Dr. Jesus Rocca nacion
Endocrinólogo
2015

ENFERMEDAD HEPÁTICA GRASA ENFOQUE ACTUAL

Obesidad

↓

Resistencia a la Insulina

↓

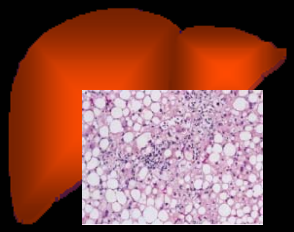
Sd. de Resistencia a la Insulina (Sd. Metabólico)

↓

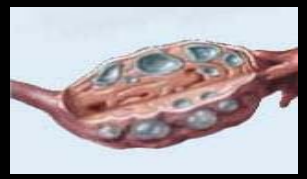
Prediabetes

↓

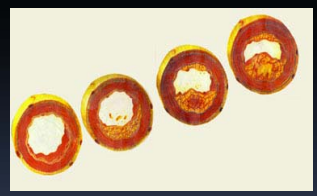
DM 2



Enfermedad Hepática Grasa

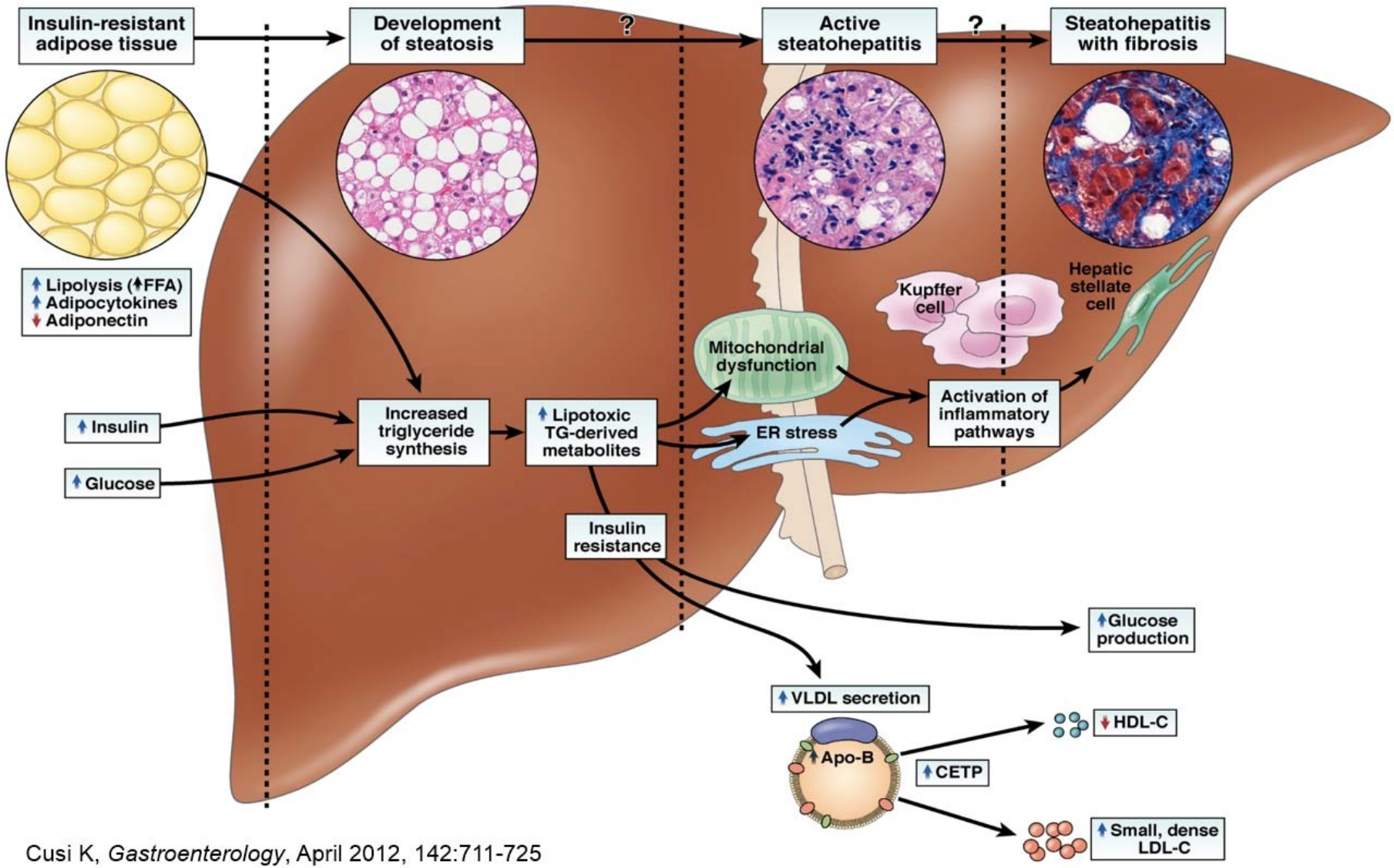


SOP



Aterosclerosis

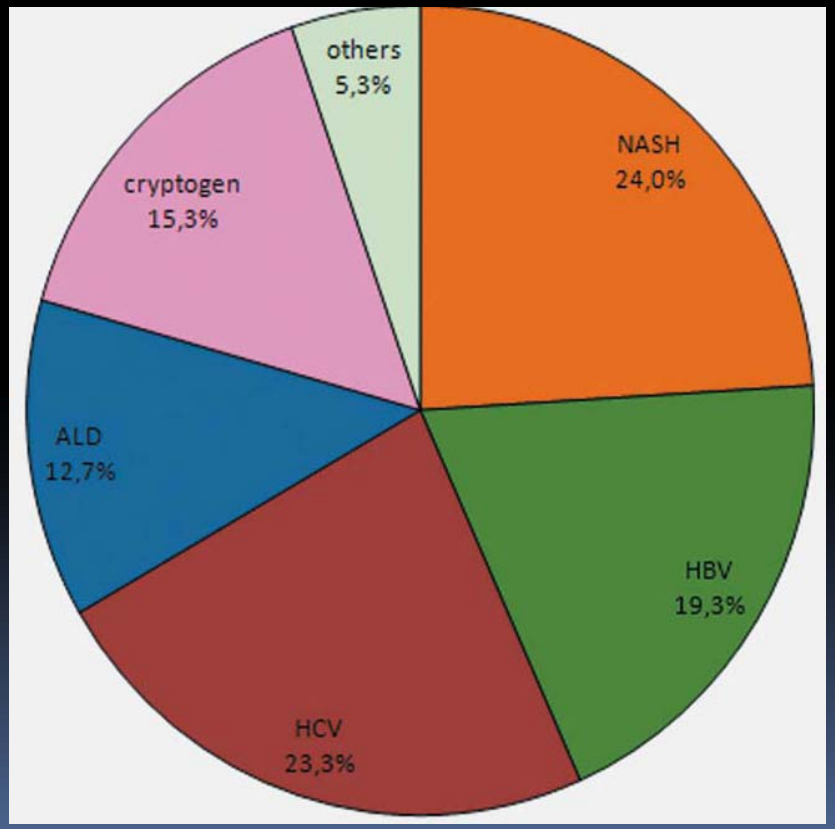
From Obesity/Lipotoxicity to NASH and Cirrhosis



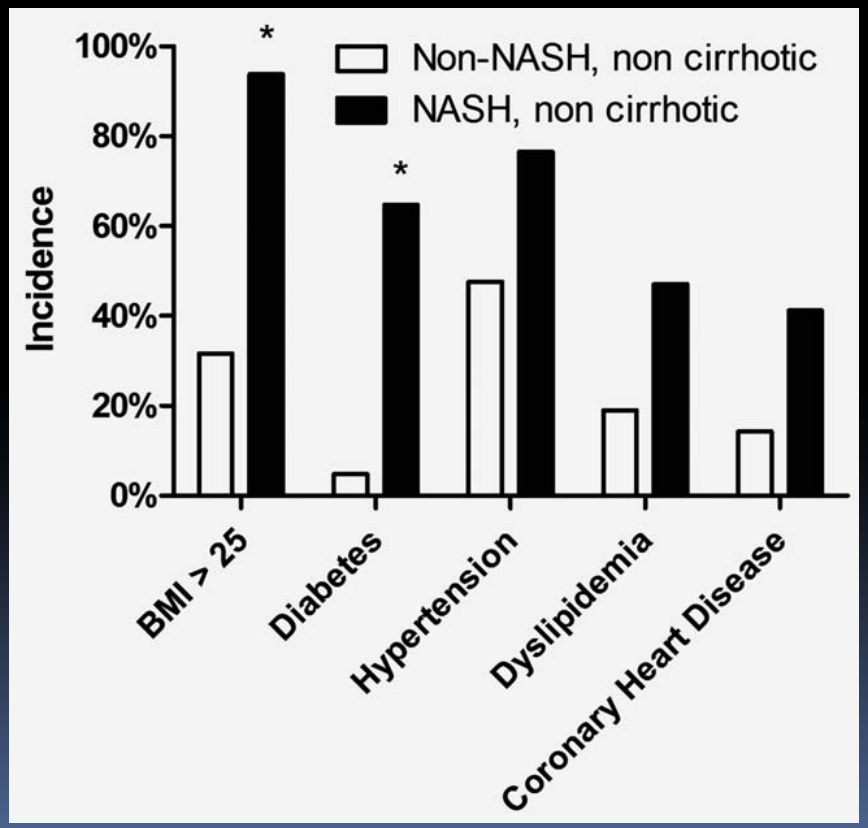
Cusi K, *Gastroenterology*, April 2012, 142:711-725

