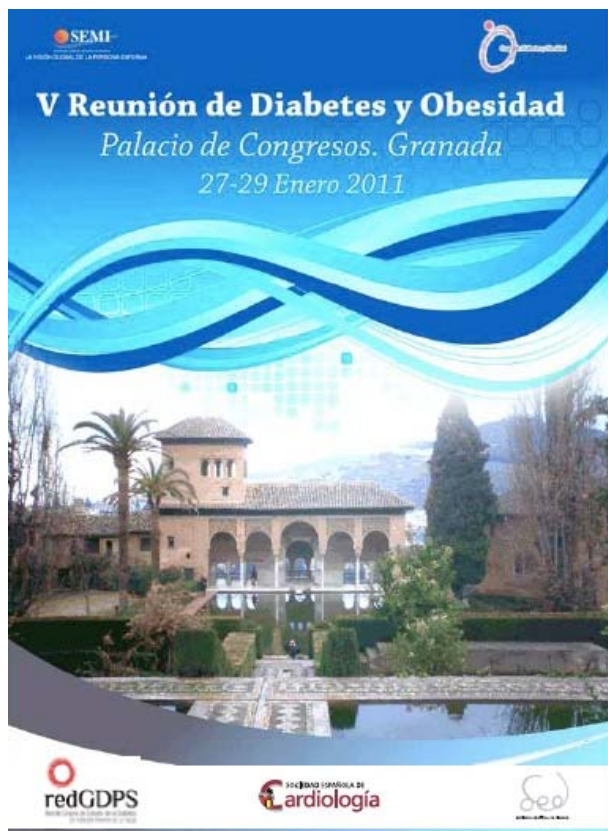


Dieta Mediterránea, Diabetes y obesidad

Evidencias fisiopatológicas



Centro de Investigación Biomédica en Red
Fisiopatología de la Obesidad y Nutrición

Francisco Pérez Jiménez

Unidad de Lípidos y Arteriosclerosis. Hospital Universitario
Reina Sofía. Universidad de Córdoba



El problema de la diabetes tipo 2 en el mundo. Nature 2005

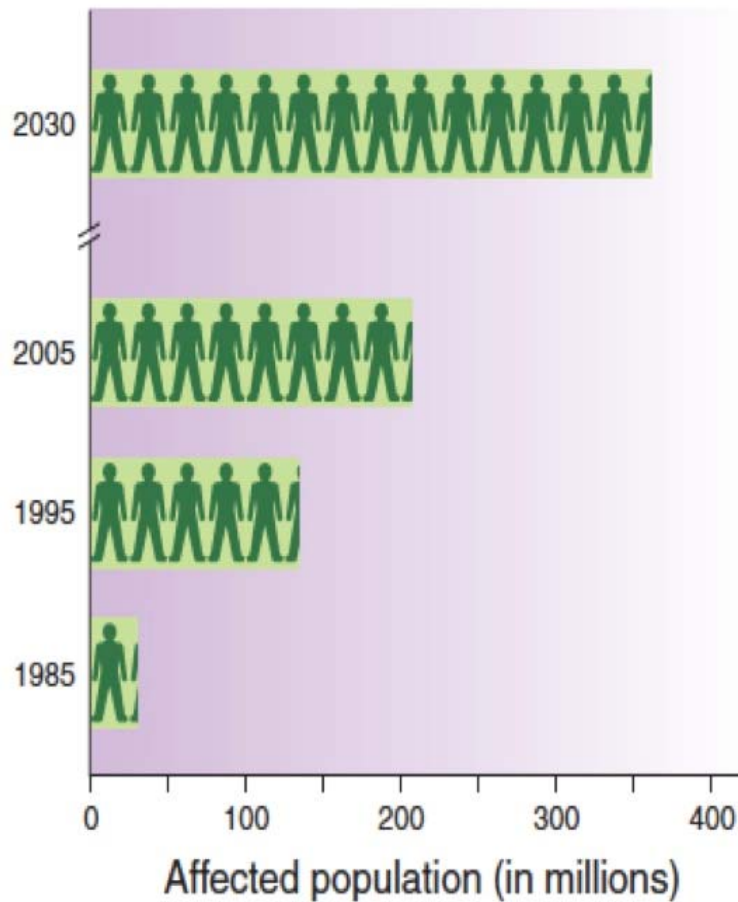


Figure 1 Worldwide diabetic population (in millions). Data sources: World Health Organization and Wood Mackenzie.

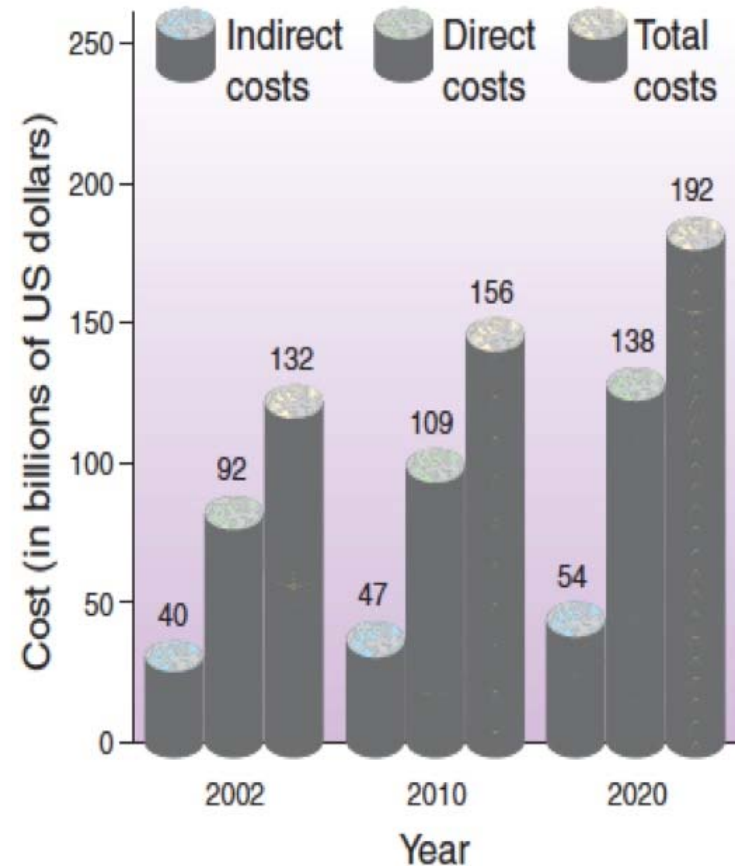
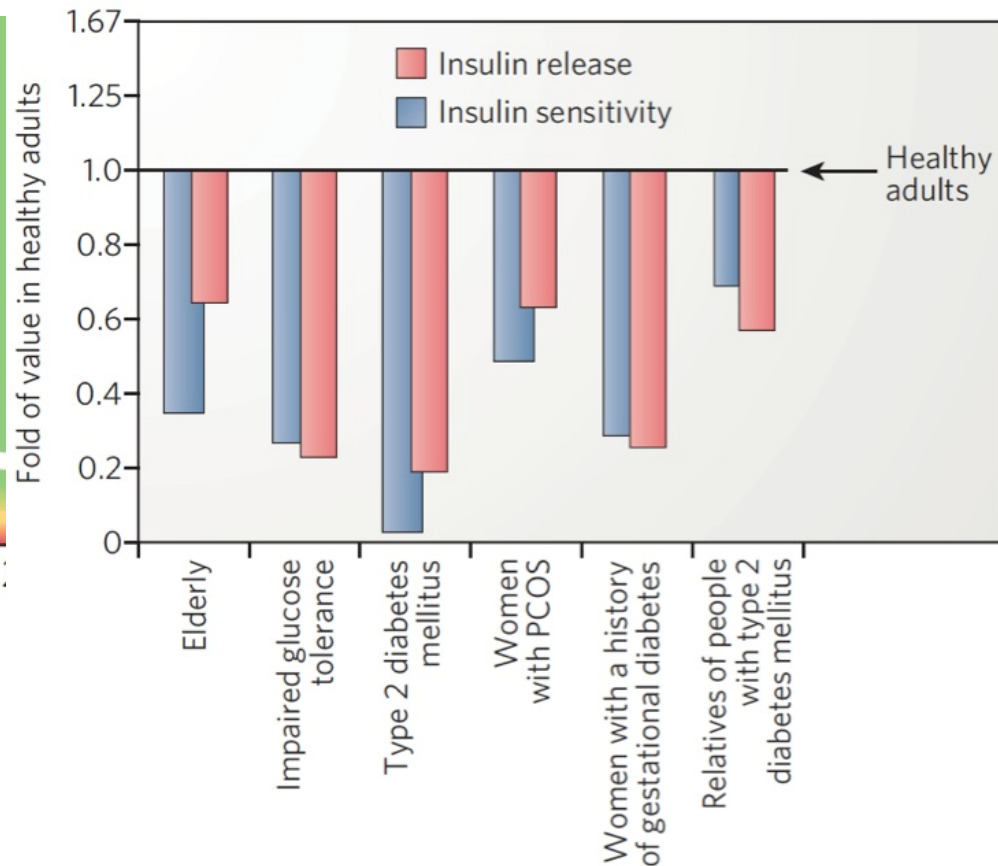
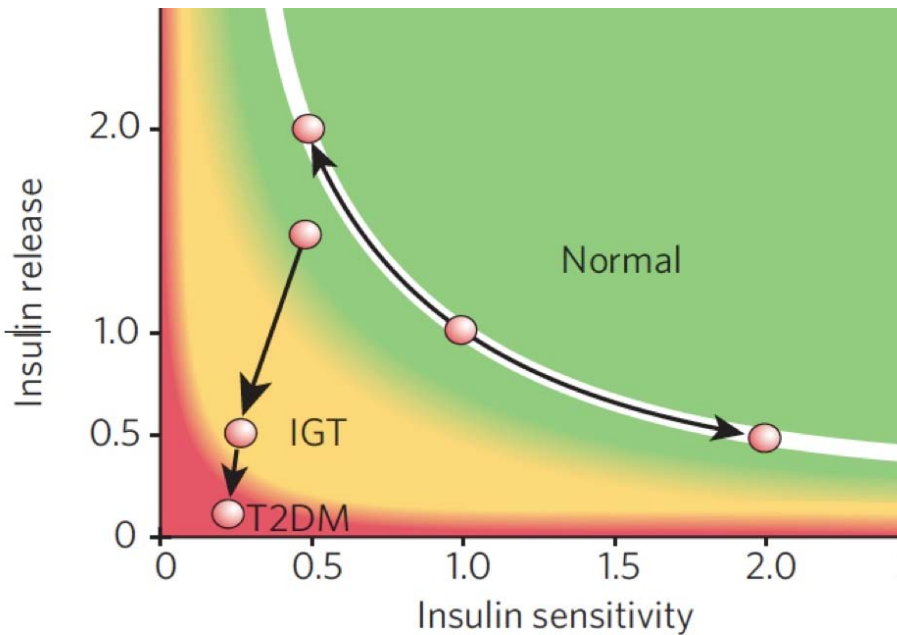


Figure 2 Estimated financial costs of diabetes in the US. Indirect costs, lost productivity; direct costs, medical expenses. Data source: American Diabetes Association.

La relación entre producción y sensibilidad a la insulina en distintas situaciones de salud y enfermedad.

SE Kahn. Nature 444. 14 December 2006



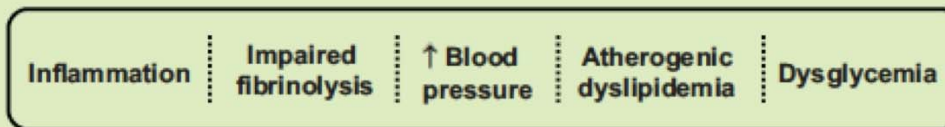
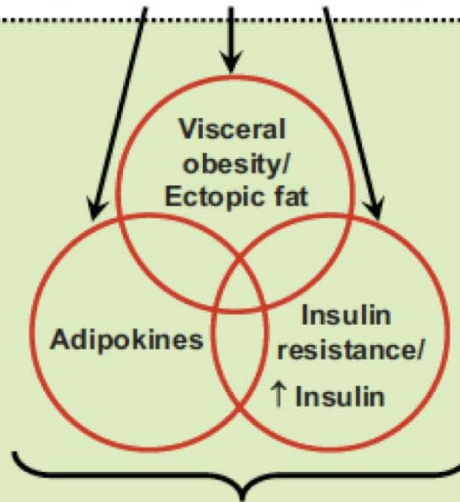
La compleja realidad del SM. ATVB, J Després 2008

A

Genetic and environmental determinants

- Energy dense diet
- Genetic variation
- Age and Gender
- Lack of physical activity
- Smoking
- Stress
- Neuroendocrine abnormalities
- Steroid hormones
- Susceptible endocannabinoid system
- Drugs

B



- Syndrome X (Reaven)
- Insulin resistance syndrome



Based on key pathophysiological markers

C

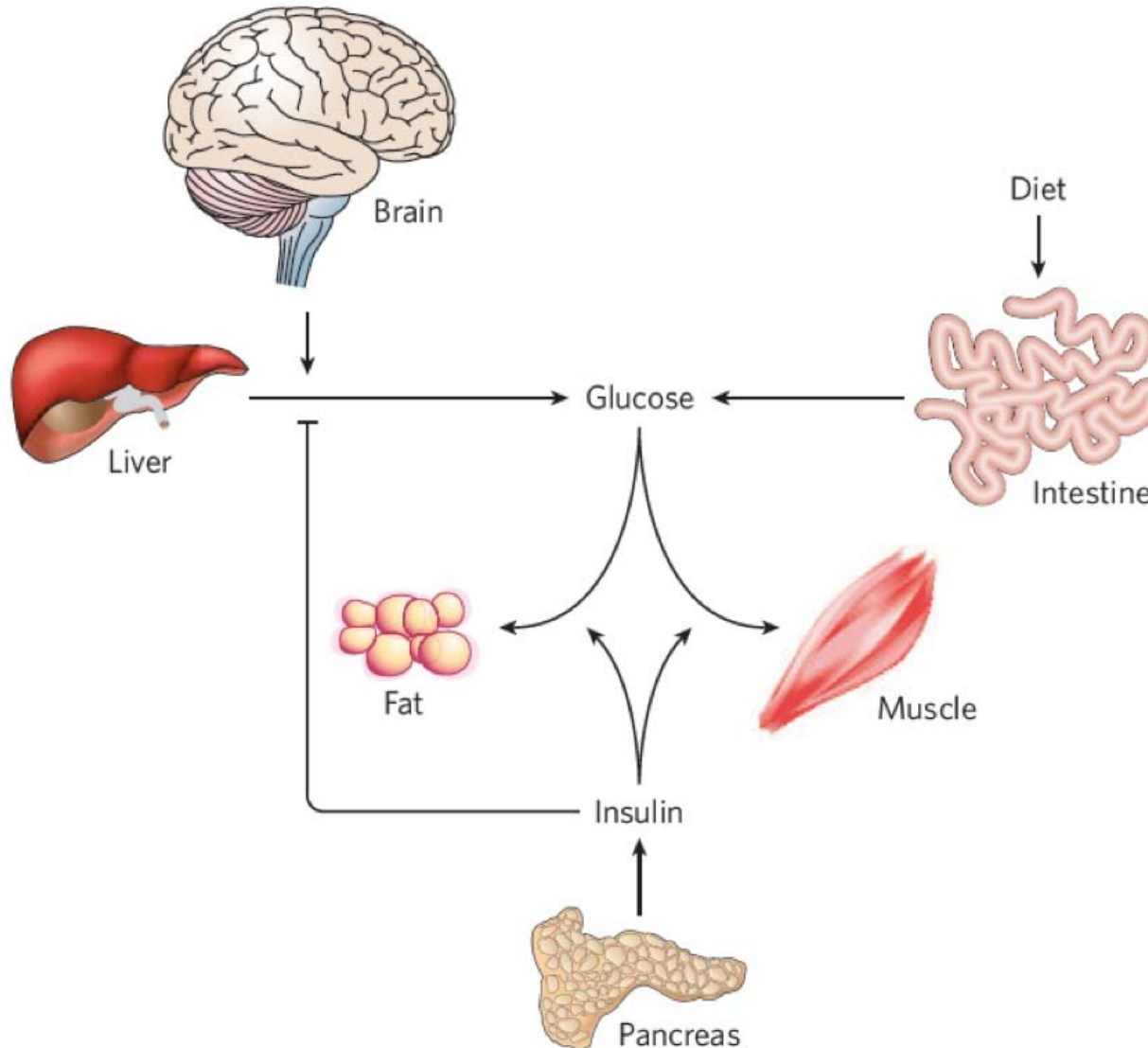
- Metabolic syndrome (NCEP-ATP III or IDF)



