smart et al. Br J Sports Med 2018;52:834-843

Effects of isometric resistance training on resting blood pressure: individual participant data meta-analysis

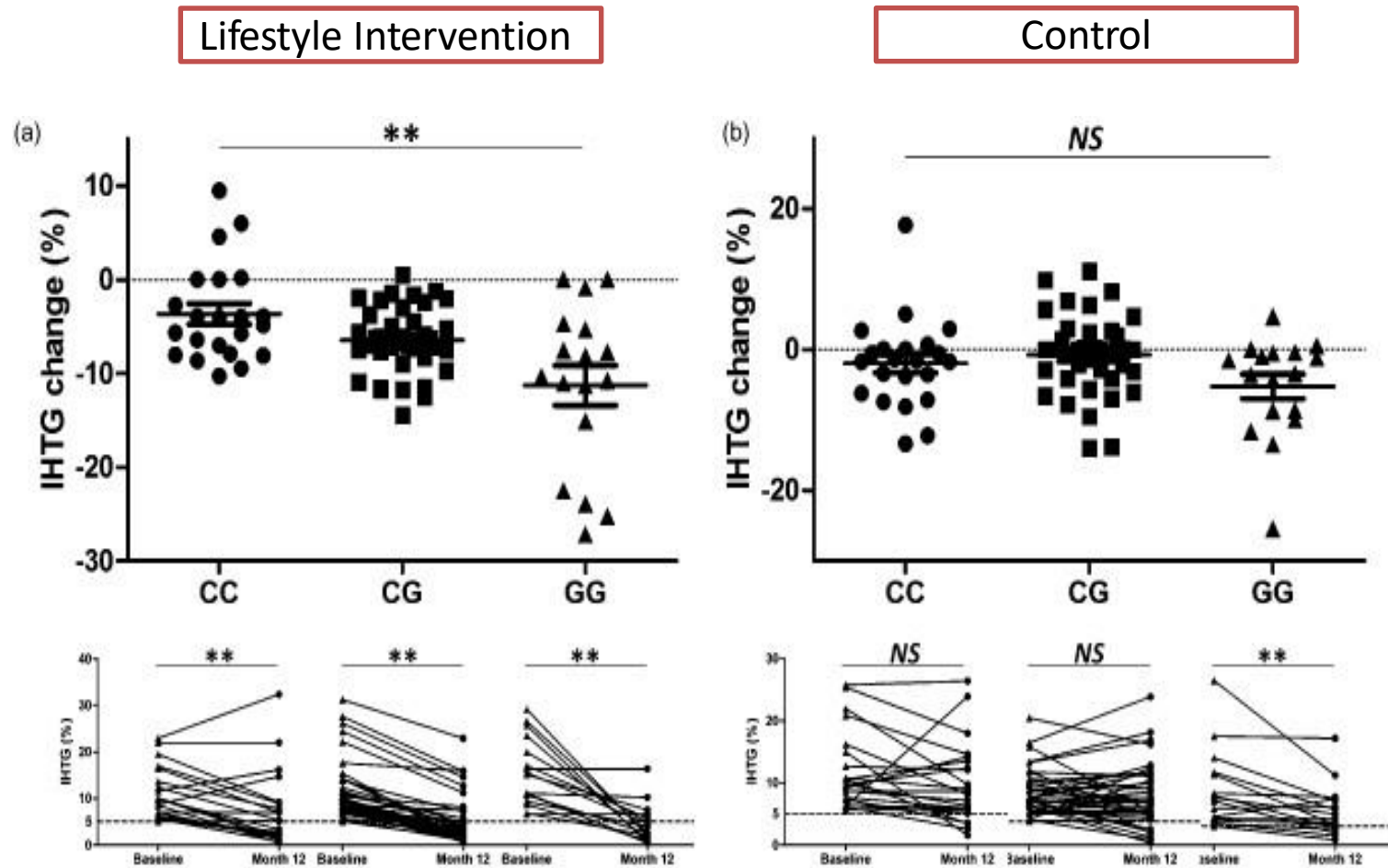


TAS



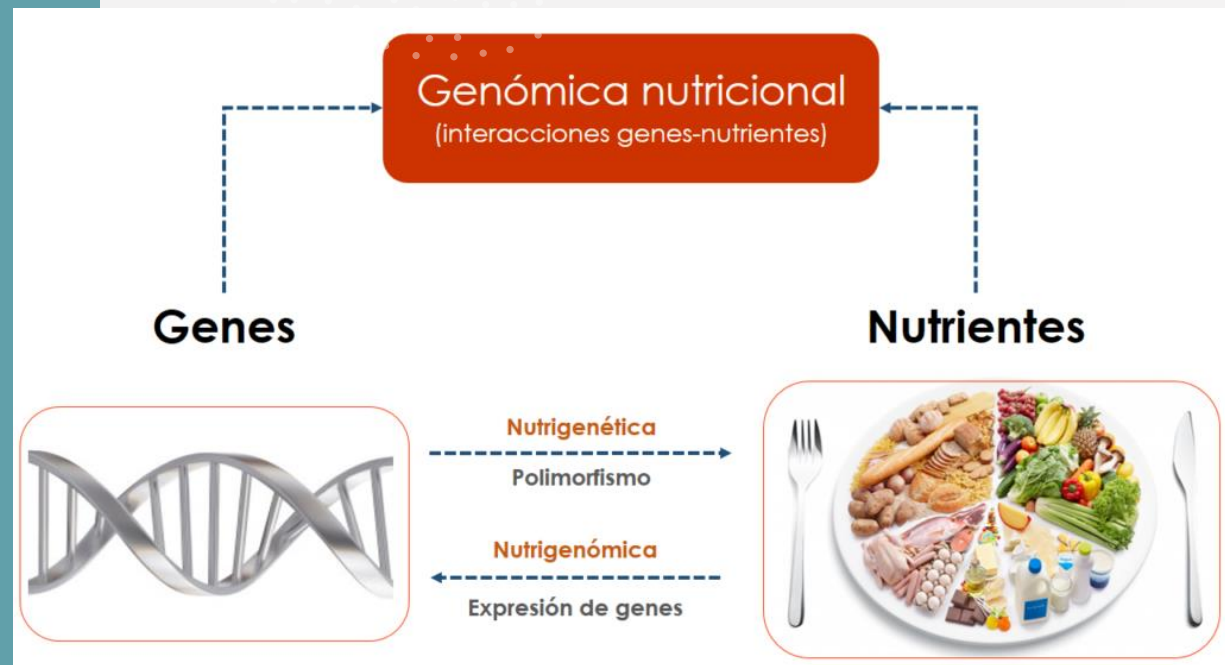
TAD

PNPLA3 Influences Response to Lifestyle Modification in NAFLD



IHTG change: CC: $3.7 \pm 5.2\%$, CG: $6.5 \pm 3.6\%$ and GG: $11.3 \pm 8.8\%$ ($p=0.002$)

NUTRICION INTEGRAL PERSONALIZADA



NASH

LIFESTYLE INTERVENTION 1 YEAR

Energy restriction

Hypo-caloric diet:

1200-1800 kcal/d or deficit of 500-750 kcal/day

Low fat or low carbohydrate or **Mediterranean diet** tailored for patients preferences

Dietary composition

CARBOHYDRATES:

Reduce added sugar
avoid sugar sweetened beverages
complex carbohydrates in moderation (40% of calories), high in fiber

FATS:

Reduce saturated/trans fat & cholesterol
Increase n-3 FA and MUFA

Dietary patterns

- a) Minimize **Fast Food**
- b) Prefer Mediterranean Diet.

Physical activity

- a) Aerobic $\geq 3/w$ (150 min/w)
- b) Resistance $\geq 2/w$
- c) Minimize sedentary time

Nutraceuticals

- a) Coffee may be advised if there are not contraindications
- b) Omega 3 supplement (DHA) could be considered (if not sufficiently consumed by diet)

Behavioral strategies to facilitate adherence; Comprehensive lifestyle program, high-intensity sessions, regular self-monitoring of food intake & physical activity, enhancement of self-efficacy, setting realistic weight management goals, negotiating dietary and activity goals, positive feedback on dietary composition improvement

Compute NASH resolution score 1y

< 46.15

Recommend drug therapy

46.15 - 69.72

Consider drug therapy

> 69.72

Long term weight loss maintenance





U de rehabilitación hepática



la evidencia existente muestra claramente que el ejercicio programado con o sin pérdida de peso debe ser empleado como "**rehabilitación hepática médica**" para los pacientes que están en riesgo o que tienen NAFLD.

Antes de medicarse no olviden activarse
(vida activa) y sanarse (vida sana)





MÁSTER EN HEPATOLOGÍA



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