Cáncer Hepático y Enfermedad Hepática Grasa

Etiología del Carcinoma Hepatocelular

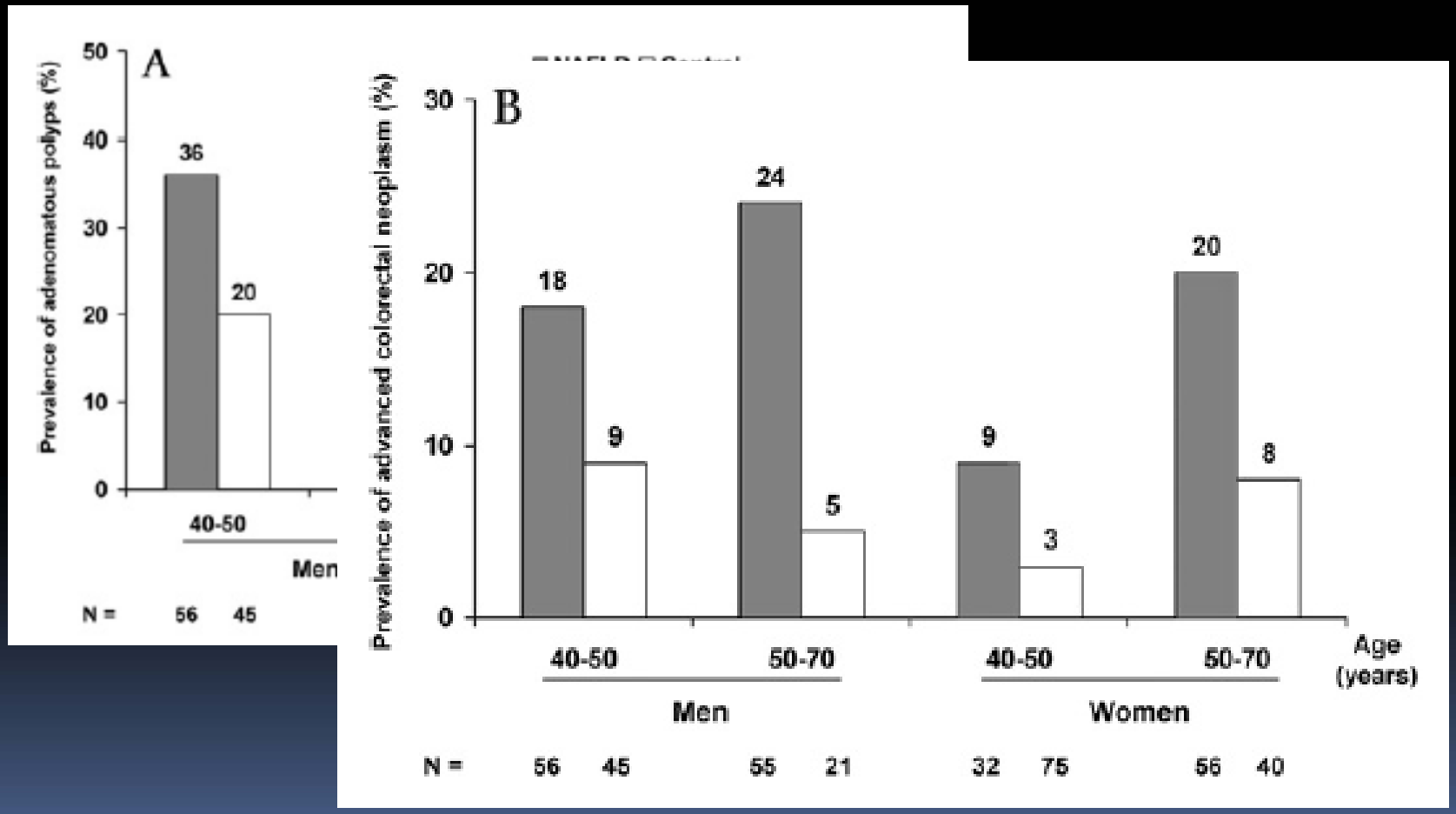


Incidencia de Sd. Metabólico con Carcinoma Hepatocelular No Cirrótico



Int. J. Cancer: 128, 2436–2443 (2011)

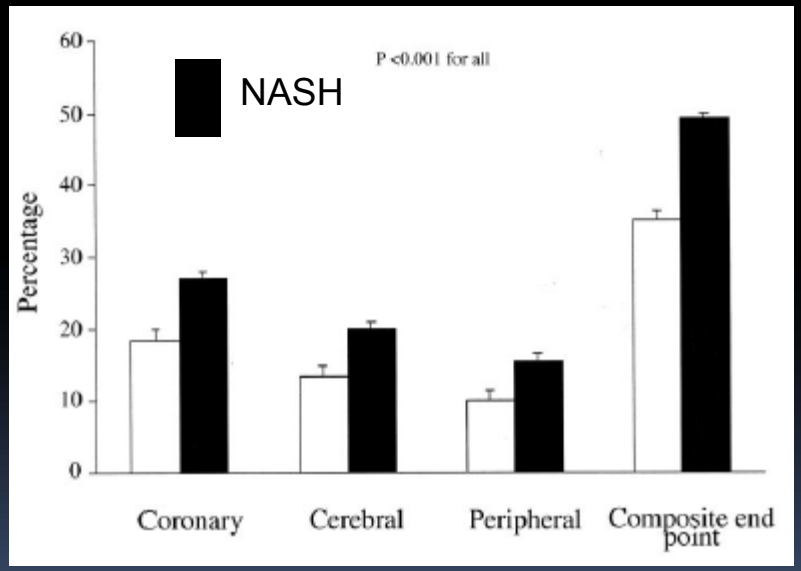
Alta Incidencia de Neoplasias Colorrectales en Pacientes con EHGNA



Wai Sun Wong. Gut, 60, 829, 2011

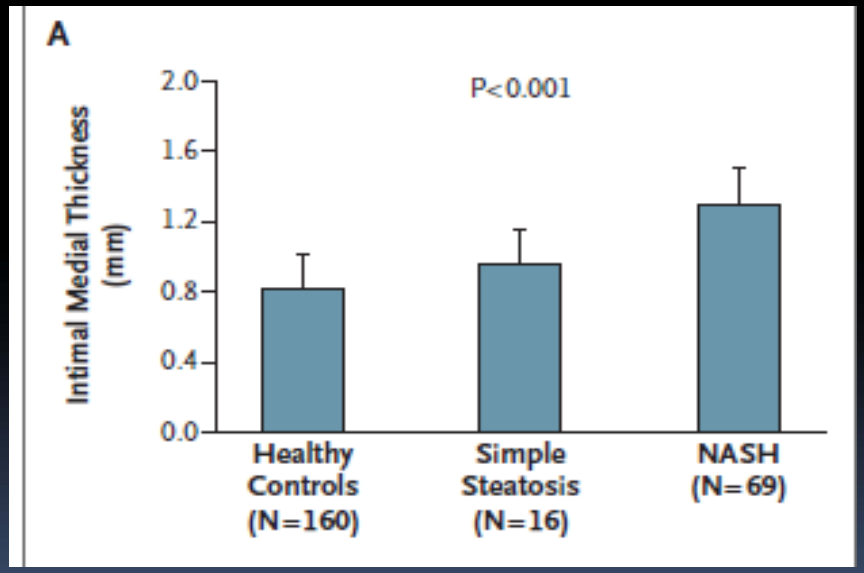
Incremento del Riesgo CV en Pacientes con NASH