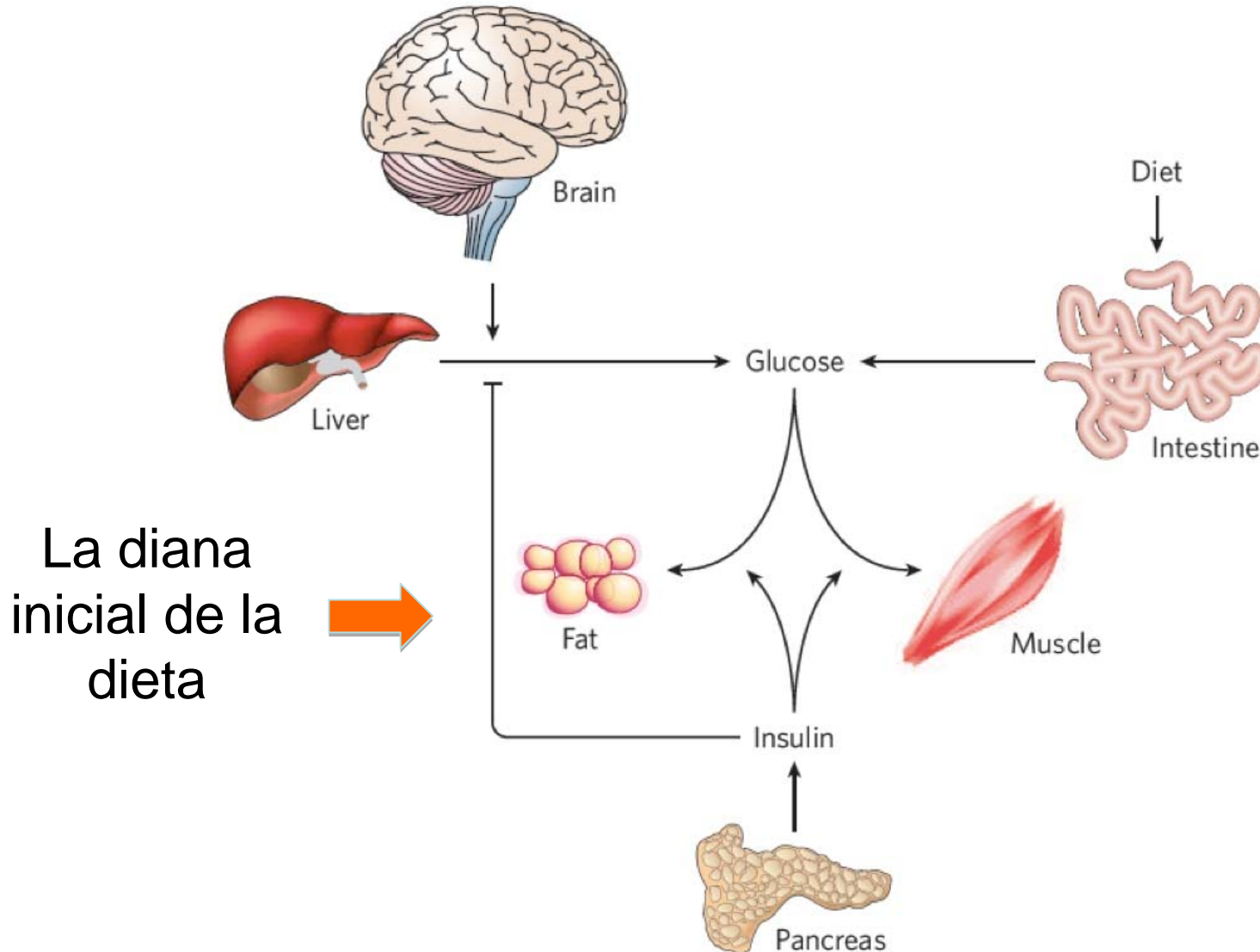
Based on clinical tools:

- Waist girth
- HDL-cholesterol
- Blood pressure
- Triglycerides
- Glucose

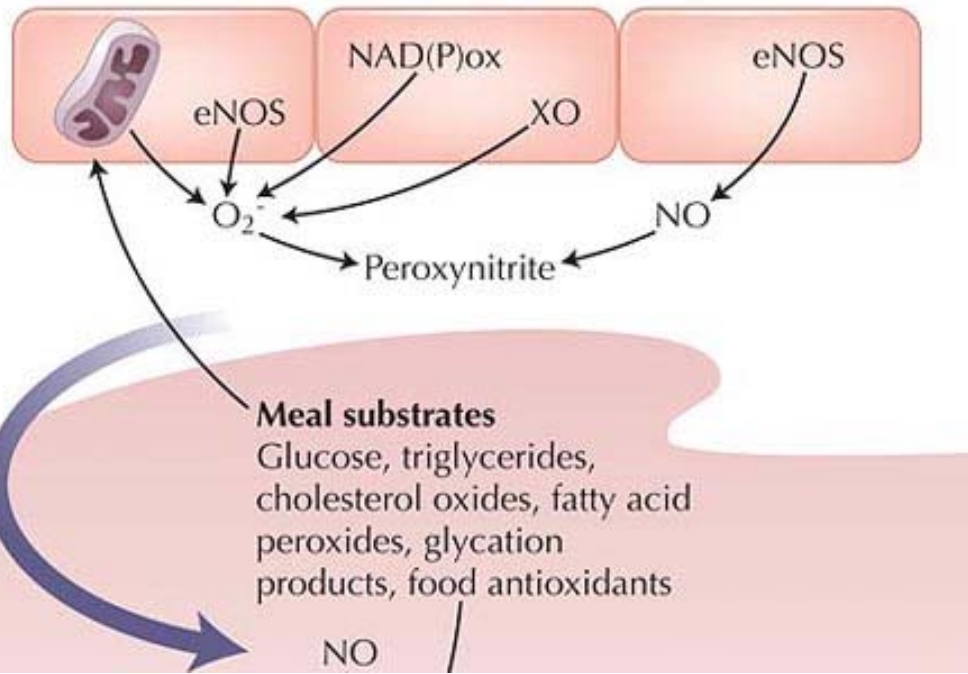
La compleja regulación de la glucosa. E Rosen. Nature 2006. 444:847



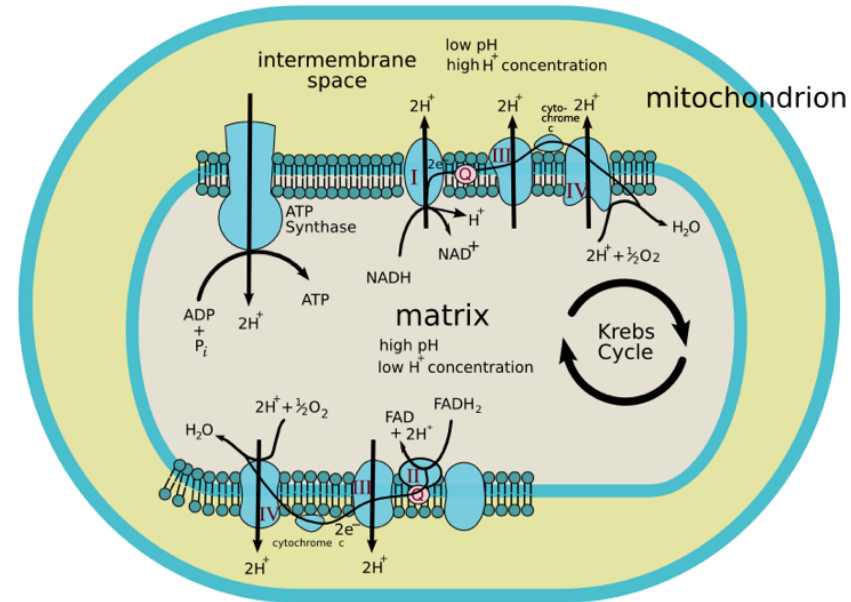
La compleja regulación de la glucosa. E Rosen. Nature 2006. 444:847



Consecuencias del exceso de sustratos: Sobrecarga de capacidad adipocitaria con una sobreproducción de especies reactivas de oxígeno (superóxido, H_2O_2) y de nitrógeno



Mitochondrial Electron Transport Chain

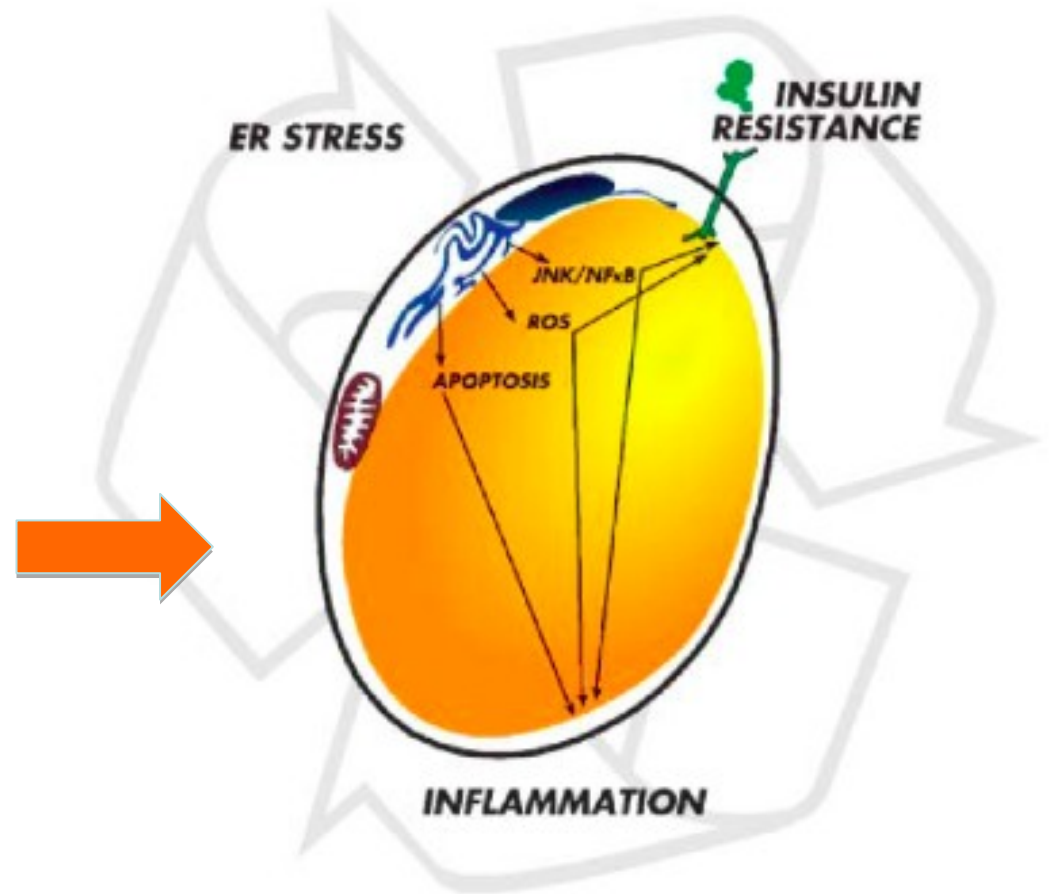


MF Gregor. J Lipid Res 2007; 48:1905

Sobrecarga
grasa

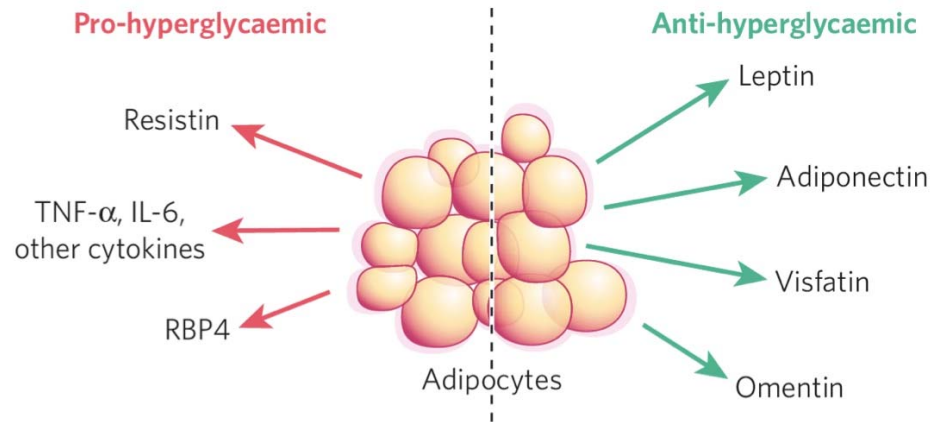


**FUNCTIONAL
ADIPOCYTE**

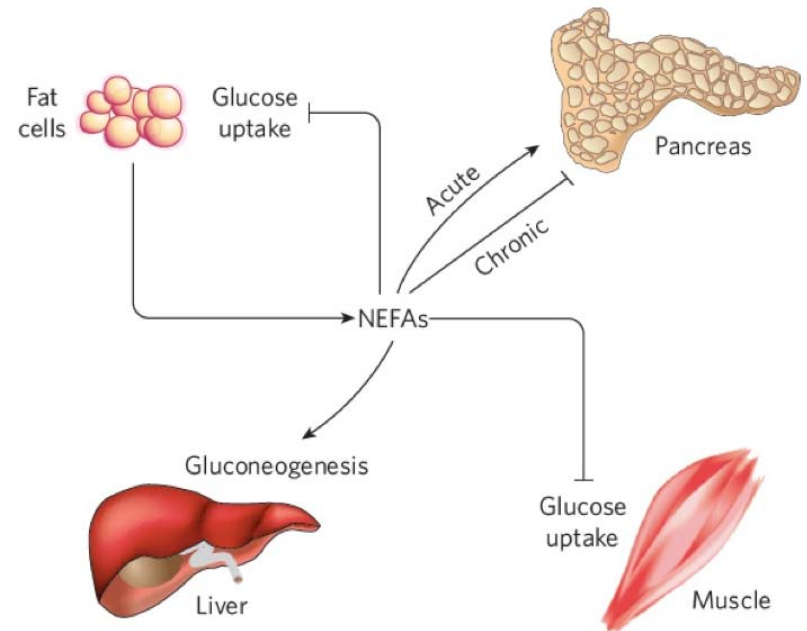


**DYSFUNCTIONAL
ADIPOCYTE**

E Rosen. Nature 2006. 444: 847. Mecanismos que relacionan el adipocito con la resistencia a la insulina

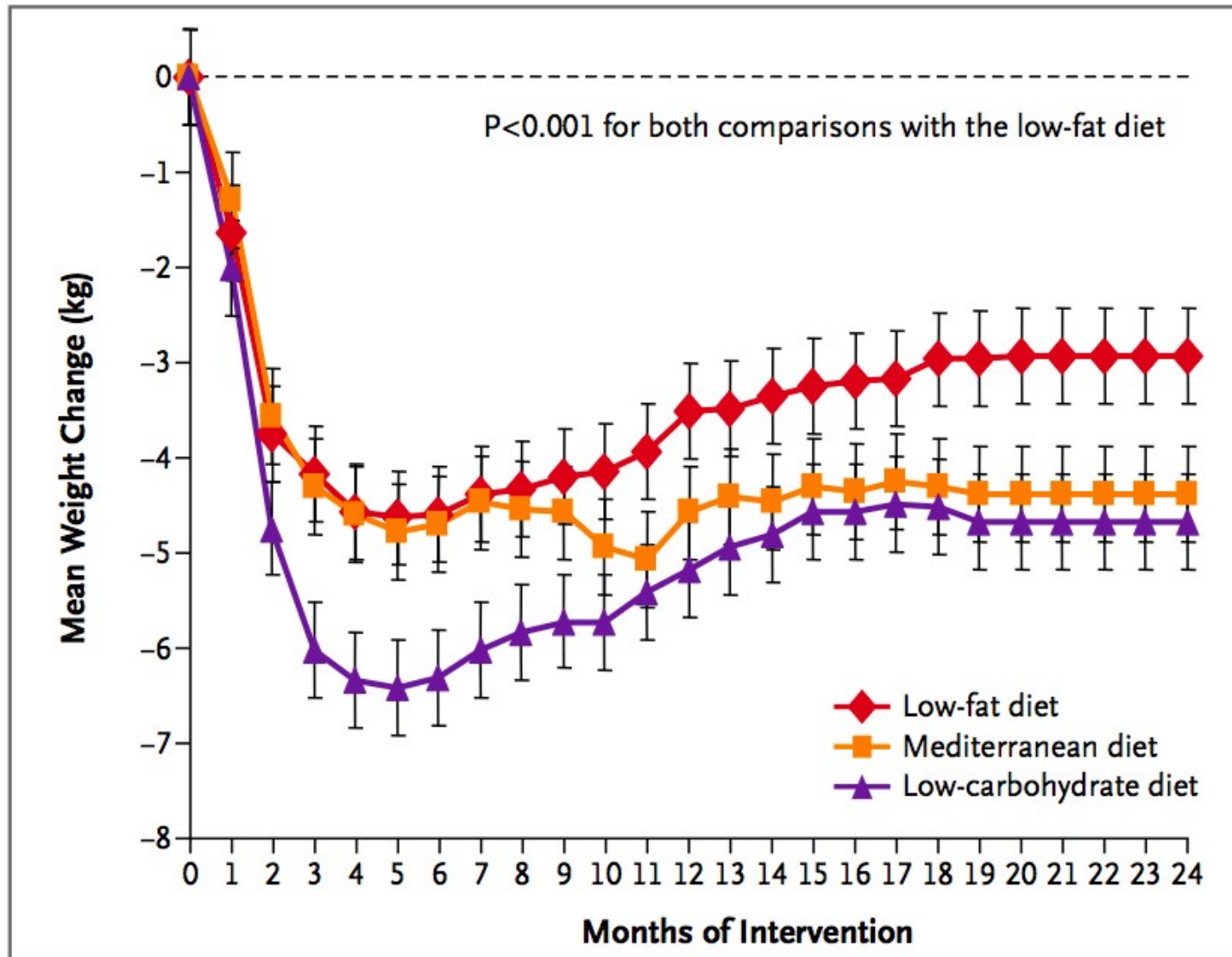


Los adipocitos secretan múltiples proteínas implicadas en el metabolismo de la glucosa, con acción antidiabética o amentando la resistencia a la insulina