ECV en DM2 con o sin NASH



DIABETES CARE, VOLUME 30, NUMBER 5, MAY 2007

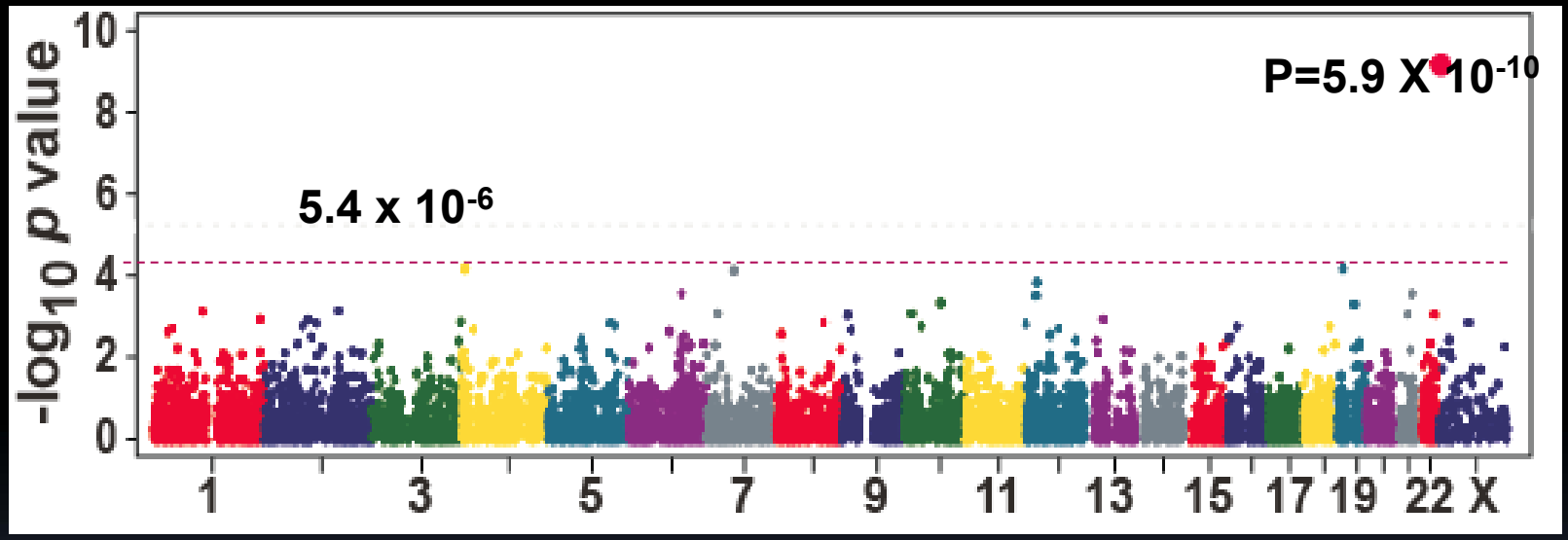
Engrosamiento de la Intima Media Carotídea en NASH



New Eng J Med 363;september 30, 2010

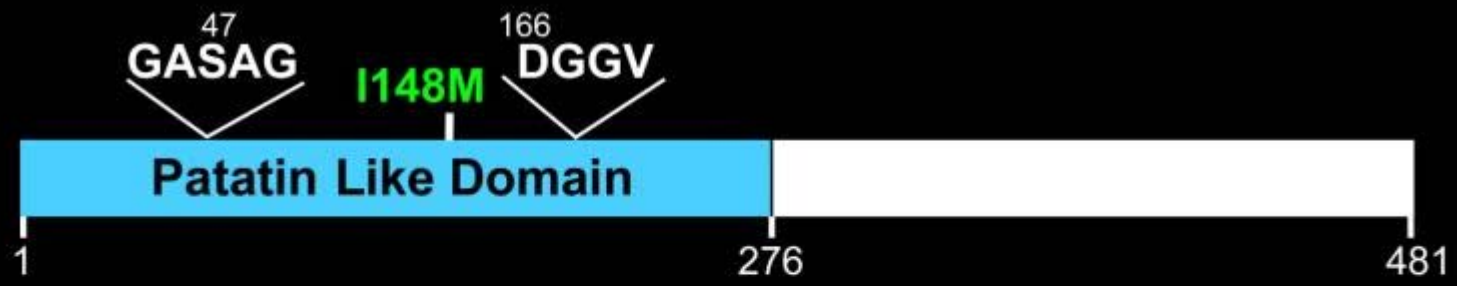
Genome-wide Association Study of Fatty Liver in Dallas Heart Study Cohort

(2,111 patients and 9,299 Non-synonymous SNPs)



Chromosome

PNPLA3: A Member of the Patatin-like Phospholipase Family



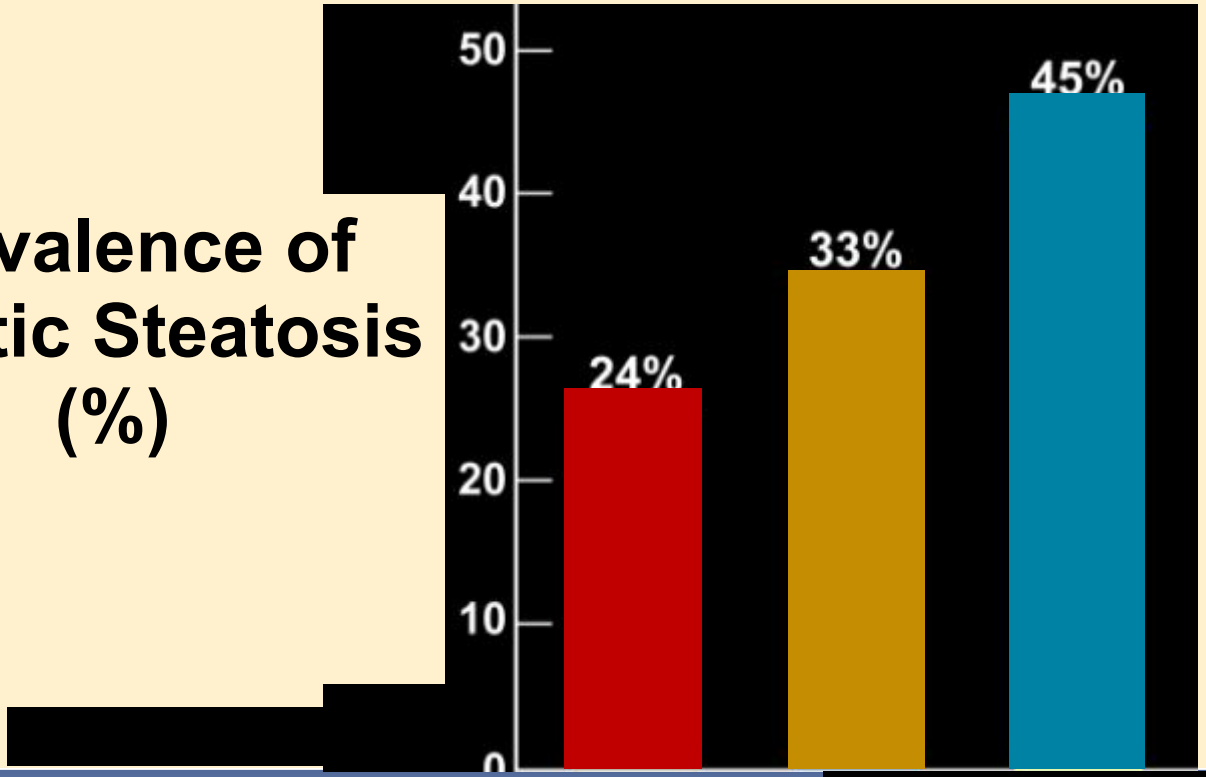
- Resembles patatin: major potato protein
- Nonspecific lipase activity (breaks down fat)
- Expressed high level in fat & liver
- Increased with feeding

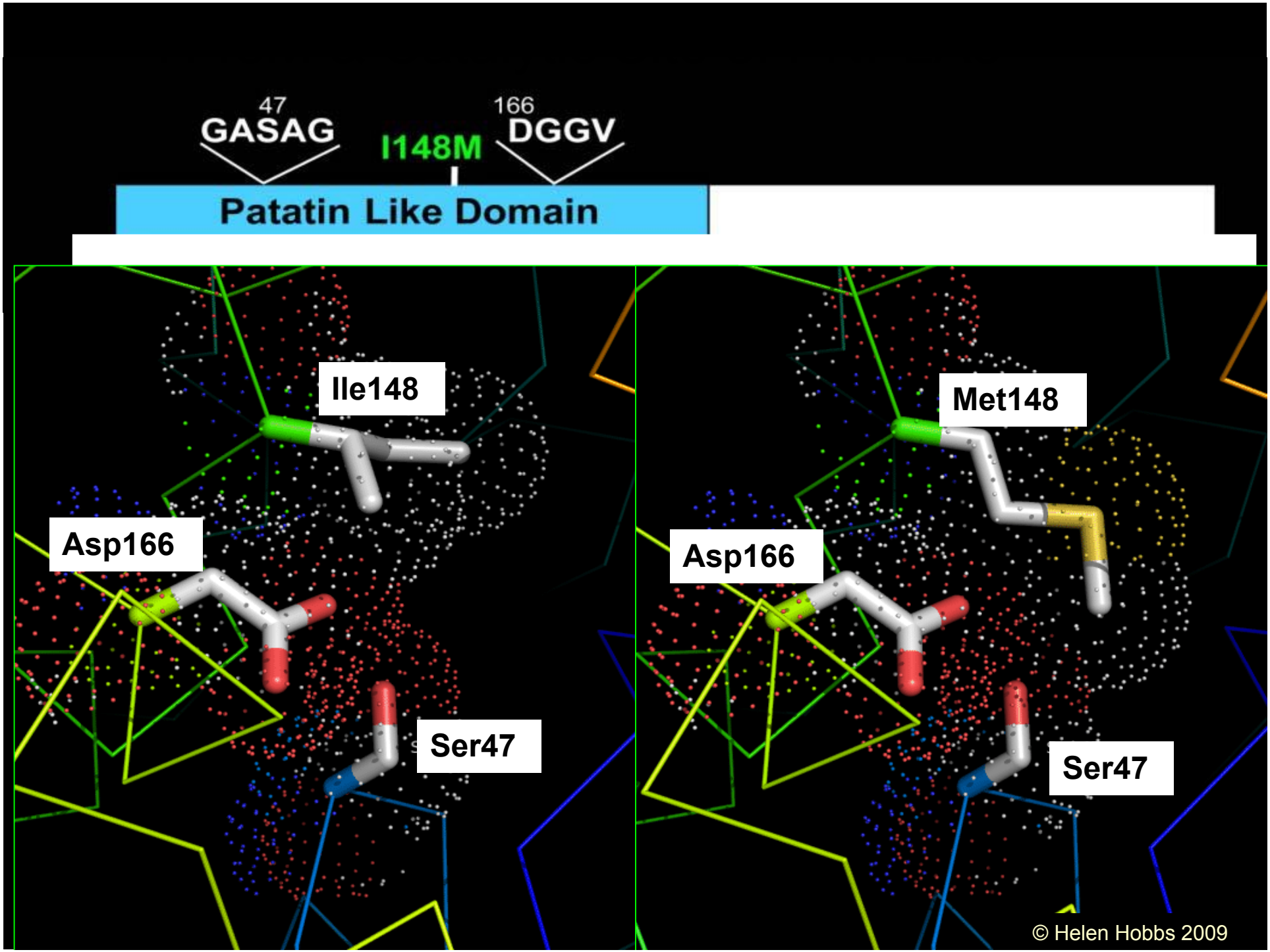
Baulande *et al.* JBC 276:33336, 2001

Jenkins *et al. JBC* 279:48968, 2004

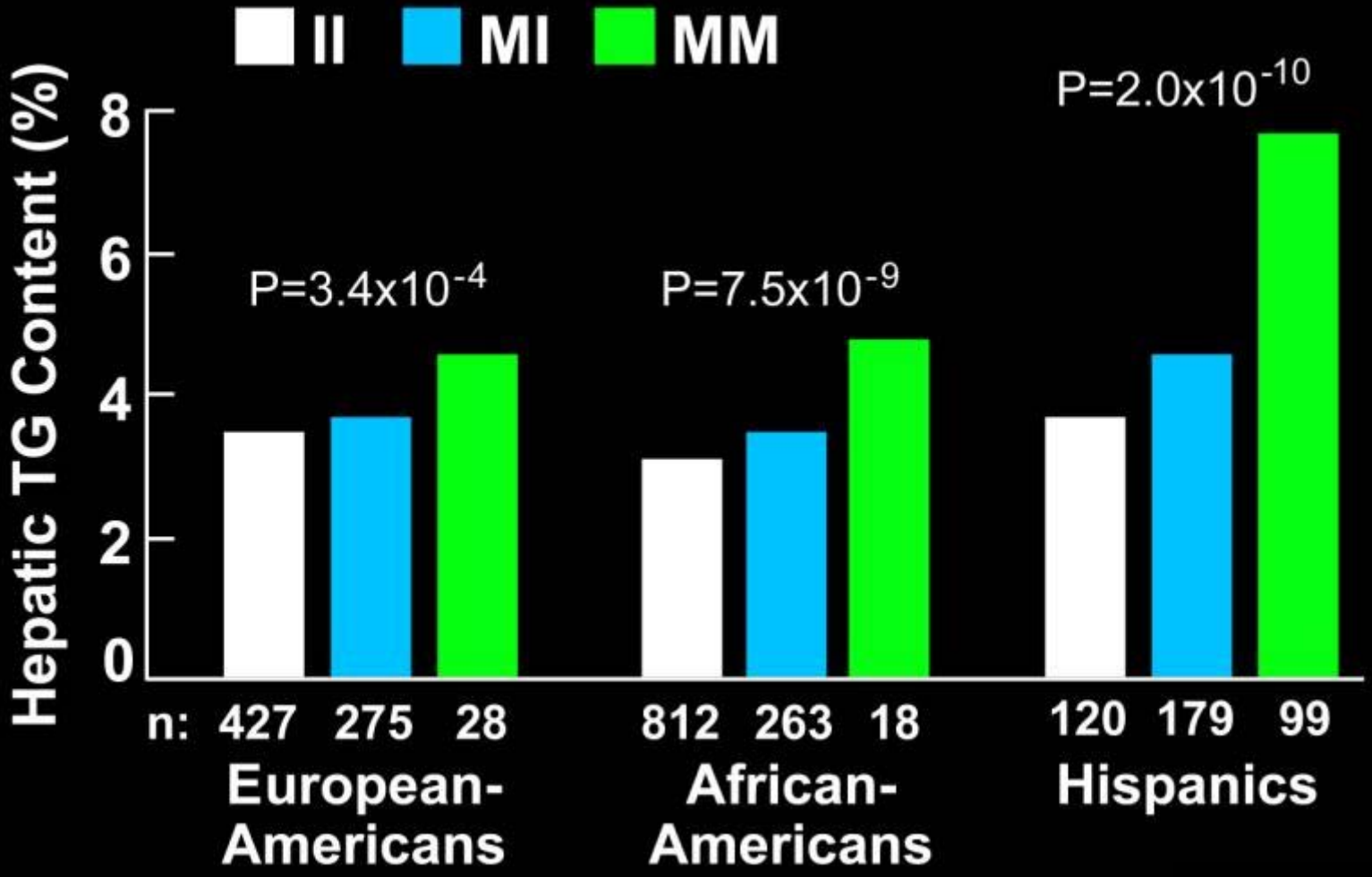
Genetic Contribution to Ethnic Differences in Hepatic Steatosis

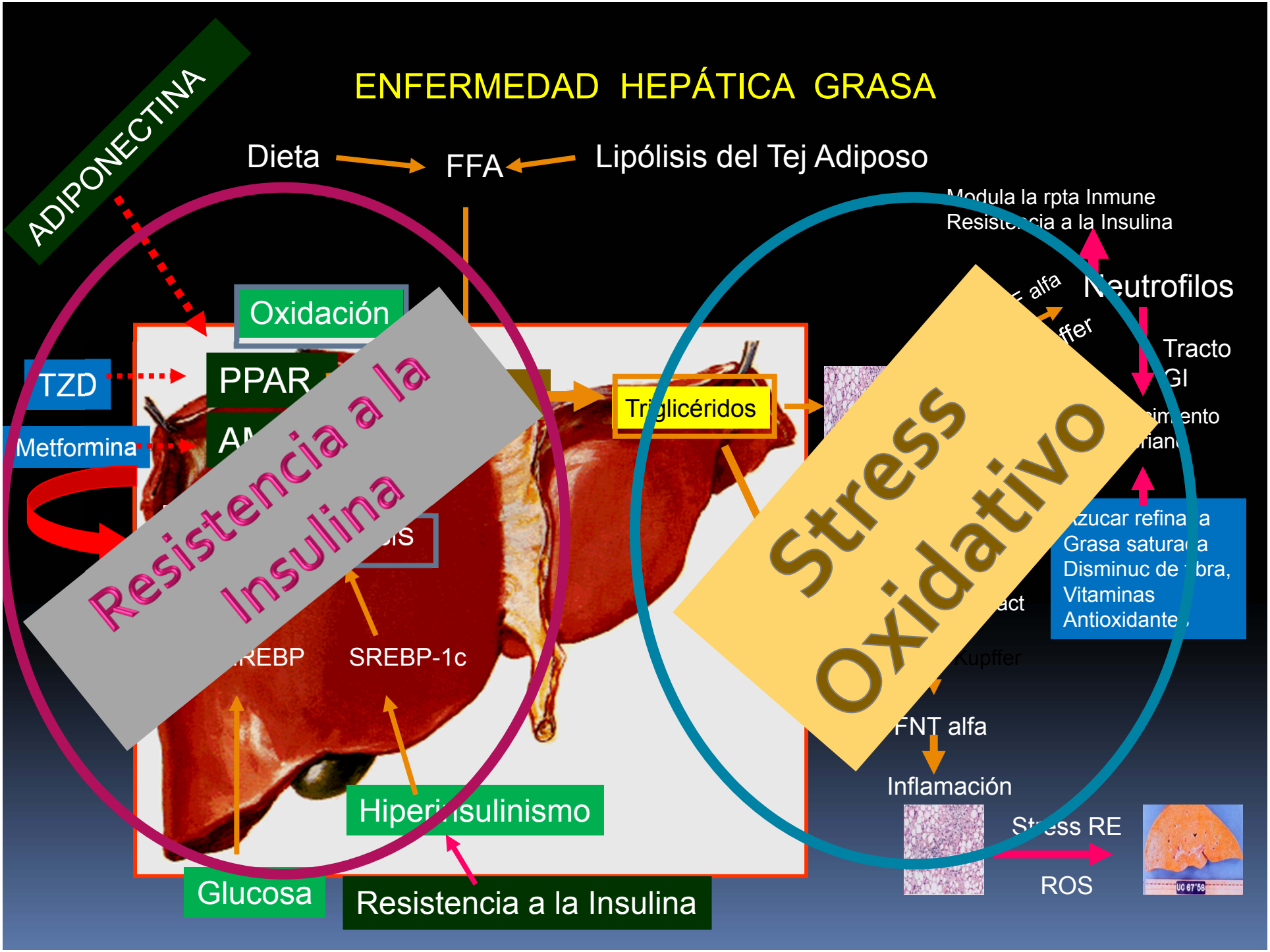
	African-Americans	European-Americans	Hispanics
Minor Allele Frequency	0.17	0.23	0.49