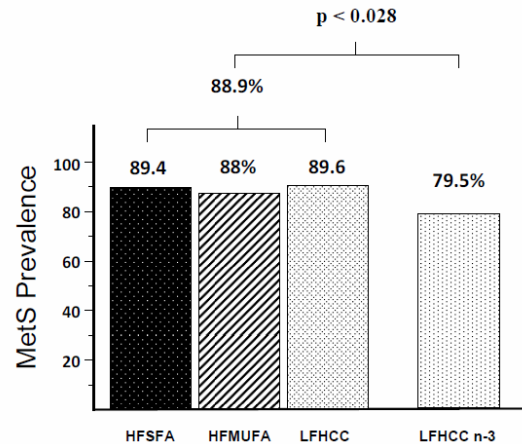
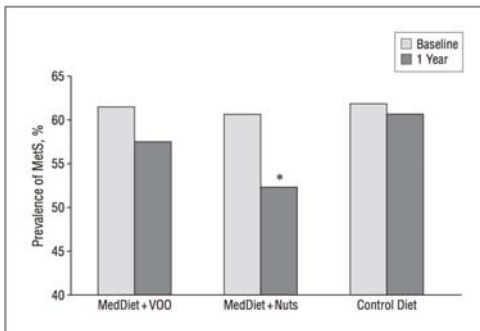
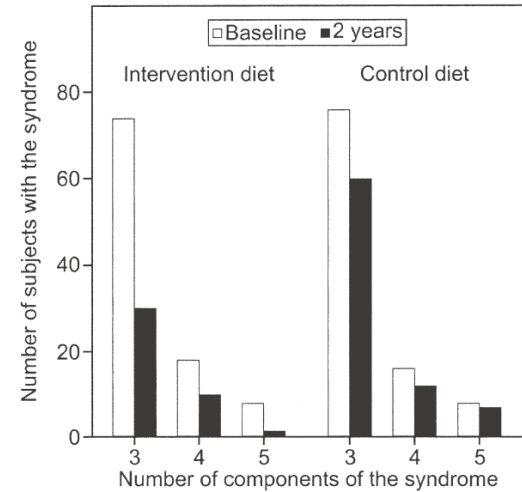
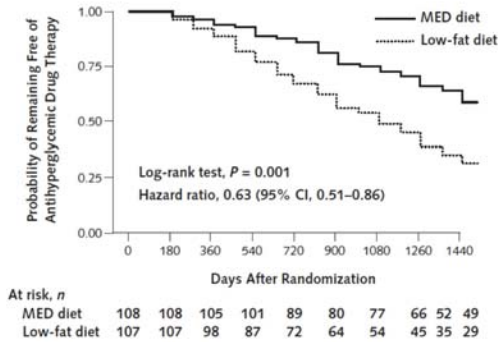
Los FFA disminuyen la captación de glucosa en el músculo y grasa, reduciendo la producción hepática de glucosa. El aumento transitorio de FFA, tras la ingesta, aumenta la secreción de insulina. La elevación crónica (en la resistencia a la insulina) reduce la secreción de insulina

Los límites de las dietas hipocalóricas. I Shai. NEJM 17 julio 2008. 322 obesos durante 2 años con tres dietas. 359:229

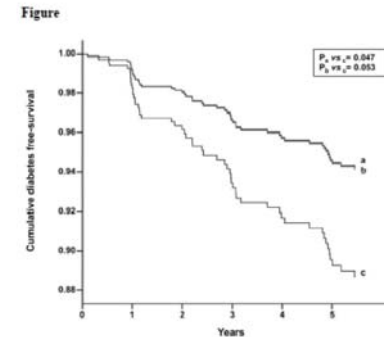


Un nuevo paradigma: ¿se puede esperar algo de la dieta al margen de restringir su aporte calórico?

Figure 2. Probability of remaining free of antihyperglycemic drug therapy.

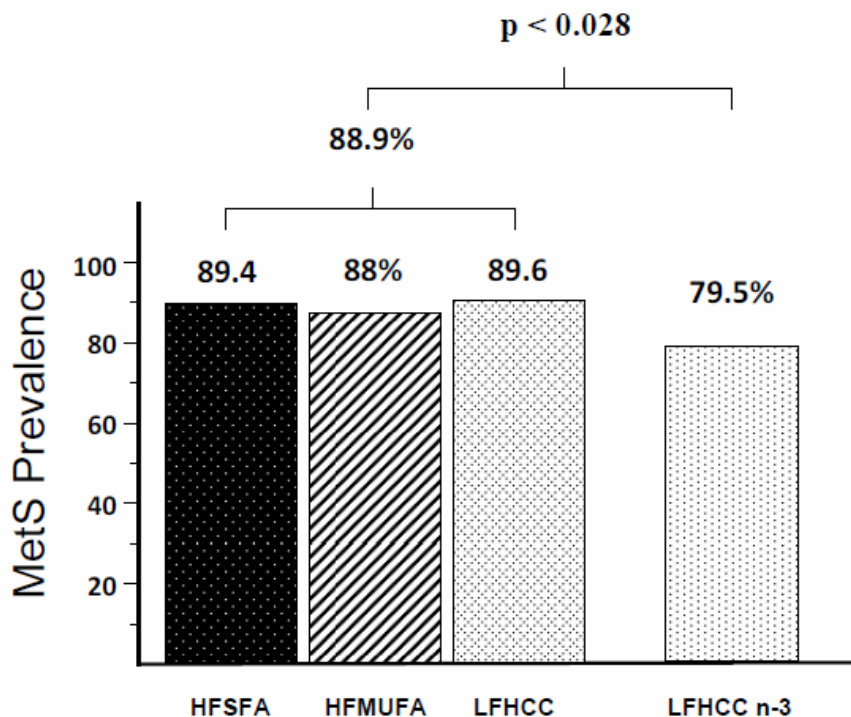


Mediterranean Diet and diabetes incidence

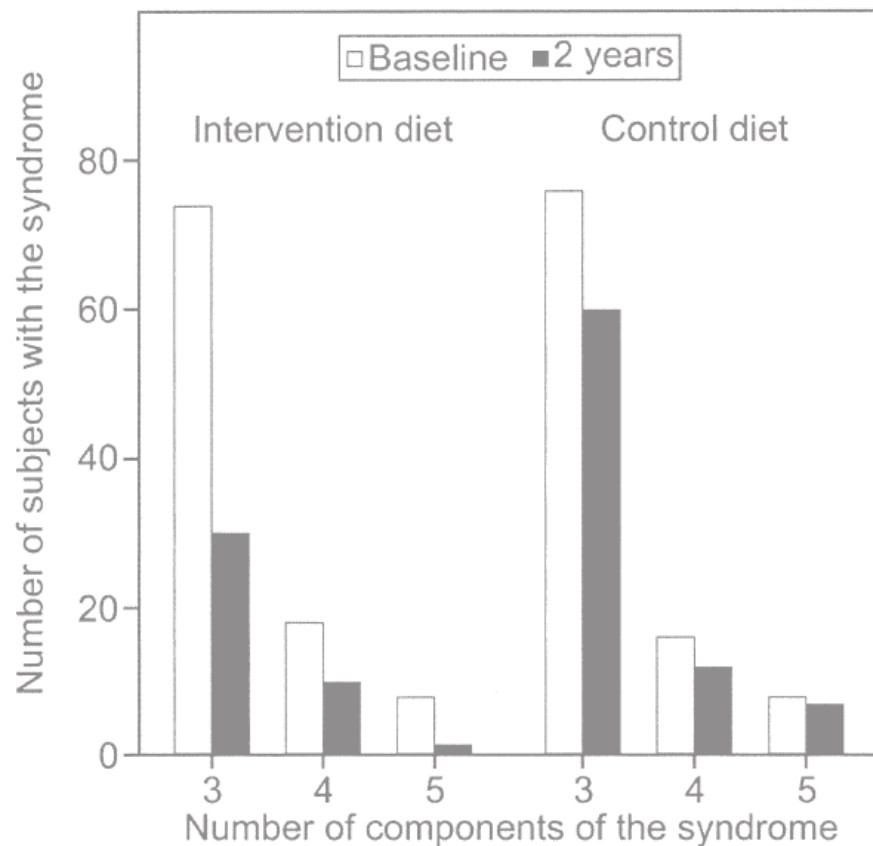


Mejoría del Síndrome Metabólico sin modificar el contenido calórico

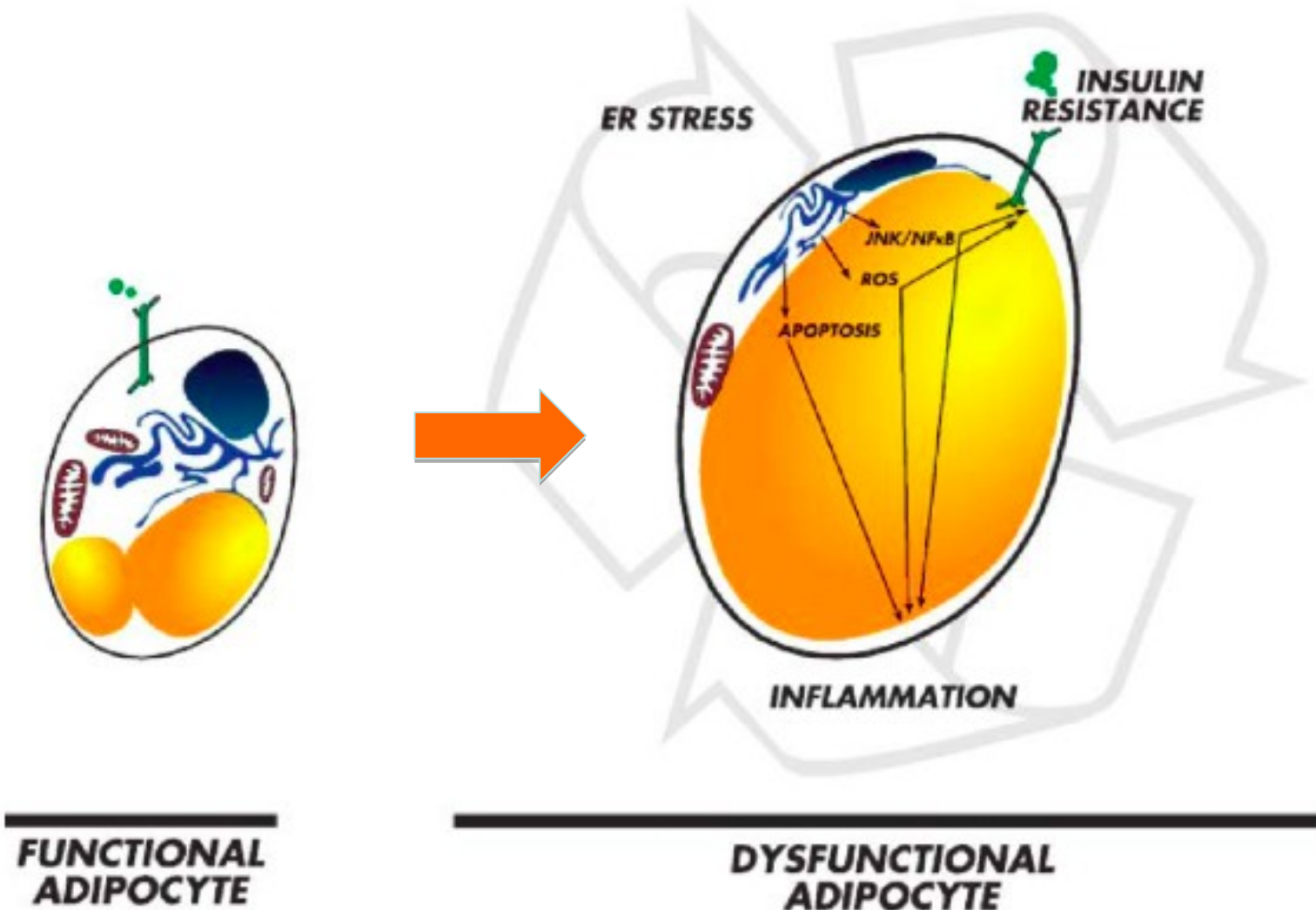
LIPGEN. Intervención en 12 semanas.
Perez-Martinez et al. (en prensa)



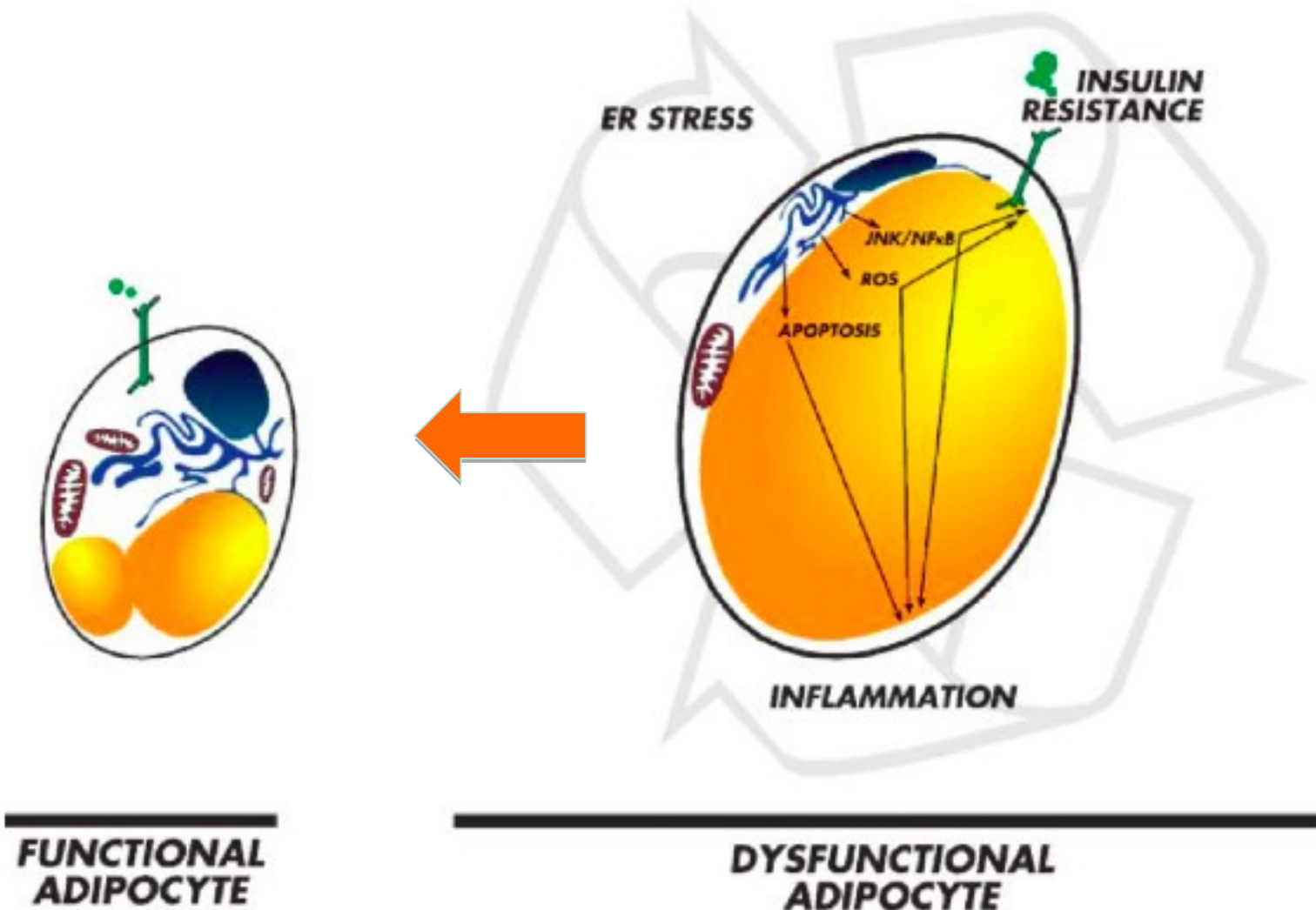
Giugliano, Ceriello, Esposito K. JACC
2006; 48: 677