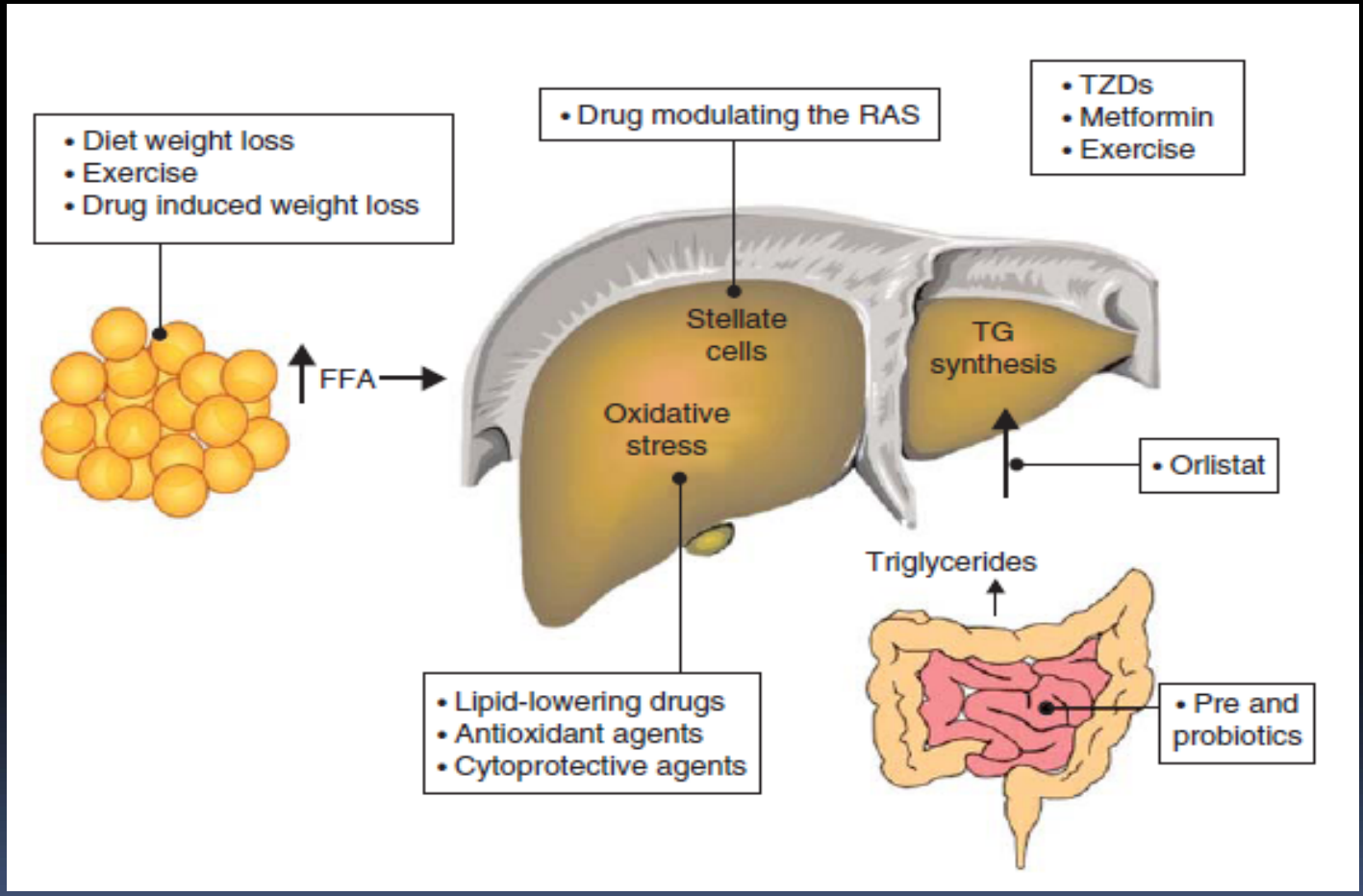

47
GASAG
166
DGGV
I148M
Patatin Like Domain
Ile148
Asp166
Ser47
Met148
Asp166
Ser47
© Helen Hobbs 2009

PNPLA3: I148M Genotype and Hepatic Triglyceride Content



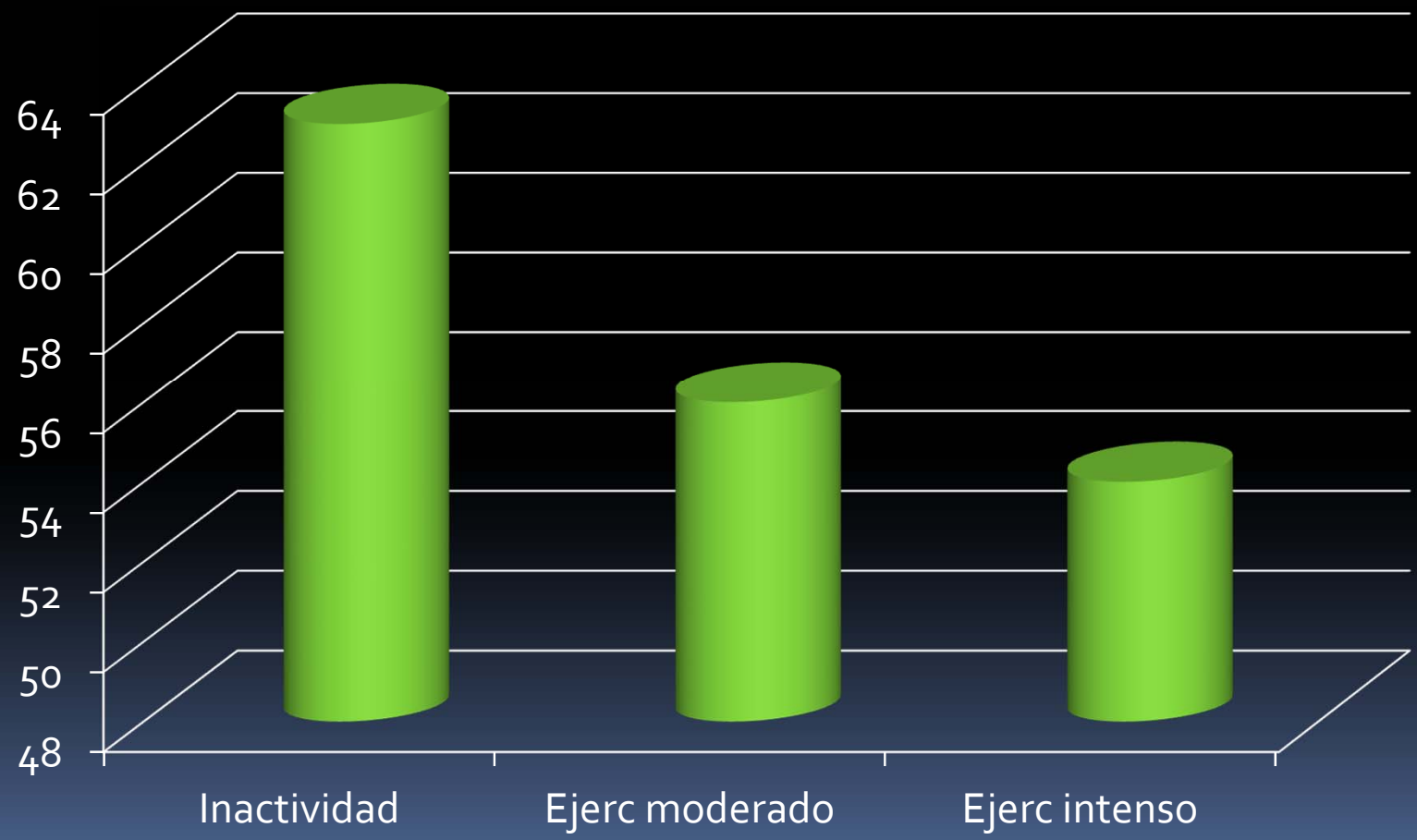

ENFERMEDAD HEPÁTICA GRASA
ADIPONECTINA
Dieta
FFA
Lipólisis del Tej Adiposo
Oxidación
TZD
PPAR
Metformina
Triglicéridos
Resistencia a la Insulina
SREBP-1c
Hiperinsulinismo
Glucosa
Resistencia a la Insulina
Stress Oxidativo
Neutrofilos
Tracto GI
Azucar refinada
Grasa saturada
Vitaminas
Antioxidantes
Kupffer
FNT alfa
Inflamación
ROS

Intervenciones Terapéuticas en la Enfermedad Hepática Grasa



Expert Opin. Emerging Drugs (2011) 16(1)

Relación Entre Intensidad del Ejercicio y NASH



Kistler. Am J of Gastroenterology, 106, 2011

New Drugs under Development (I)

Company	Drug	MoA	RoA	Phase
PharmaKing	Oltipraz	Fatty acid inhibitor	Oral	Phase 2
Novartis	Pradigastat	DGAT1 inhibitor	Oral	Phase 2
Therapix	TRX 318	CD3 antigen	Oral	Phase 2
Takeda	Roflumilast	PDE-4	Oral	Phase 2
Antipodean	Mitoquinone	Antioxidant	Oral	Phase 2
KT&G Life Sciences	MB 11055	AMPK stimulant	Undefined	Phase 2
Naia	NC 101	Undefined mechanism	Undefined	Phase 2
Galectin	GR MD 02	Galectin-3	IV and SubQ	Phase 1
Kadmon	KD 025	ROCK2 inhibitor	Oral	Phase 1
Phenex	PX 102	FXR agonist	Oral	Phase 1
Shire	SHP 626	ASBT inhibitor	Oral	Phase 1
Durect	DUR-928	Undefined small molecule	Oral	Phase 1
Daewoong	DWP-10292	Undefined small molecule	Oral	Phase 1
Gilead	GS-4997	ASK1 inhibitor	Oral	Phase 1
TaiwanJ	JKB-121	TLR-4 antagonist	Oral	Phase 1
Madrigal	MGL-3196	THR beta agonist	Oral	Phase 1
Virobay	VBY-376	Cathepsin B inhibitor	Oral	Phase 1
La Jolla	LGPC-1010	Galectin-3	Oral	Preclinical

New Drugs under Development (II)

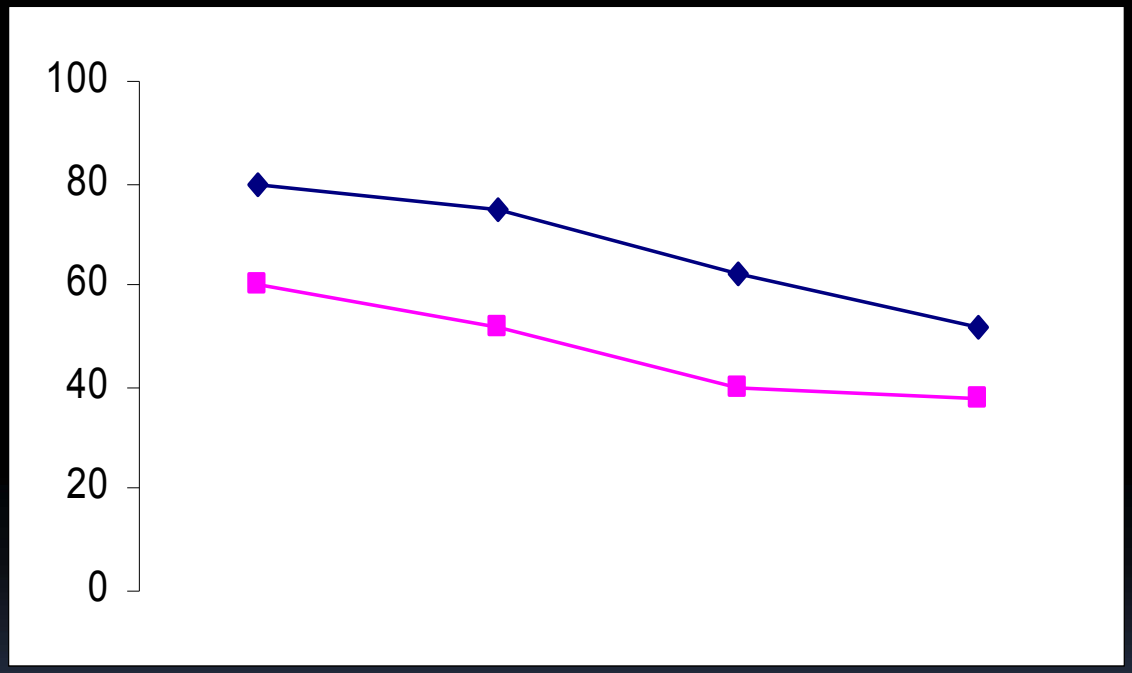
Company	Drug	MoA	RoA	Phase
Raptor	**RP103**	Antioxidant - cysteine depleting agent	Oral	Phase 3
Zydus-Cadila	Saroglitazar	PPAR agonist	Oral	Phase 3
Novo Nordisk	**liraglutide**	GLP-1	SubQ	Phase 2
Takeda	**Pioglitazone**	PPAR agonist	Oral	Phase 2
Islet Sciences	remogliflozin etabonate	SGLT-2 inhibitor	Oral	Phase 2
Aptalis Pharma	Ursodeoxycholic acid	Bile acid	Undefined	Phase 2
Gilead	**Simtuzumab**	LOXL2 antibody	IV and SubQ	Phase 2
Conatus	**Emricasan**	Caspase protease inhibitor	Oral	Phase 2
Galmed	**Aramchol**	Synthetic fatty acid/ bile acid conj	Oral	Phase 2
Tobira	**Cenicriviroc**	Dual CCR2/CC5 antagonist	Oral	Phase 2
Genfit	**GFT 505**	PPAR alpha/delta agonist	Oral	Phase 2
Intercept	**OCA**	FXR agonist	Oral	Phase 2
Phenex	**PX 104**	FXR agonist (non bile acid)	Oral	Phase 2
Mochida	icosapent ethyl ester	Caspase protease inhibitor	Oral	Phase 2
Immuron	IMM 124E	Immunomodulators	Oral	Phase 2
KT&G Life Sciences	MB 12066	Sirtuin stimulants	Oral	Phase 2

Nuevos Agentes Potenciales para el Tratamiento de la EHGNA

Benefit	Agent	Comment
Potential benefit	Pioglitazone	Improves components of the NAS score [12]. Increased risk of bladder cancer and MI [13,14].
	Vitamin E	Significant improvement in histological lesions [12]. However, may increase all-cause mortality [15].
No clear benefit	Metformin	No effect on histology [16,17].
	Statins	
	Atorvastatin	No histological data, but improves liver enzymes and radiological steatosis [18,19].
	Simvastatin	No effect on histology or liver enzymes [20].
	UDCA	Histological data lacking, four RCTs showed no effect on liver enzymes [21].
	PUFAs	No histological improvement in activity [22▪▪], but reduction in steatosis radiologically [23].
Unclear benefit	Angiotensin receptor blockers	Improvements in histology (necroinflammation and fibrosis) but study limited to seven patients [24].
	Pentoxyfylline	Improvement in NASH activity score, but not in fibrosis stage. Study limited to 55 patients [25].

Hardy. Current Opinion of Gastroenterology, 2015

Metformina y Enzimas Hepática en pacientes con NASH



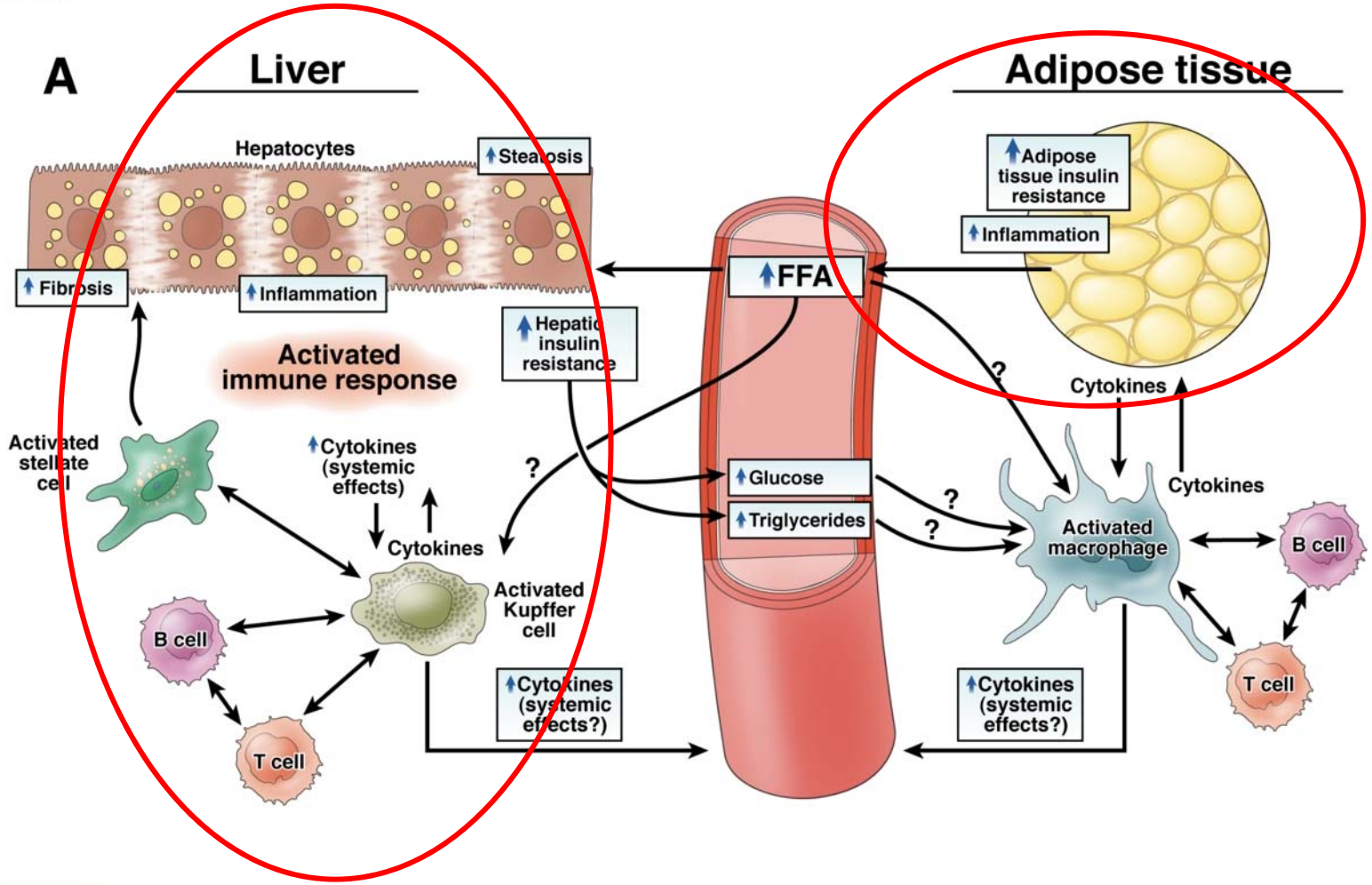
Metformina (850 mg bid) en pacientes con NASH. Seguimiento por 6 meses.