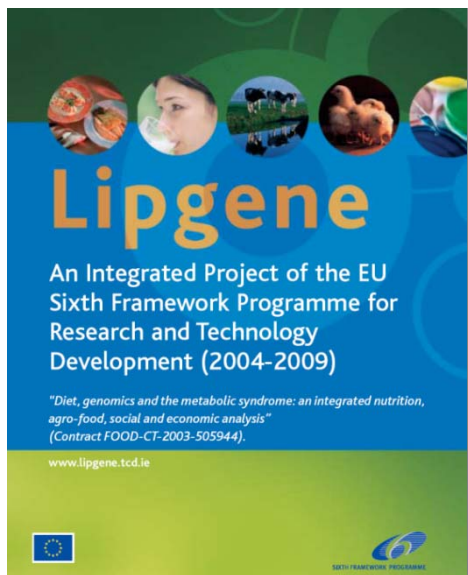


MF Gregor. J Lipid Res 2007; 48:1905



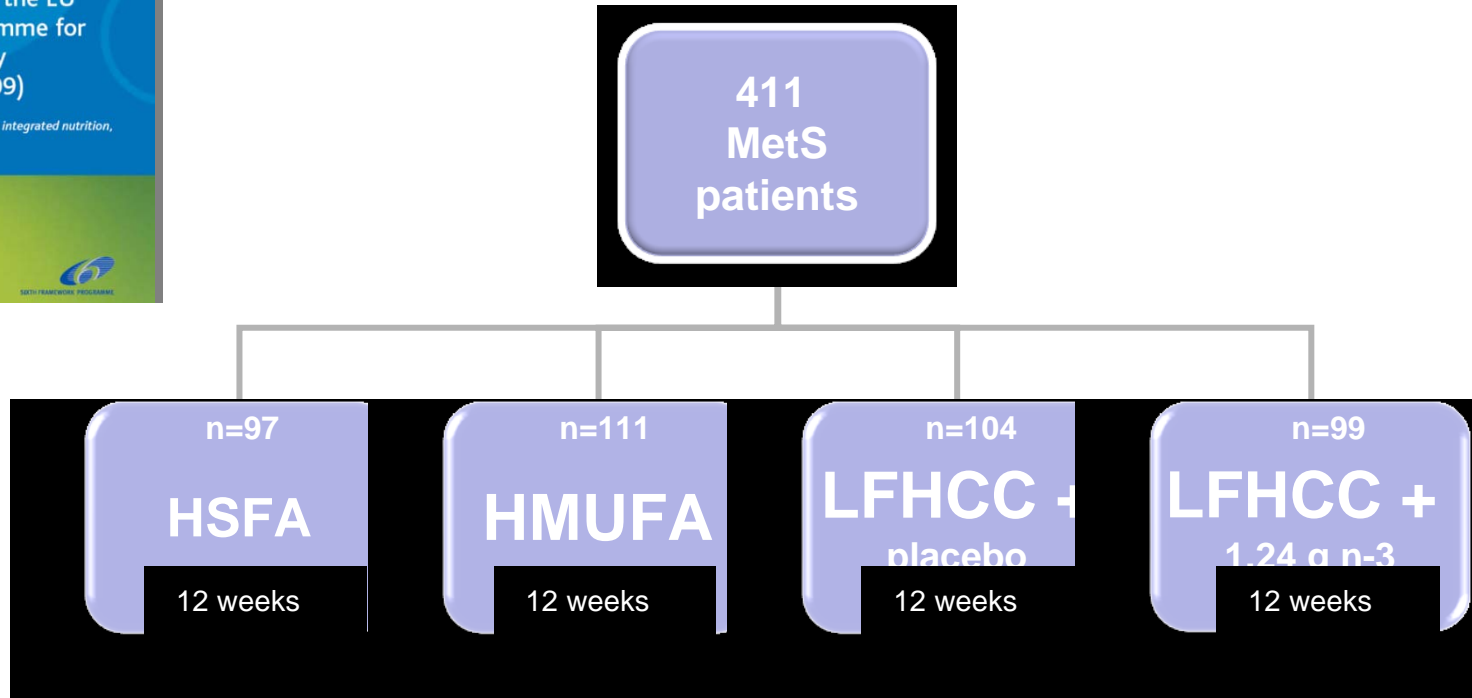
MF Gregor. J Lipid Res 2007; 48:1905





LIPGENE study

“Diet, genomics and the metabolic syndrome: an integrated nutrition, agro-food, social and economic analysis”



The composition of the diets was as follow:

- High-fat (38% energy), SFA-rich diet (16% SFA, 12 % MUFA 6% PUFA) (HSFA).
- High-fat (38% energy), MUFA-rich diet (8% SFA, 20% MUFA, 6% PUFA) (HMUFA).
- Low-fat (28% energy), high-complex carbohydrate diet (8% SFA, 11%; MUFA; 6% PUFA), with 1g/d high oleic sunflower oil (placebo) (LFHCC)
- Low-fat (28% energy), high-complex carbohydrate diet (8% SFA, 11% MUFA; 6% PUFA), with 1.24 g/d supplement of EPA and DHA (ratio 1.4:1) (LFHCC n-3).

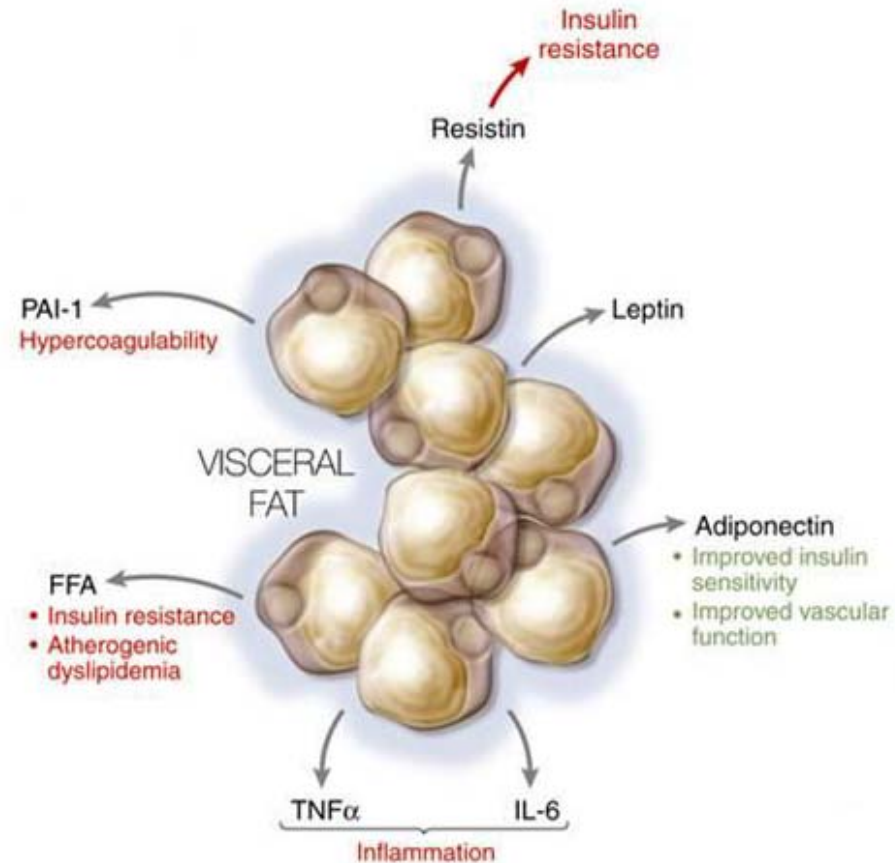
Mecanismos de la disfunción adipocitaria que favorecen la resistencia a la insulina

-Estrés Oxidativo

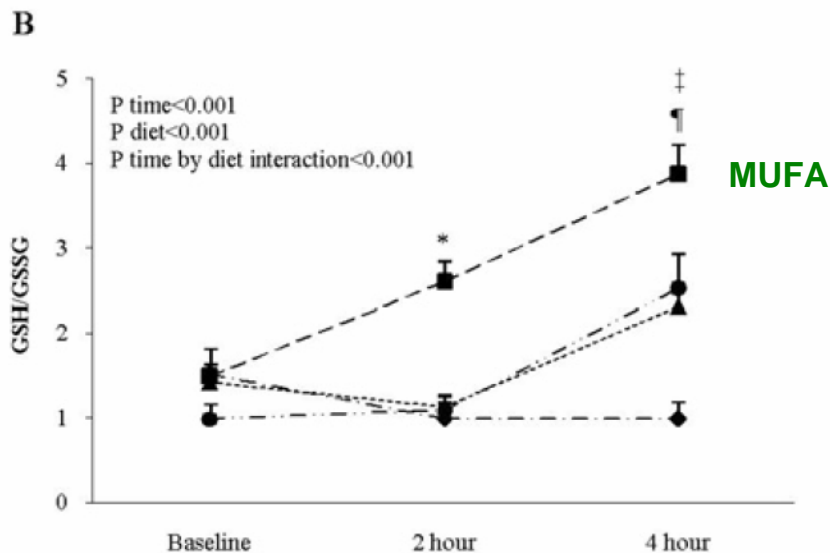
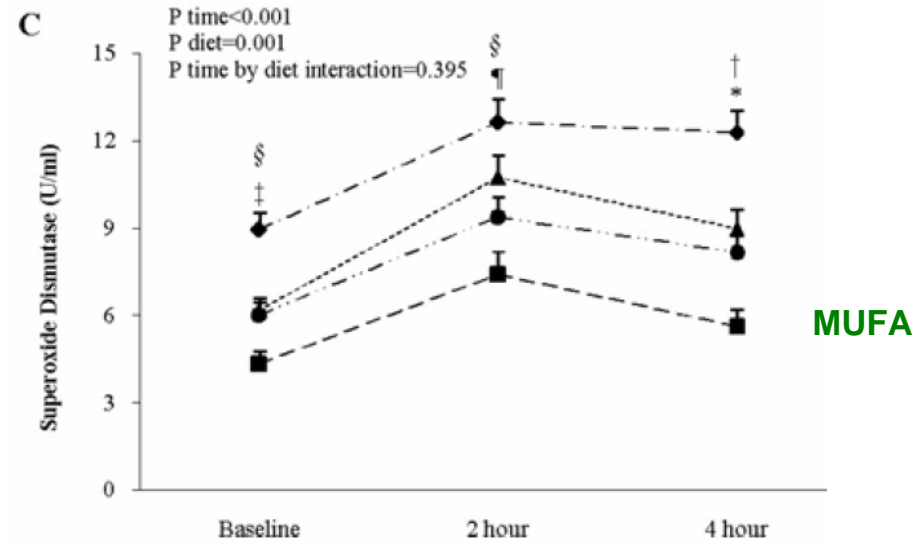
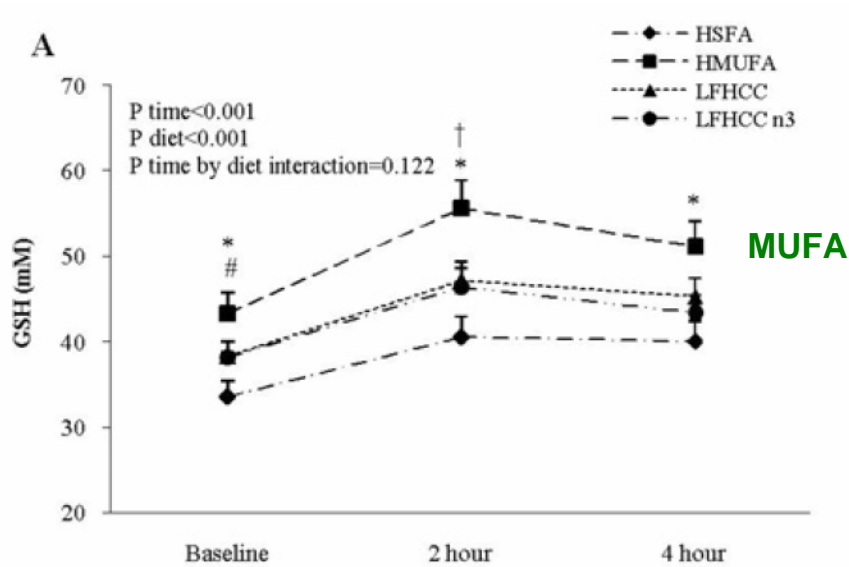
-Producción de citocinas

-Inflamación

-Ambiente protrombótico



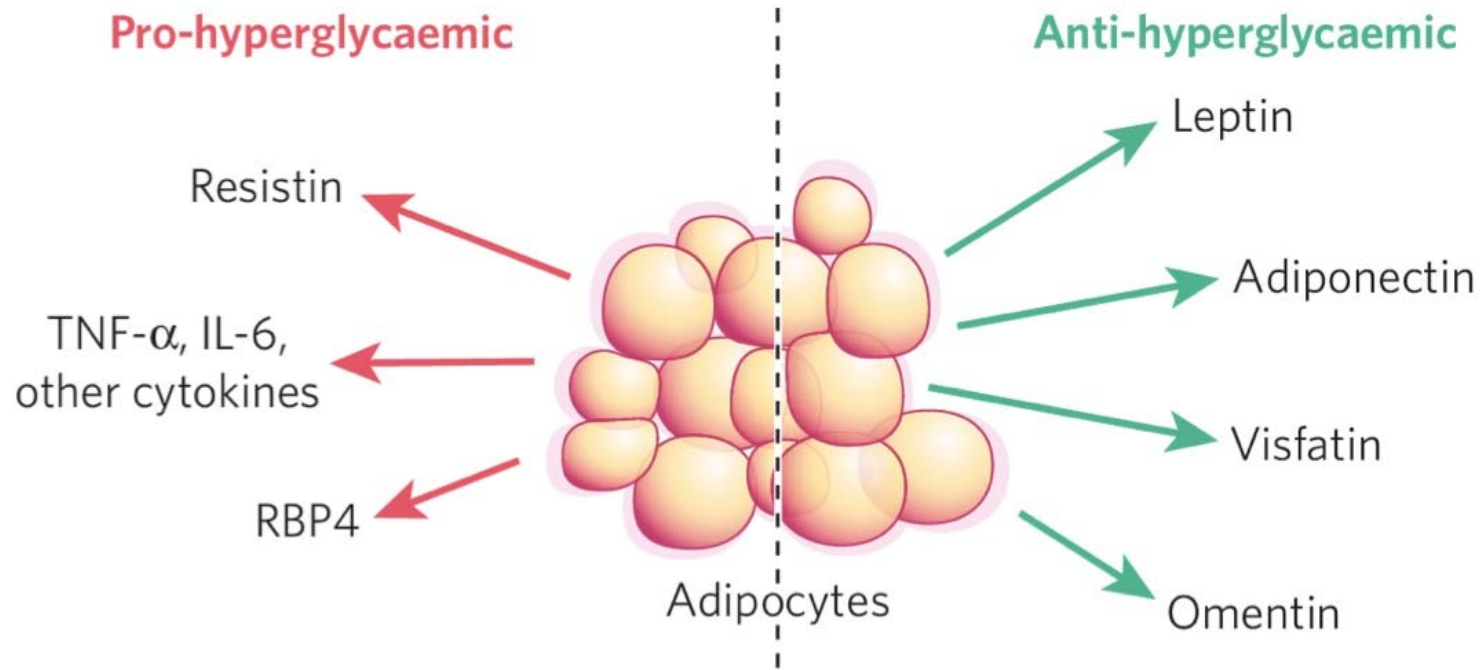
Estrés Oxidativo con diferentes dietas, en pacientes con Síndrome Metabólico



Perez-Martinez et al . Clin Sci 2010;119

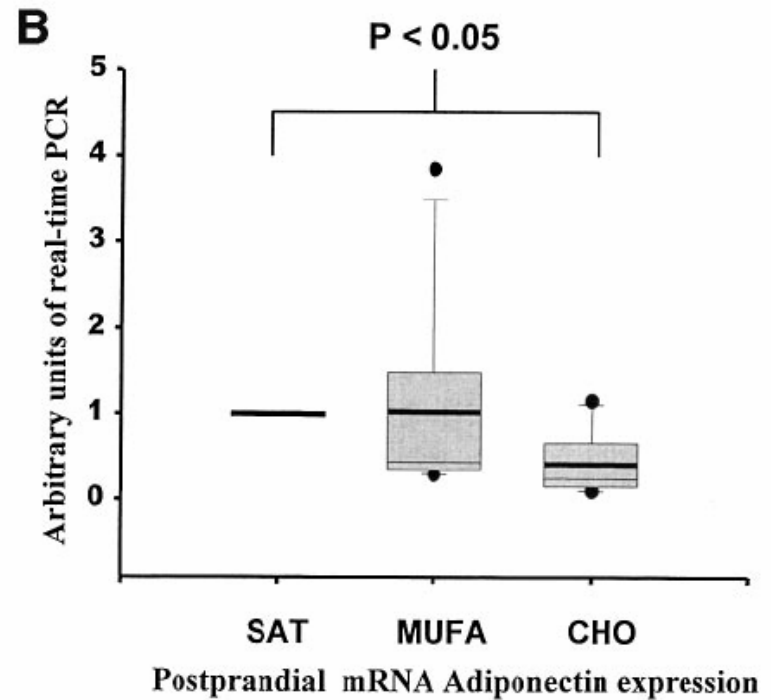
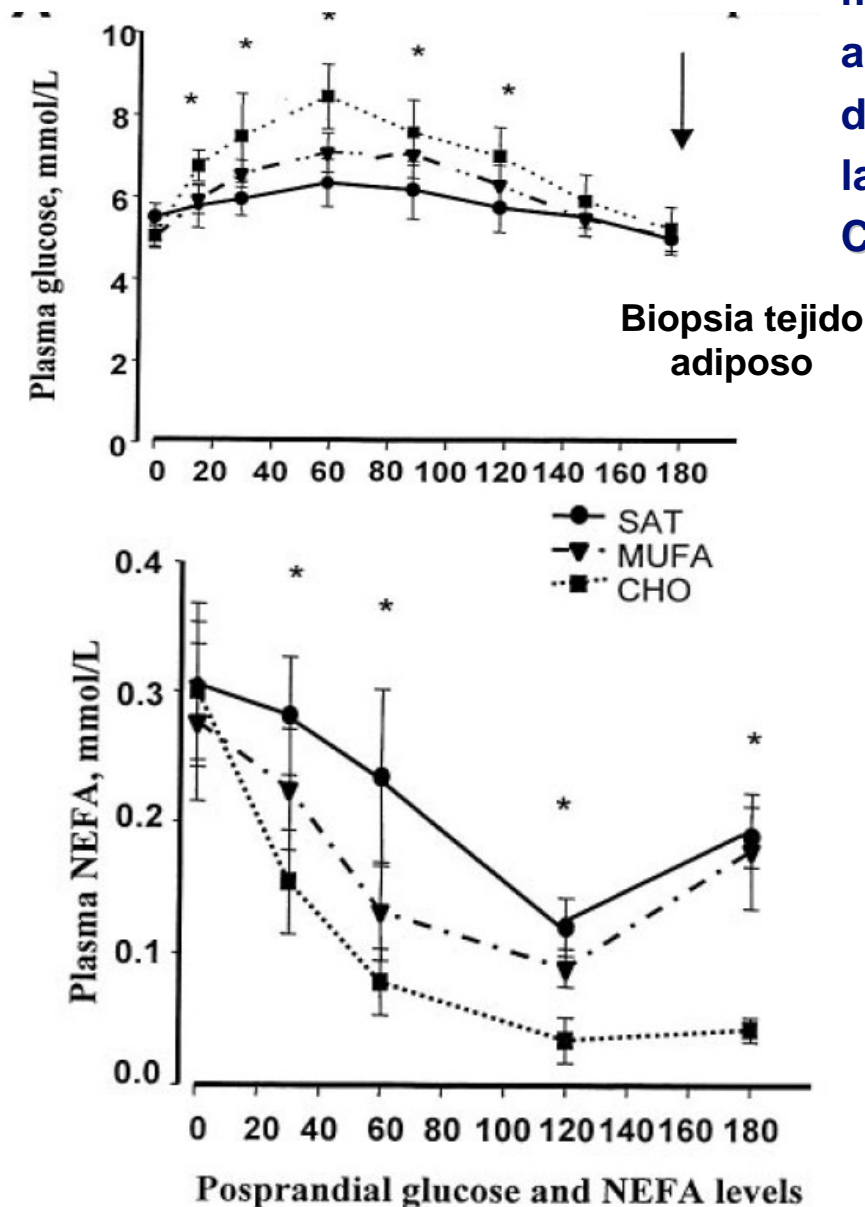
Se demuestra que la dieta rica en MUFA mejora el estrés oxidativo postprandial medido por los niveles de glutatión reducido (GSH) y oxidado (Disulfuro de glutatión: GSSG), así como el cociente GSH/GSSG.