Alim Pharmac and Therap 2004,19,537-544

	Pacientes	Duración	N	Dosis Metformina	Hallazgos
1	NAFLD confirmado histologicamente	1 año	15	mg/kg	Pruebas de función hepáticas.
2	NASH Confirmado Histologicamente	6 m	7	1500 mg/d	Normalización de TGP
3	NASH	4 m	20	1500 mg/d	Normalización de Pruebas De función hepàtica. Disminucion del volumen Hepático.
4	NASH Confirmado Histologicamente	48 s	10	2000 mg/d	Mejora de los parámetros De función hepática.
5	NASH Confirmado Histologicamente < 18 años	24 s	10	1000 mg/d	Mejora de Pruebas de Función hepatica en 40-50 %, sensibilidad a la Insulina y calidad de vida.

1 Alimentary Pharmacol and Therap 2004,20,23-29
2 Indian Journal of Gastroenterol 2004, 23,12-15
3 Lancet 2001, 358,893-894
4 Gastroenterology 2005,128:A-769
5 Therapeutics 2005,21:871-879

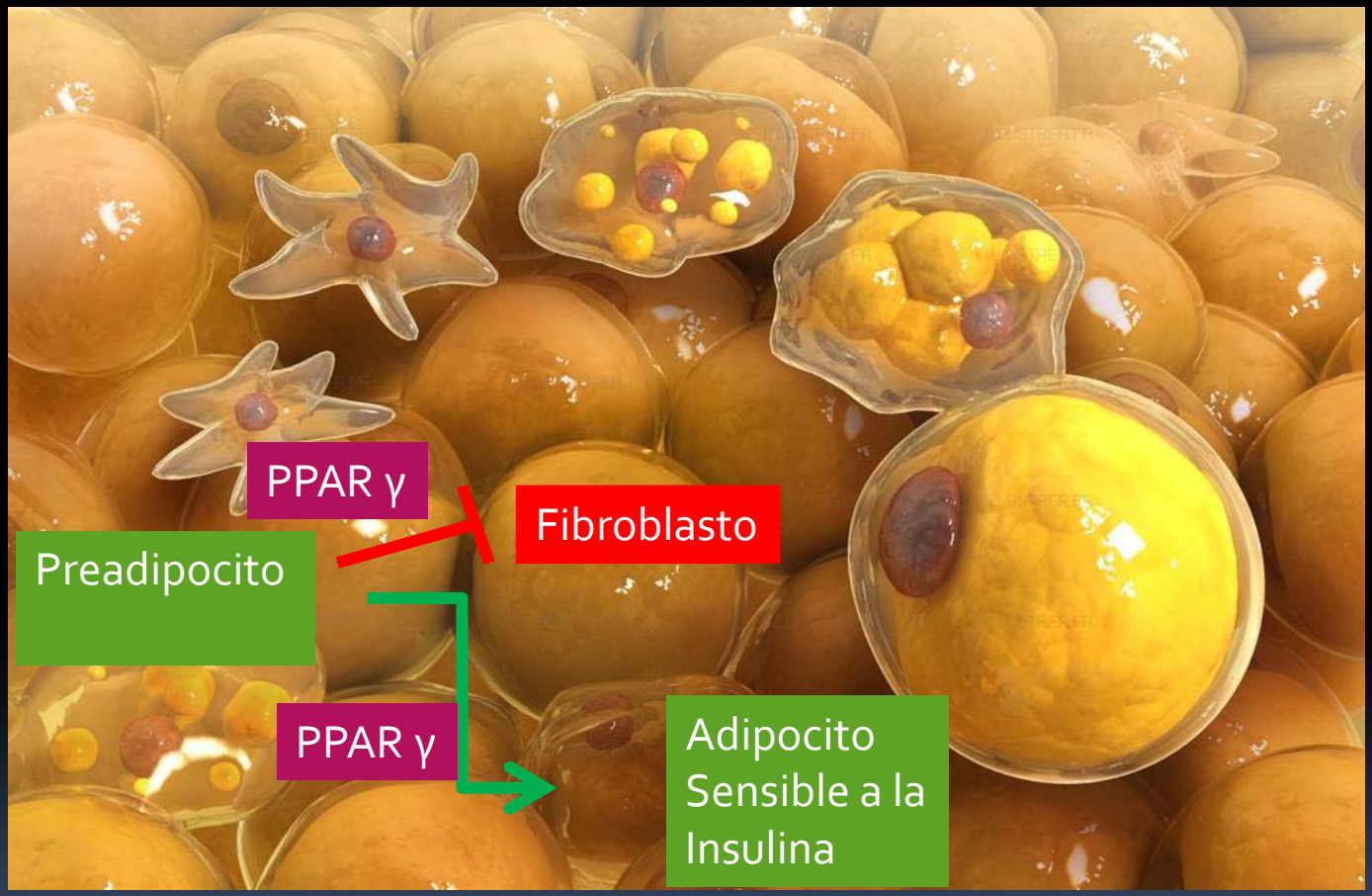
Rationale for Pioglitazone in NASH



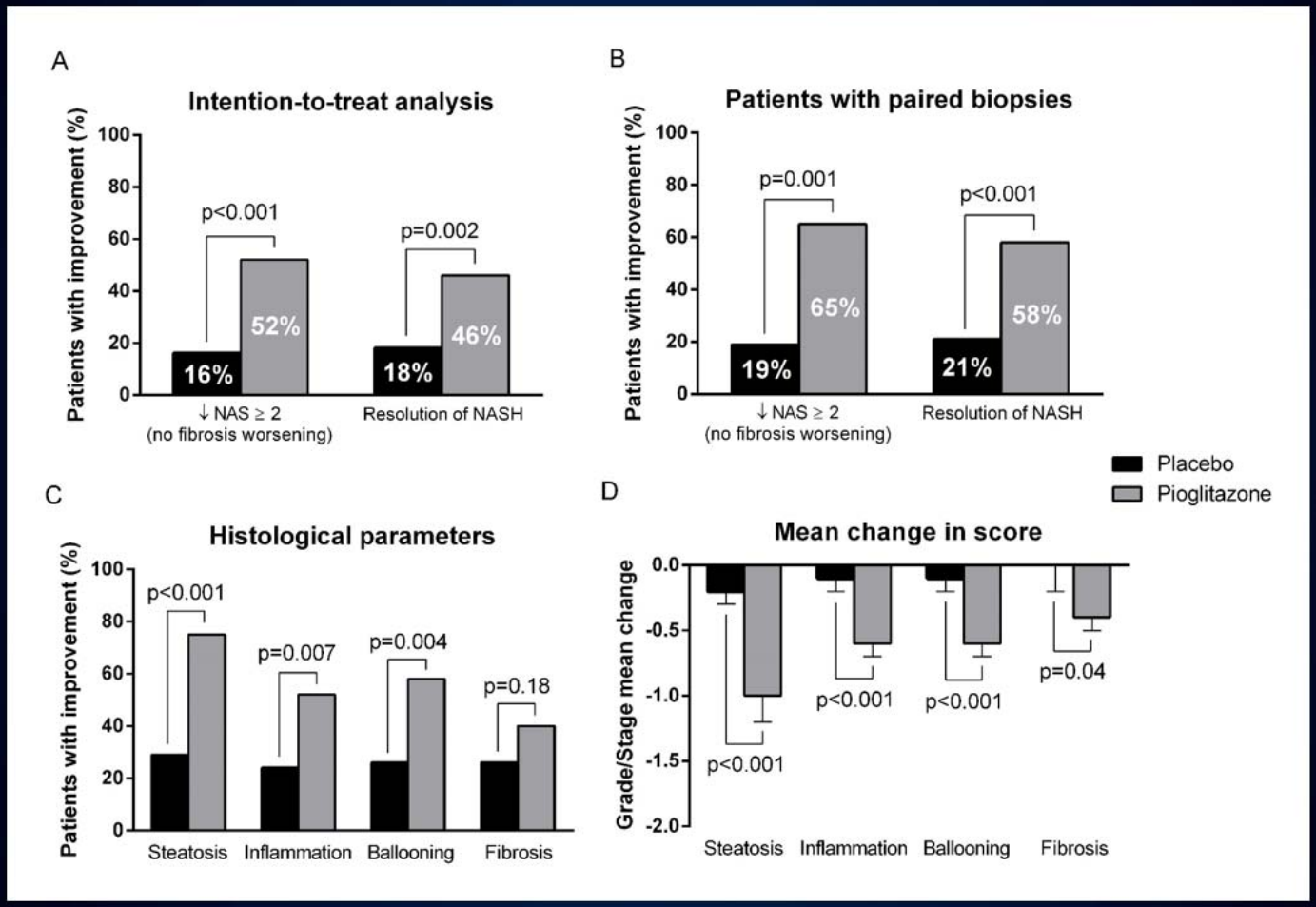
UF UNIVERSITY of FLORIDA College of Medicine