E Rosen. Nature 2006. 444: 847. Mecanismos que relacionan el adipocito con la resistencia a la insulina

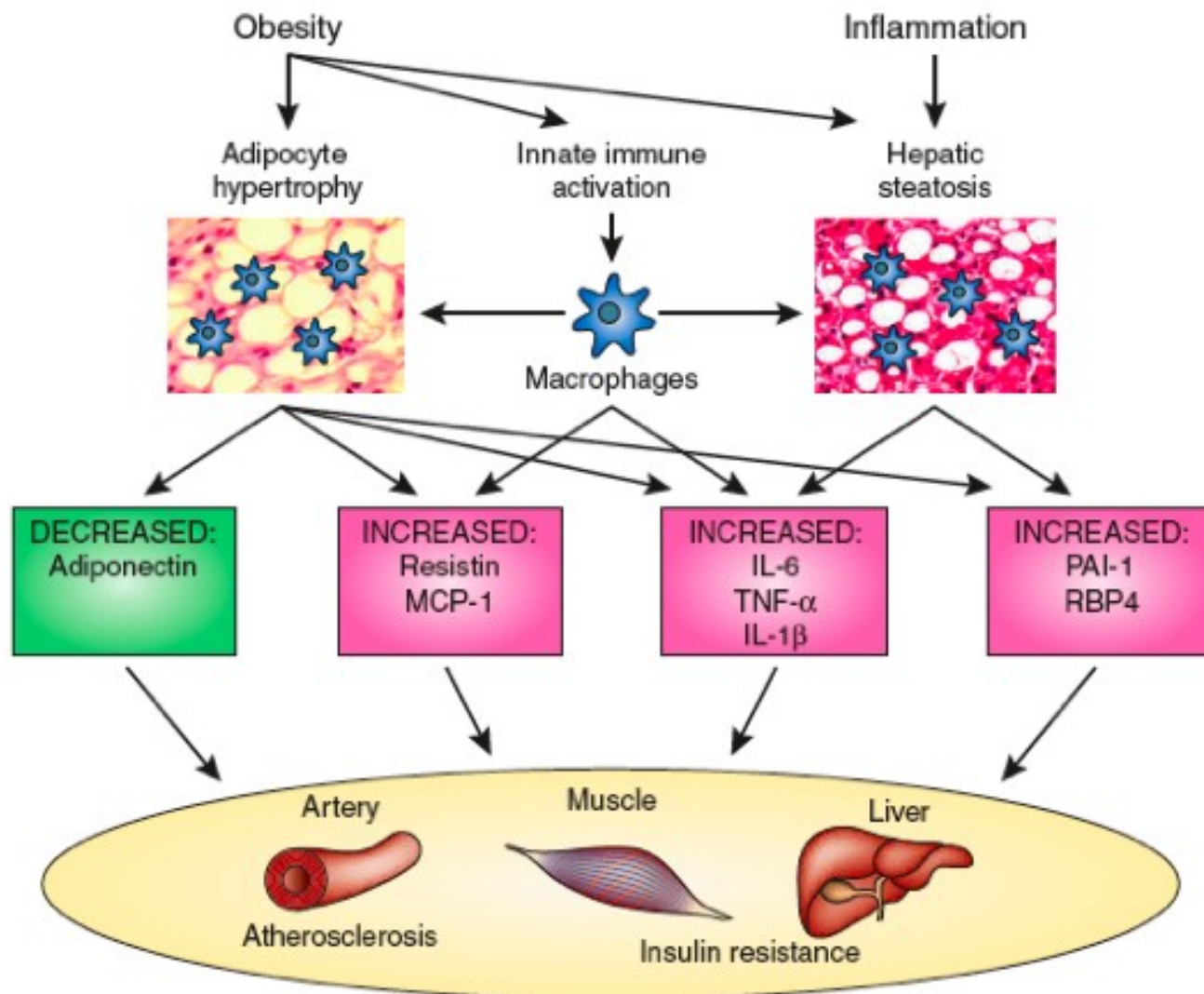


Los adipocitos secretan múltiples proteínas implicadas en el metabolismo de la glucosa, con acción antidiabética o amentando la resistencia a la insulina

La respuesta postprandial de glucosa y ácidos grasos libres, a tres desayunos diferentes, muestra que con el desayuno rico en HHCC aumentó la glucosa y los AGL, produciendo un descenso de Adiponectina del tejido adiposo a las 4 horas de la ingesta. Paniagua et al. Diabetes Care 2007; 30:1717

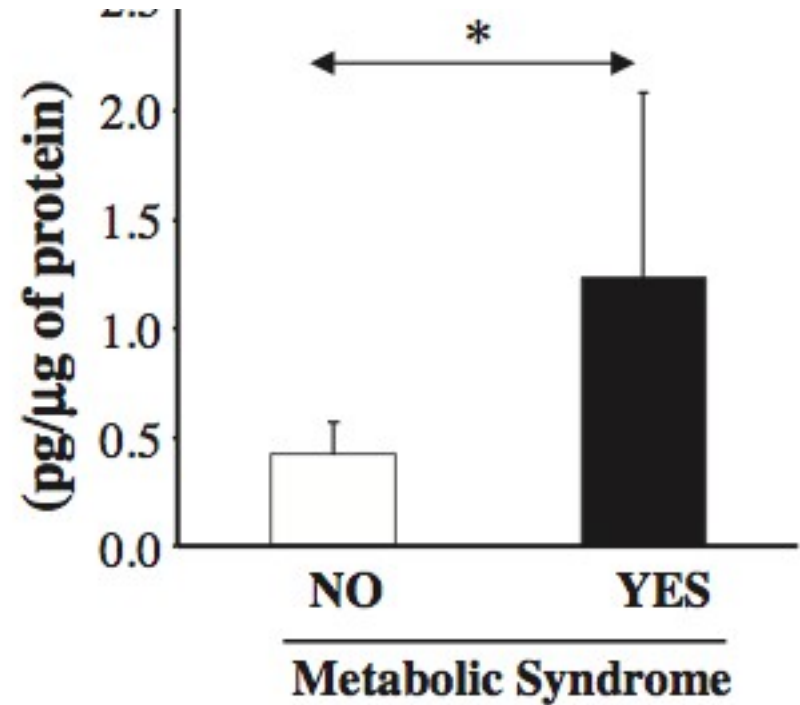
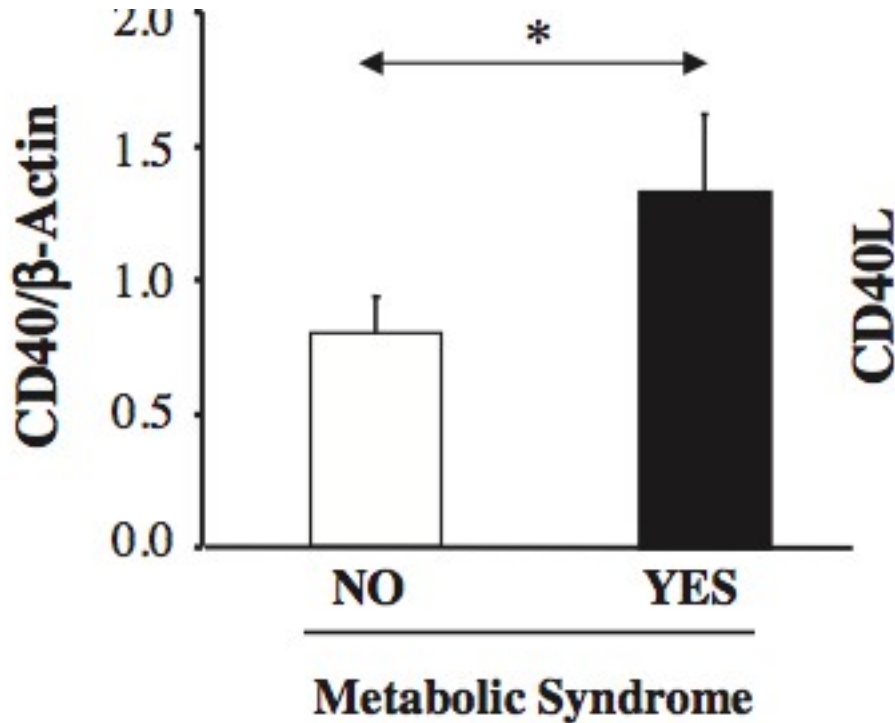


Inflamación en la disfunción adipocitaria y su papel en la resistencia a la insulina

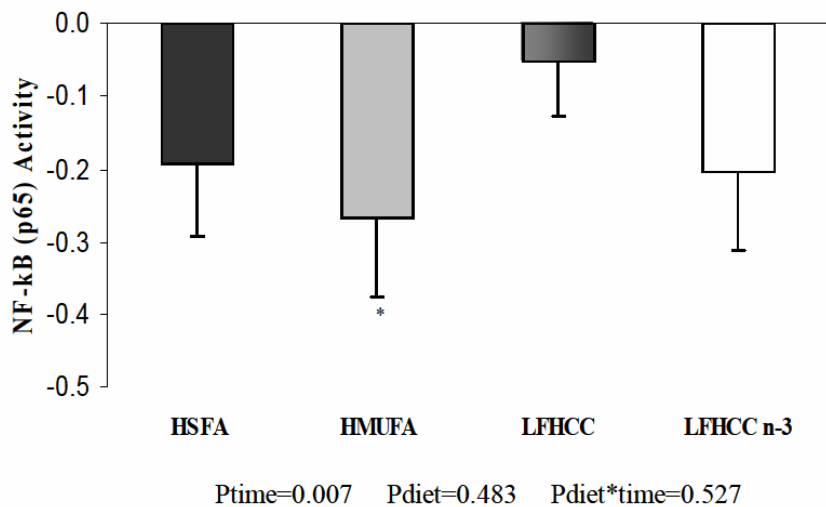


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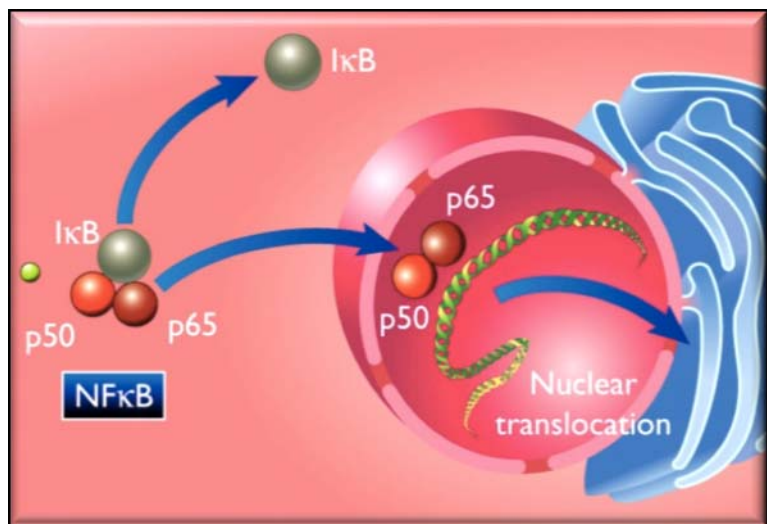
CD40 y CD40 ligando están elevados en pacientes con SM, en células mononucleares periféricas. C Natal. J Clin Endocrinol Metab 2008; 93: 2319



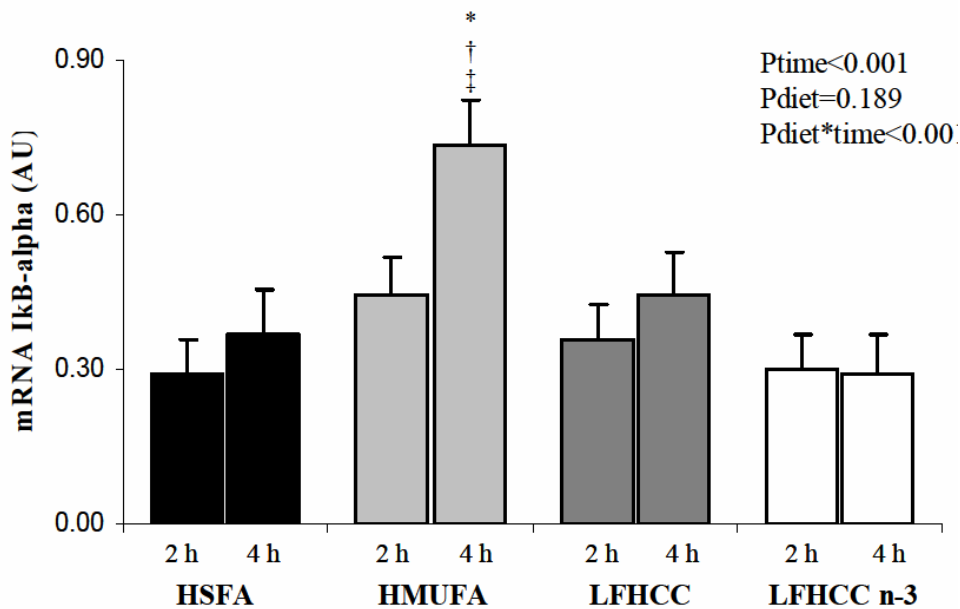
High monounsaturated fatty acids diet improves the postprandial inflammatory state in subjects with Metabolic Syndrome



The long-term consumption of HMUFA diet attenuated the postprandial inflammatory state associated with MetS.



A



Cruz-Teno et al . submitted 2010

Gene expression changes in mononuclear cells in patients with metabolic syndrome after acute intake of phenol-rich virgin olive oil

Camargo A. et al. BMC Genomics. 2010 Apr 20;11(1):253

Two virgin olive oil-based breakfasts: high (398 ppm) vs low (70 ppm) content of phenolic compounds

Postprandial gene expression microarray analysis was performed on peripheral blood mononuclear cells at the postprandial period

Se identificaron 98 genes expresados diferencialmente (79 subexpresados y 19 sobreexpresados).

Los compuestos fenólicos indujeron una respuesta inhibitoria concertada en distintos Genes implicados en el proceso inflamatorio, mediados por NF- κ B, cytokines, mitogen-activated protein kinases MAPKs or arachidonic acid pathways

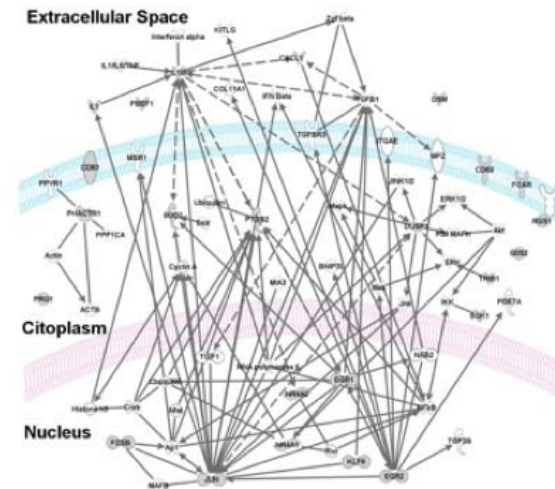
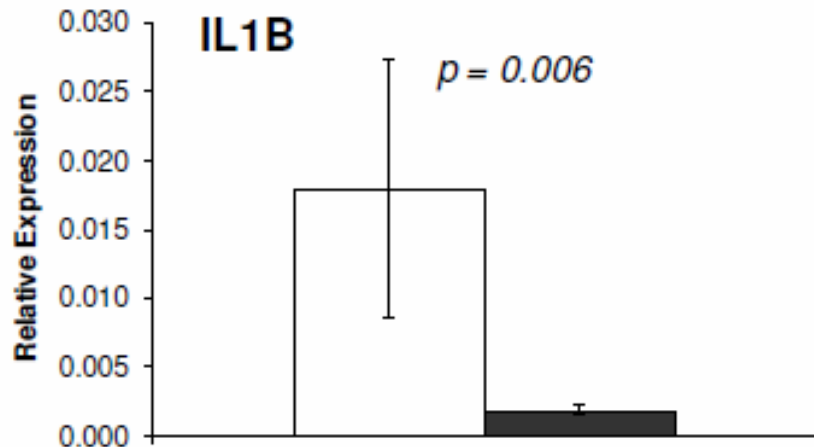
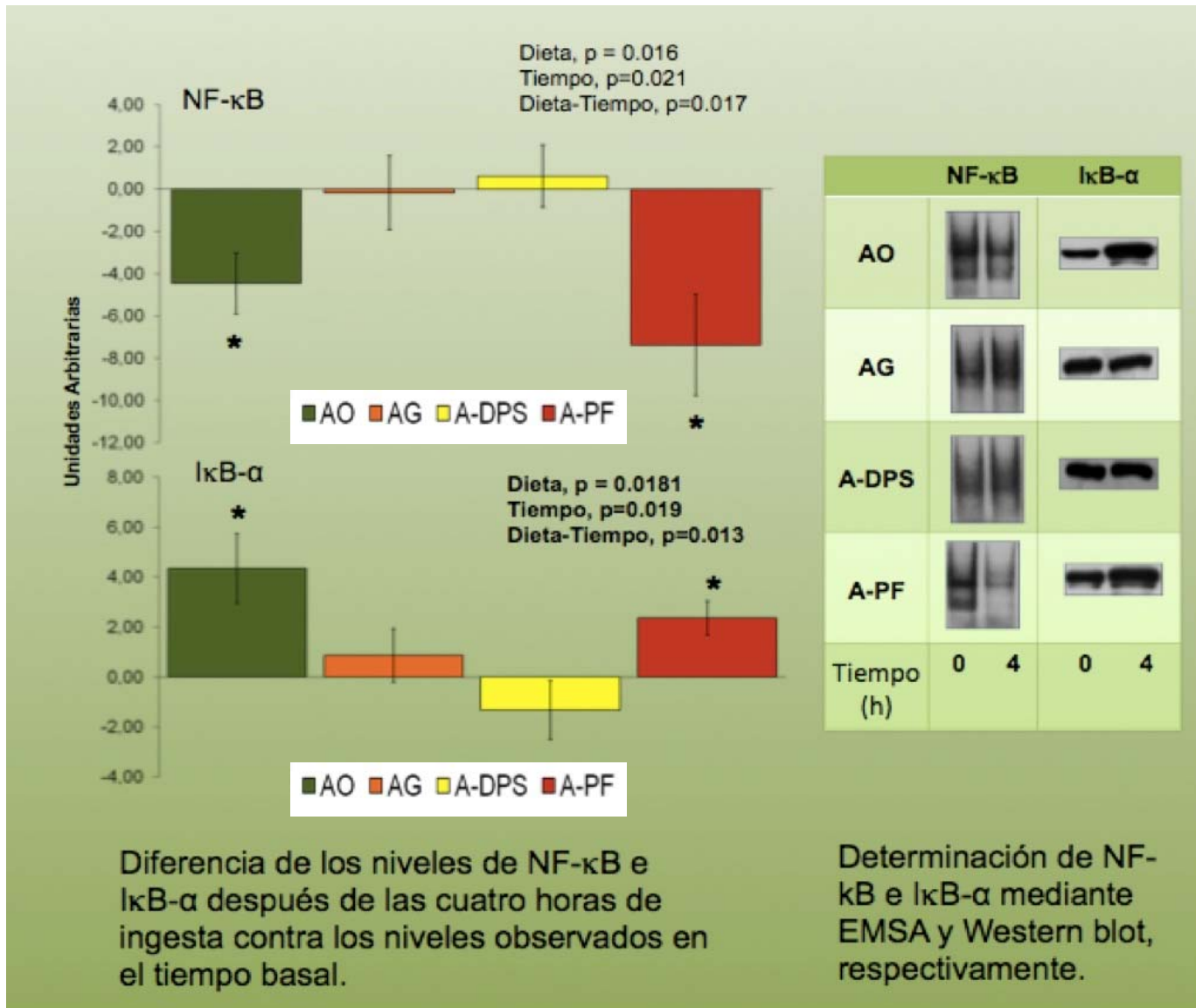


Figure 2 . Ingenuity Pathway Analysis Network.

Intake of virgin olive oil rich in phenol compounds is able to repress the in vivo expression of several pro-inflammatory genes, thereby switching the activity to a less deleterious inflammatory profile.

Un alimento diseñado para reducir la respuesta inflamatoria reproduce el efecto de un alimento natural



Monounsaturated Fat-Rich Diet Prevents Central Body Fat Distribution in Insulin-Resistant Subjects

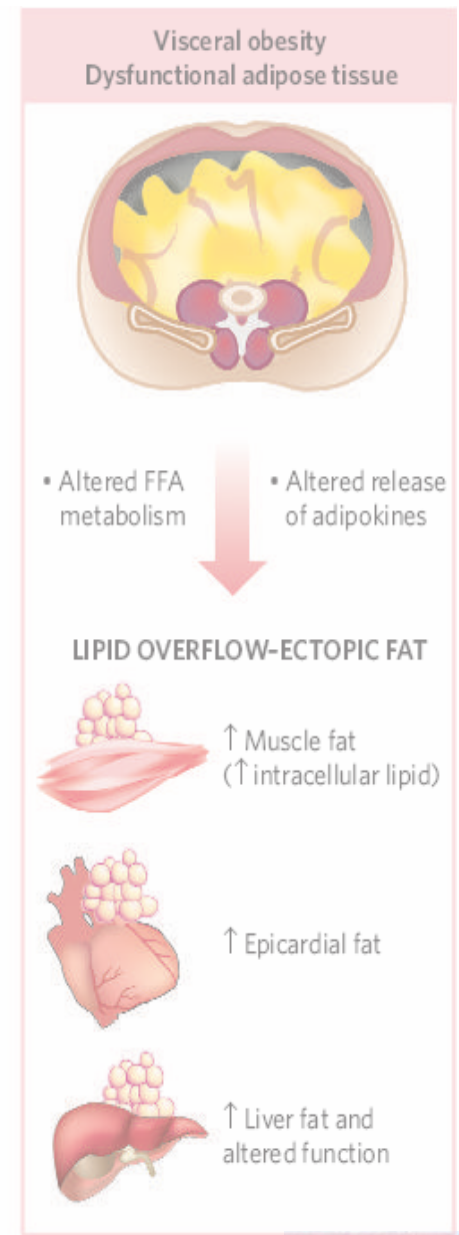
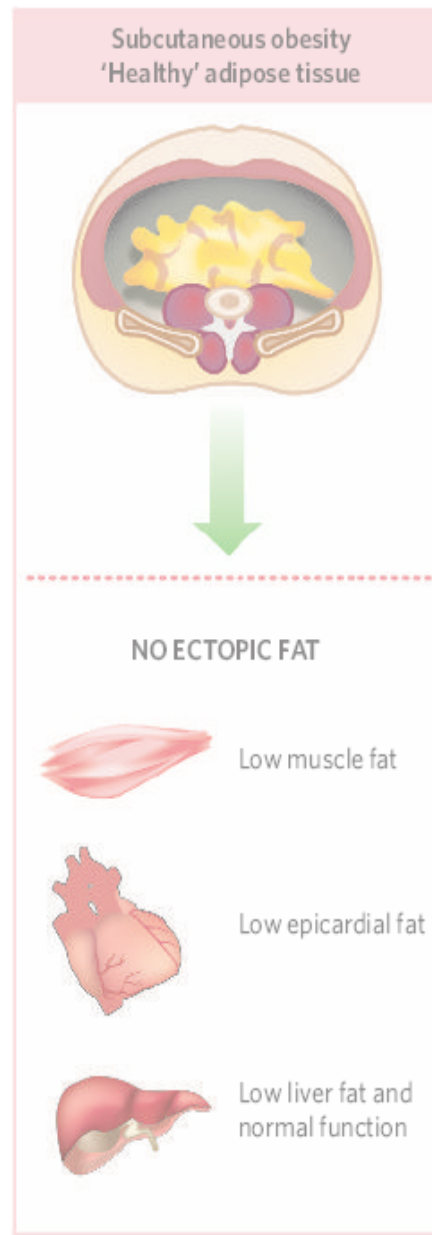
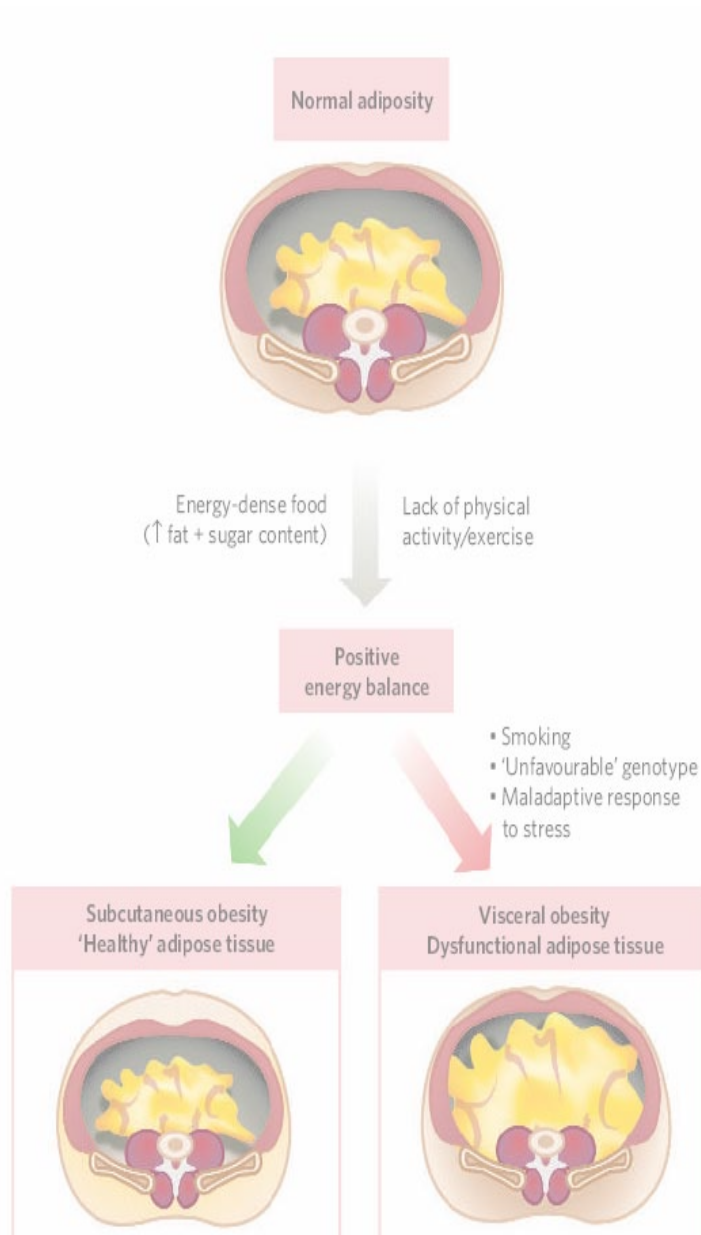
Table 1—Composition and body fat distribution after three dietary interventions in insulin-resistant subjects

	Baseline	High-SAT diet	High-MUFA diet	High-CHO diet	P value
Energy expenditure (kJ/min)	5.36 ± 0.40	5.49 ± 3.90	5.23 ± 0.37	5.02 ± 0.36	0.30
Anthropometry					
Weight (kg)	84.4 ± 5.7	83.2 ± 5.7	83.6 ± 5.8	81.8 ± 6.03	0.3
Total body fat (kg)	36.8 ± 4.1	35.0 ± 4.0	35.6 ± 4.0	34.9 ± 4.3	0.1
Lean body mass (kg)	47.5 ± 2.5	48.1 ± 2.5	48.9 ± 2.6	46.8 ± 2.1	0.2
Waist-to-hip ratio	0.99 ± 0.01	0.99 ± 0.01	0.98 ± 0.01	0.98 ± 0.01	0.9
DEXA analysis					
Total body trunk (g)	—	37,101 ± 2.026	38,154 ± 1,911	39,134 ± 2,104	0.3
Fatty body trunk (g)	—	14,313 ± 1.362	14,842 ± 1,437	16,459 ± 1,653	<0.05
Total body limb (g)	—	36,420 ± 3.886	36,239 ± 3,862	32,887 ± 3,825	0.7
Fat in arm (g)	—	7,097 ± 1.528	7,652 ± 1,339	7,225 ± 1,830	0.4
Fat in leg (g)	—	8,517 ± 1.588	8,036 ± 1,398	7,358 ± 1,253	<0.05
Fat trunk-to-fat leg ratio	—	1.9 ± 0.3	2.1 ± 0.2	2.50 ± 0.2	<0.05

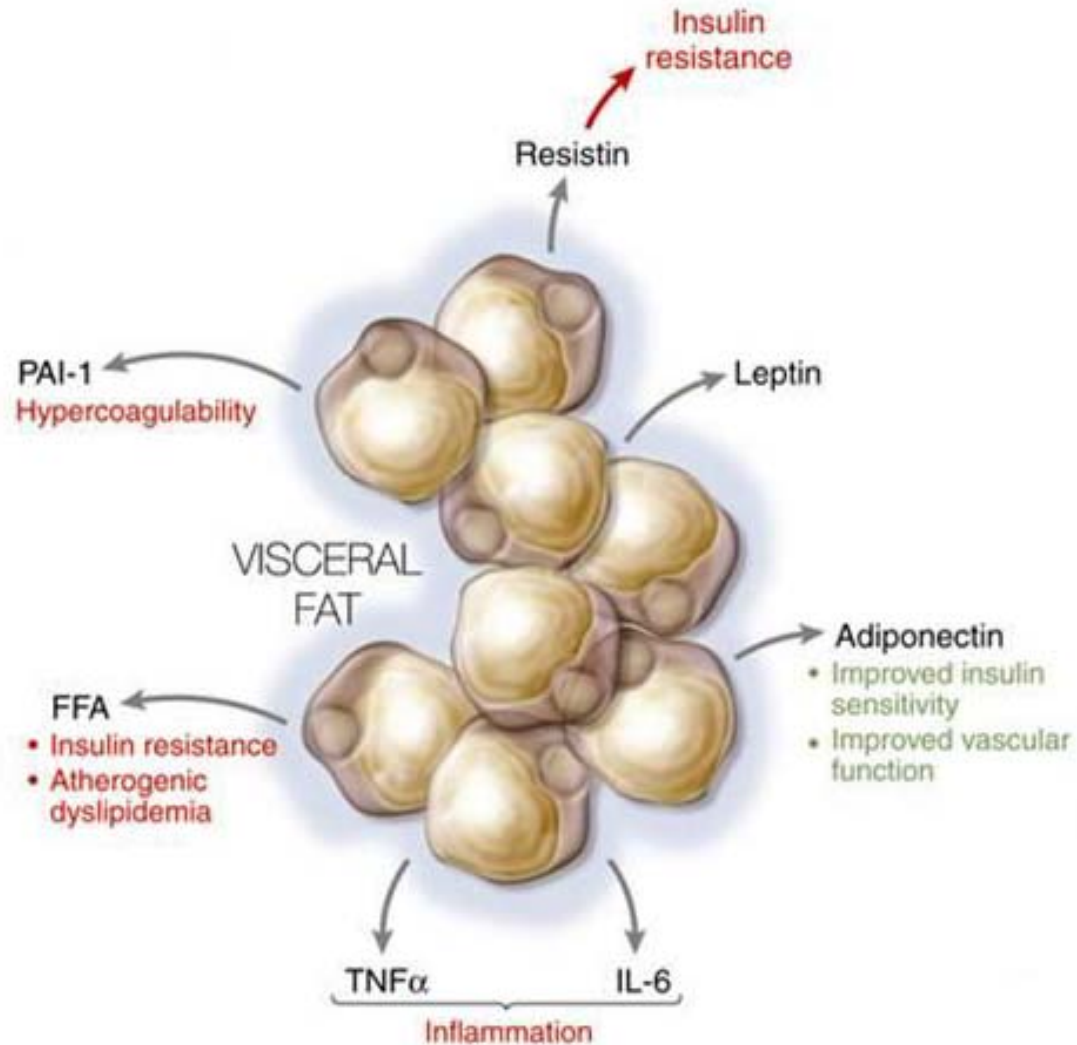
Data are means ± SEM. P value determined by ANOVA for repeated variables.

Weight, body composition, and resting energy expenditure remained unchanged during the three sequential dietary periods. Using DEXA we observed that when patients were fed a CHO-enriched diet, their fat mass was redistributed toward the abdominal depot, whereas periphery fat accumulation decreased compared with isocaloric MUFA-rich and high-SAT diets

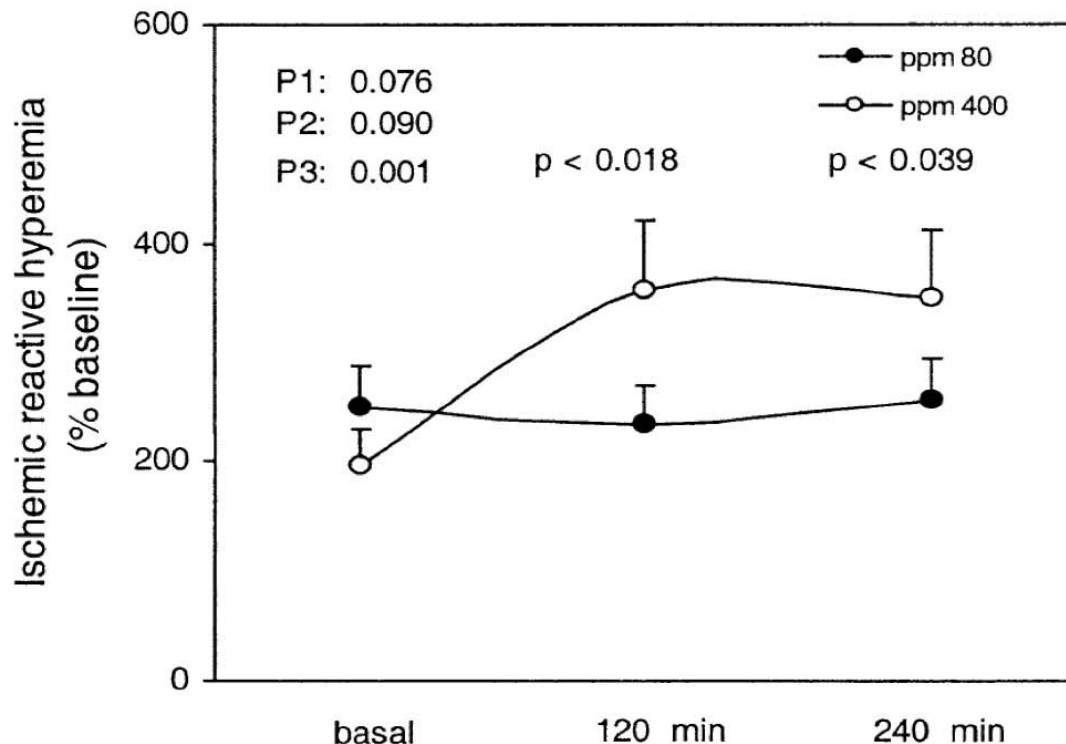
Paniagua JA et al. *Diabetes Care*, 2007; 30:1717-20.



Estado Protrombótico en la disfunción adipocitaria



La ingesta de un aceite rico en antioxidantes mejora el flujo vascular. el estrés oxidativo y la biodisponibilidad de NO . Ruano J., Am J Coll Cardiol 2005: 46: 1864

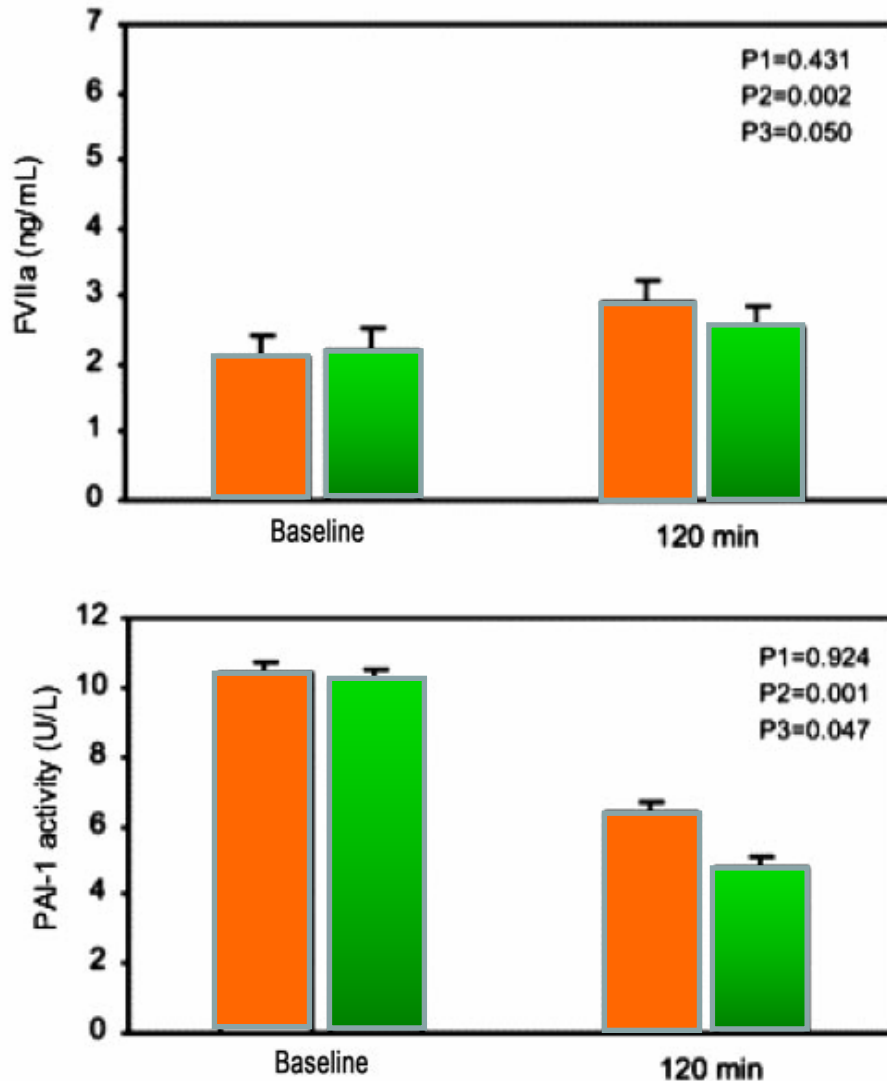


Variables	Oils	Time		p Value
		0 min	120 min	
NO _(x) (μmol·l ⁻¹)	80 ppm	25.4 ± 4.9	26.4 ± 4.1	<0.001
	400 ppm	26.3 ± 4.5	32.9 ± 4.6	
LPO (μg·ml ⁻¹)	80 ppm	0.4 ± 0.5	3.2 ± 2.4	<0.005
	400 ppm	0.7 ± 0.7	2.3 ± 2.1	
8-epi-F _{2α} (ng·ml ⁻¹)	80 ppm	3.6 ± 0.7	4.5 ± 0.6	<0.001
	400 ppm	4.6 ± 0.7	3.2 ± 0.6	

Analysis of variance for repeated samples.

LPO = lipoperoxides; NO_(x) = nitrates/nitrites; 8-epi-F_{2α} = 8-epi prostaglandin-F_{2α}.

The Intake of phenol-rich virgin olive oil improves the postprandial prothrombotic profile in hypercholesterolemic patients



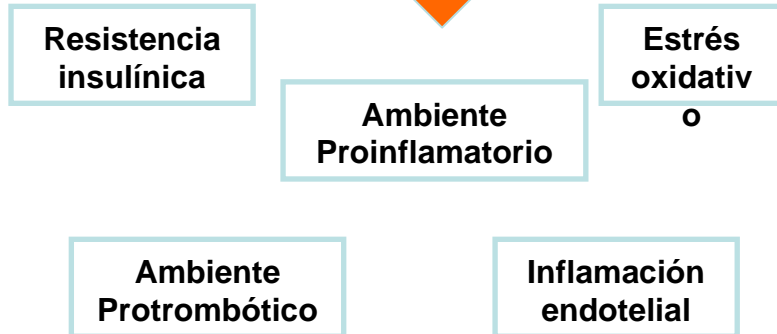
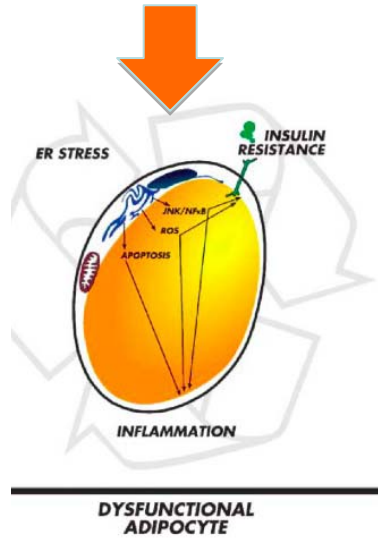
There was a smaller increase in FVIIa activated after the ingestion of an olive oil with a high content of phenols than after the olive oil with a low content of these compounds.

PAI-1 activity showed a greater postprandial decrease after the intake of the olive oil with high phenolic content, whereas it correlated negatively with fasting adiponectin concentrations and positively with HOMA-IR

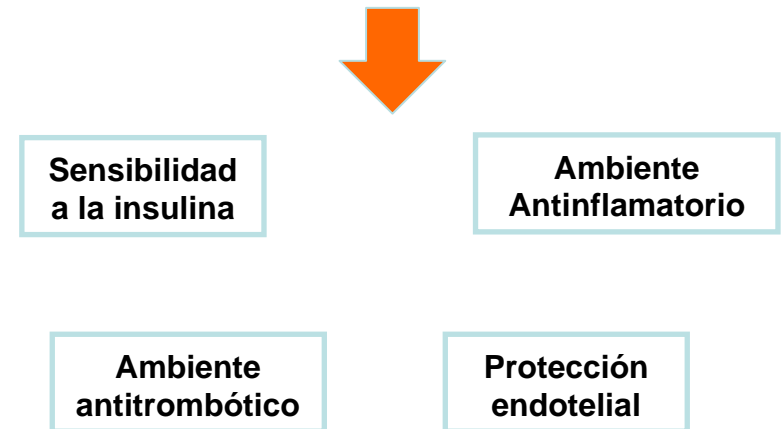
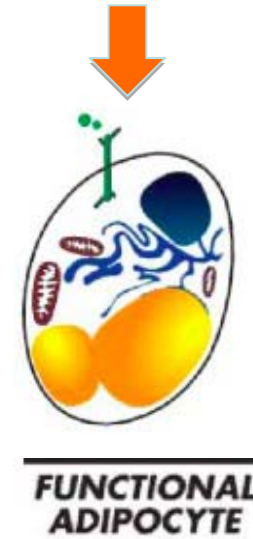
FIGURE 2. Mean (\pm SD) acute effect on postprandial plasma factor VII antigen (FVIIa), activated factor VII (FVIIa), and plasminogen activator inhibitor-1 (PAI-1) activity after the ingestion of a phenol-rich olive oil breakfast (400 ppm) or a low-phenol olive oil breakfast (80 ppm). P1: diet effect; P2: time effect; P3: diet \times time interaction. ANOVA for repeated-measures. Baseline values were used as covariants.

Hipótesis: la calidad de la dieta modula la función adipocitaria

Aporte nutricional adipocitotóxico

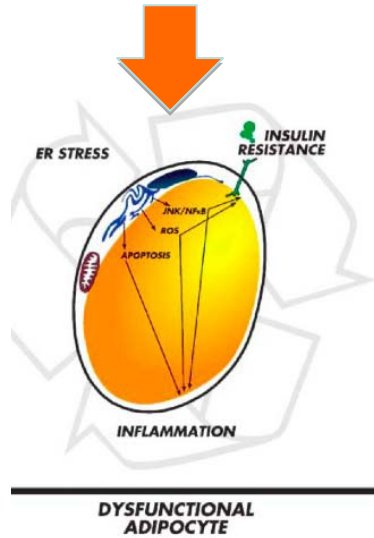


Aporte nutricional protector del adipocito



Hipótesis: la calidad de la dieta modula la función adipocitaria

Aporte nutricional adipocitotóxico



**Aclaramiento reducido
partículas postprandiales**

Resistencia
insulínica

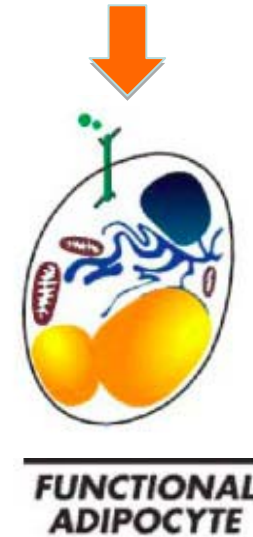
Ambiente
Proinflamatorio

Estrés
oxidativ
o

Ambiente
Protrombótico

Inflamación
endotelial

Aporte nutricional protector del adipocito



**Aclaramiento eficiente de
partículas postprandiales**

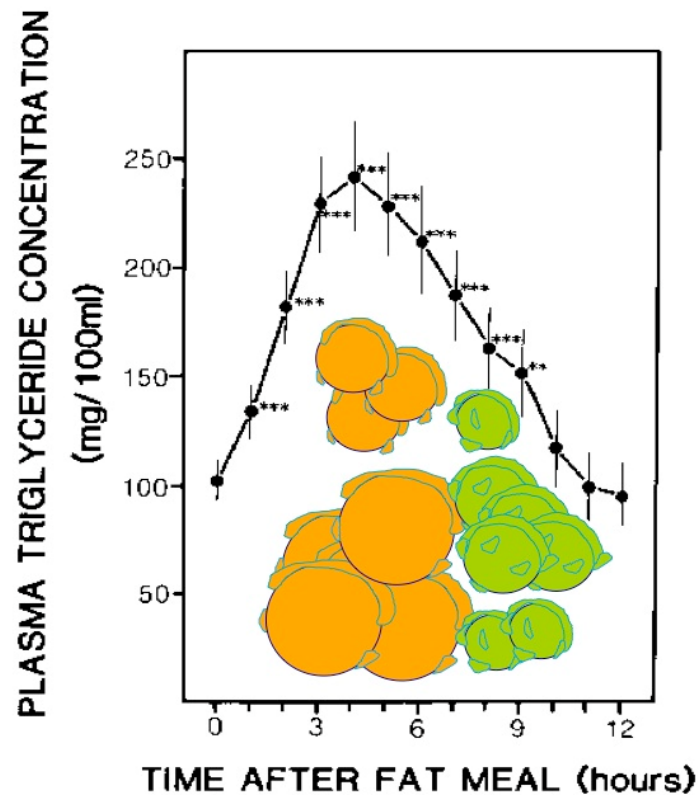
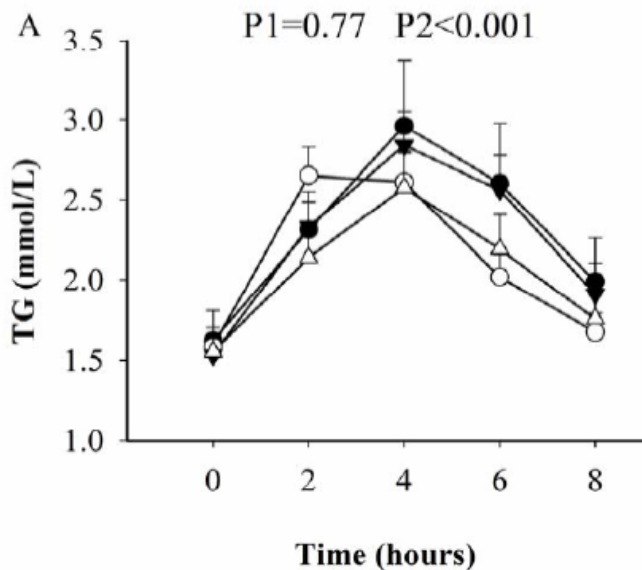
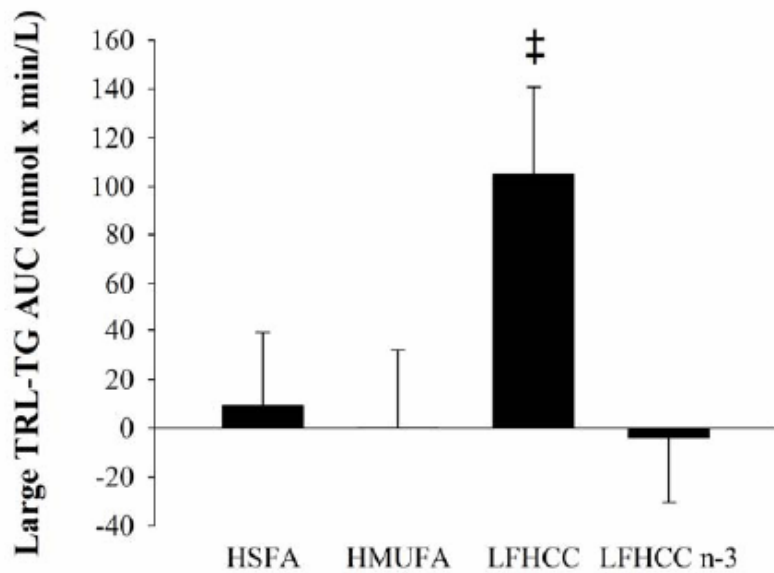
Sensibilidad
a la insulina

Ambiente
Antinflamatorio

Ambiente
antitrombótico

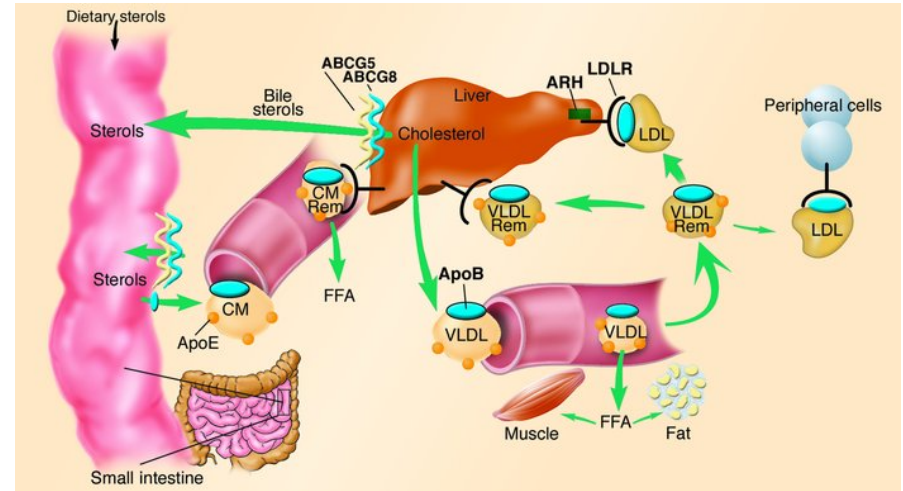
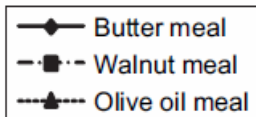
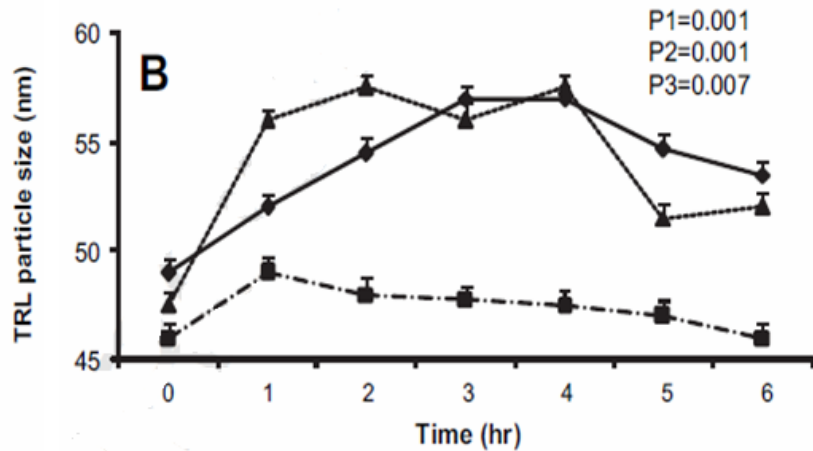
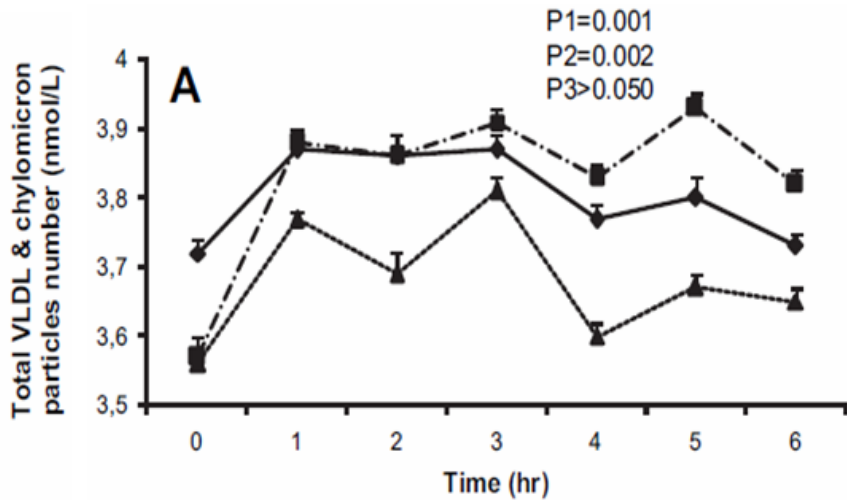
Protección
endotelial

Beneficial long-term effects of a low-fat, high complex carbohydrate diet supplemented with long-chain n-3 PUFA on postprandial lipoprotein metabolism in patients with MetS



Jimenez Y et al. J Nutrition 2010

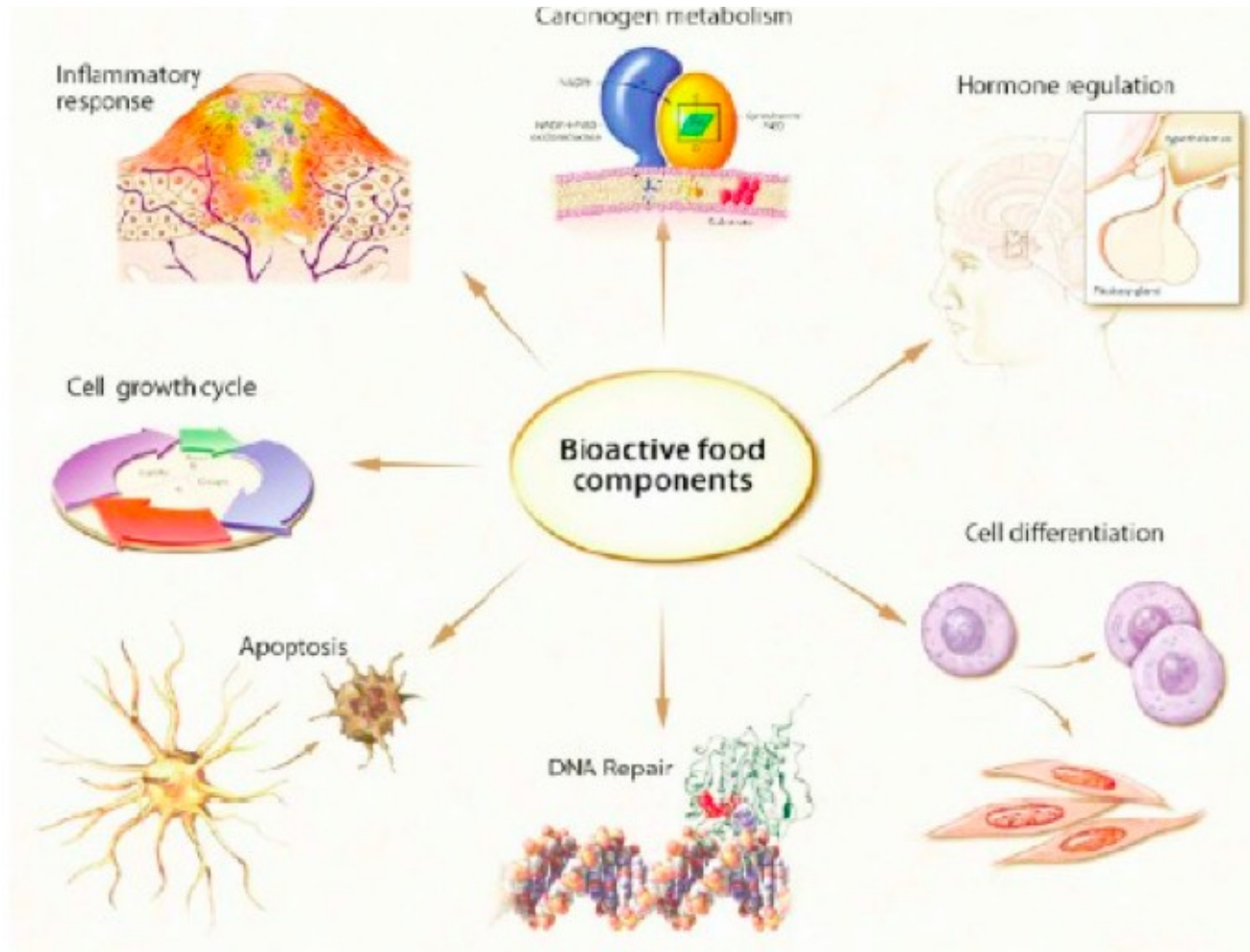
Consumo de dietas con diferente contenido graso influencia el tamaño y número de partículas ricas en triglicéridos durante el estado postprandial



Short-term intake of the Mediterranean diet and the acute intake of an olive oil meal lead to the formation of a reduced number and higher-size TRL particles compared with other fat sources.

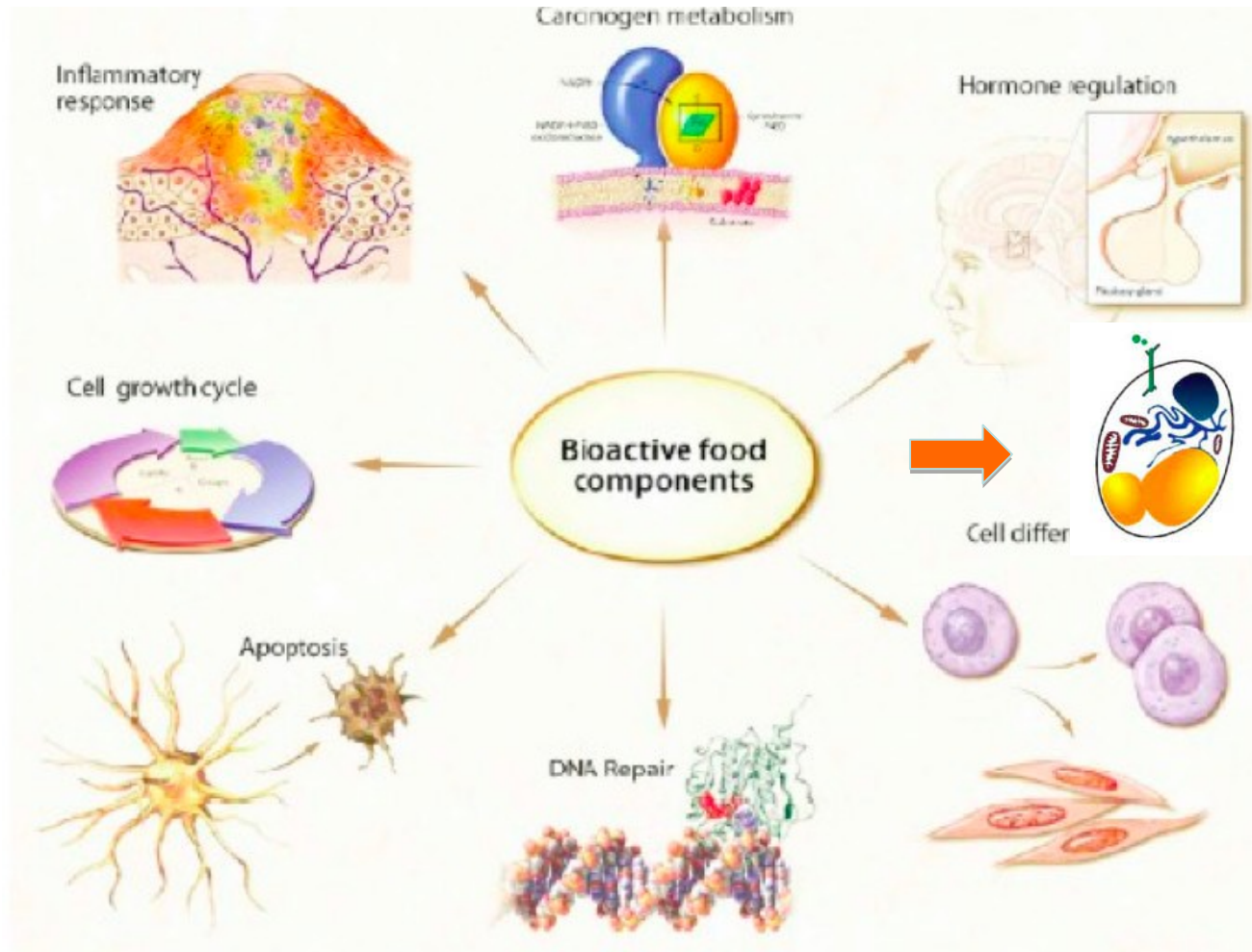
Perez-Martinez et al . Nutr Metab Cardiovasc Dis 2010

Un paradigma: biomodulación a través de la dieta



E Trujillo; J Am Diet As, 2006; 106: 403

Un paradigma: biomodulación a través de la dieta

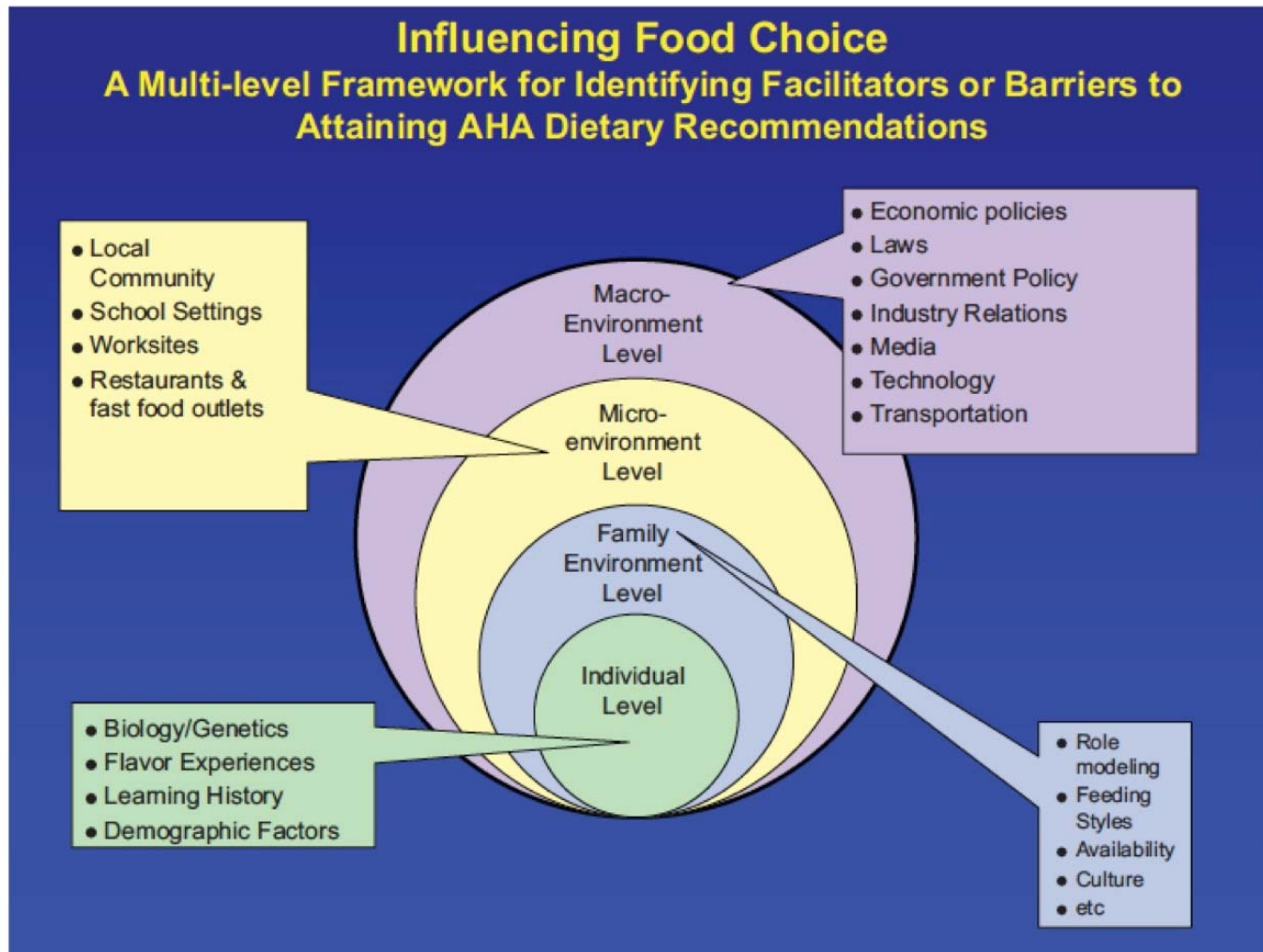


E Trujillo; J Am Diet As, 2006; 106: 403

Realidad de la práctica clínica

AHA Nutritional Guidelines: un complejo problema que es incompatible con abordajes simples

1162 *Circulation* March 3, 2009



CONSIDERACIONES PRÁCTICAS

1. El clínico, aparte de las políticas de salud pública, puede hacer un abordaje personal importante para sus pacientes.
2. El fracaso en modificar el peso con cambios en el aporte calórico podemos paliarlo si modificamos la calidad de la dieta.
3. Se podrá avanzar con dietas diseñadas, en las que se introduzcan cambios cualitativos basados en microcomponentes específicos.
4. Estaría por definir la potencialidad saludable de los cambios de modelos de dieta sobre eventos clínicos.

CordiPrev



ClinicalTrials.gov

A service of the U.S. National Institutes of Health

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[No Study Results Posted](#)

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CORonary Diet Intervention With Olive Oil and Cardiovascular PREvention (CORDIOPREV)

This study is currently recruiting participants.

Verified by Hospital Universitario Reina Sofia, September 2010

First Received: June 18, 2009 Last Updated: September 8, 2010 [History of Changes](#)

Sponsor:	Hospital Universitario Reina Sofia
Information provided by:	Hospital Universitario Reina Sofia
ClinicalTrials.gov Identifier:	NCT00924937

Diseño del estudio

- **Ensayo clínico randomizado, simple ciego y controlado**



- **5 años de duración**
- **Pacientes con enfermedad coronaria de alto riesgo**



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José López Miranda

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- Pilar Lora Aguilar predoctoral
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- Residentes Medicina Interna**

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