Cusi K. Gastroenterology 2012, 142:711-25

Transdiferenciacion del Adipocito

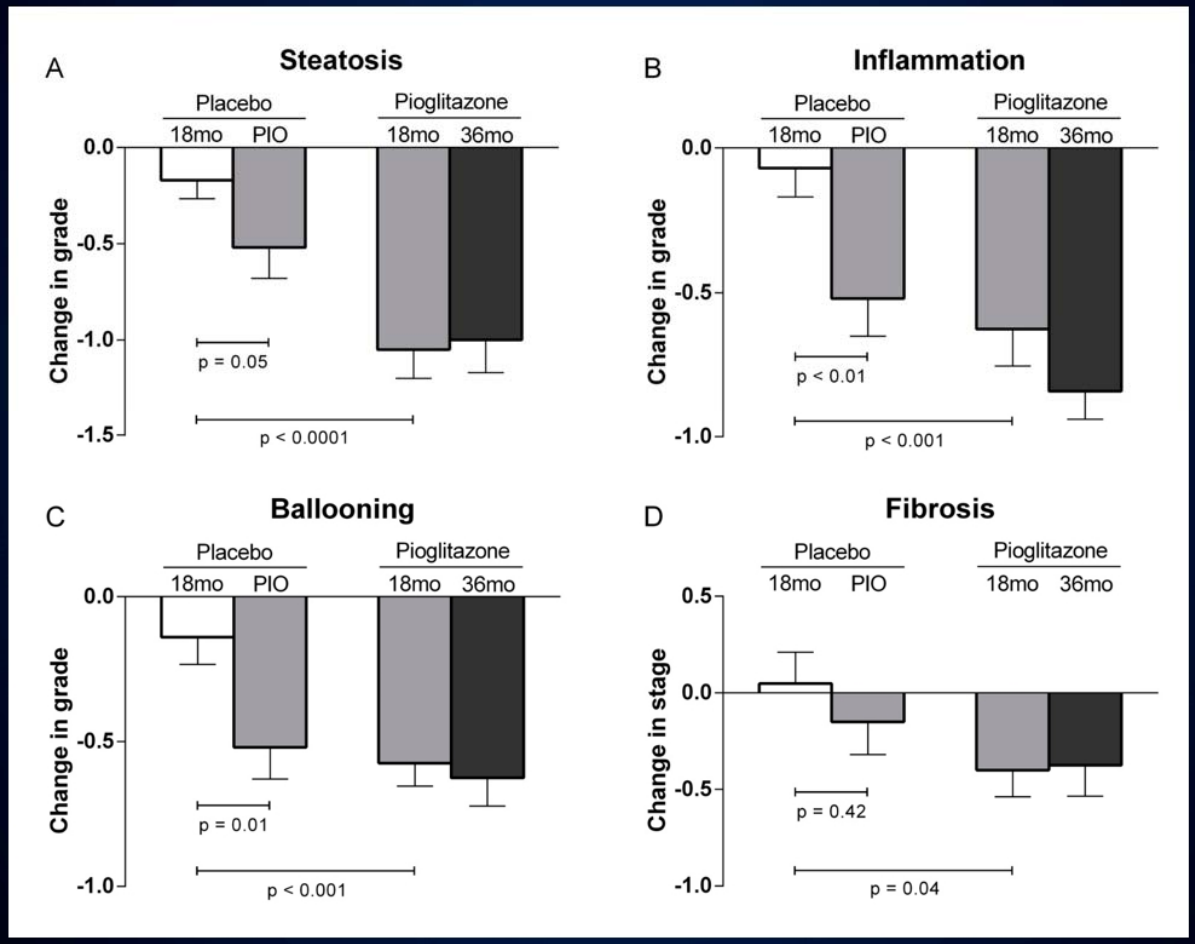


Effect of Pioglitazone on Primary Outcome*

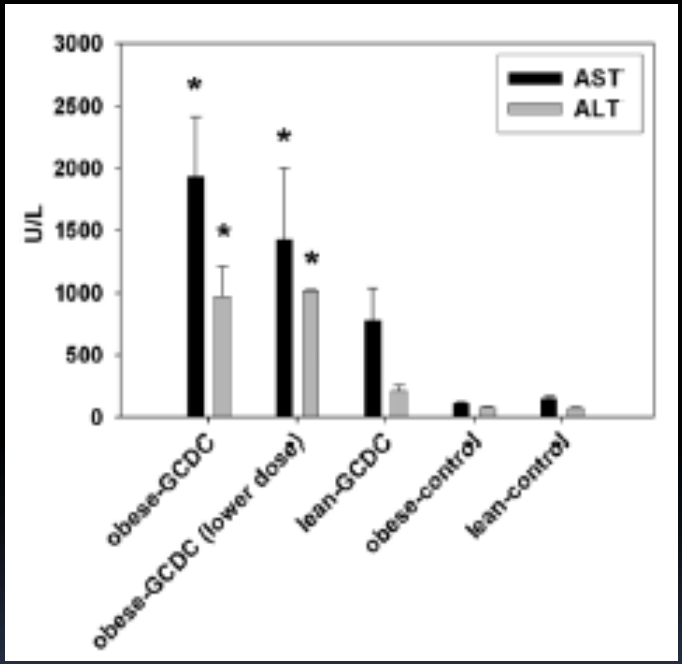


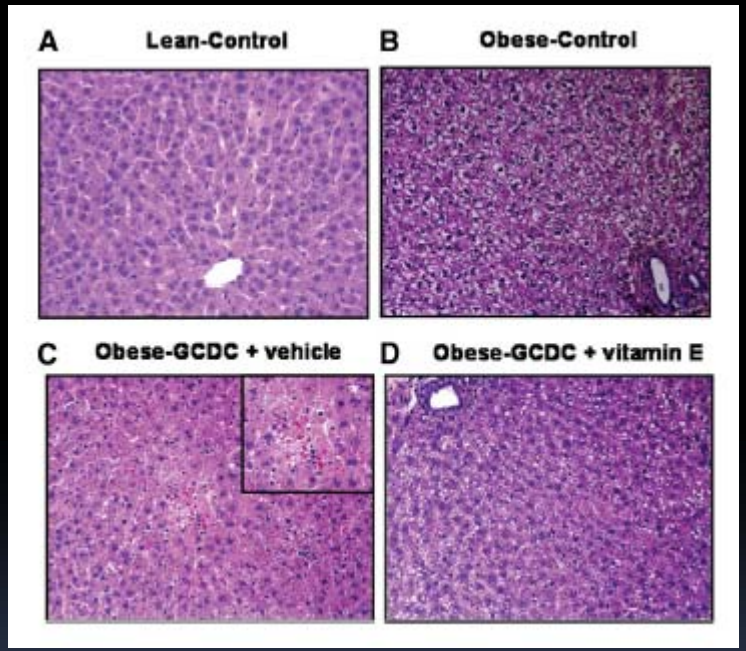
* Defined as patients with a ≥2-grade reduction in NAS (in at least 2 different categories), and without worsening of fibrosis (%). Intention-to-treat analysis considers non-completers as non-responders.

Effect of Pioglitazone on Primary Outcome*



Alfa Tocoferol y EHGNA en Ratas





Soden, Hepatology 2007

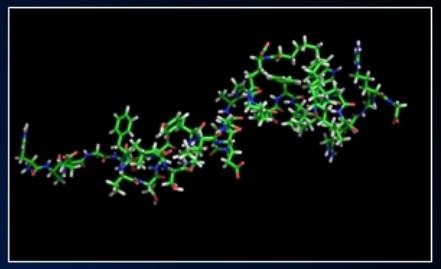
Pioglitazona vs Vitamina E

Table 2. Primary Outcome and Changes in Histologic Features of the Liver after 96 Weeks of Treatment.

Variable	Placebo	Vitamin E	Pioglitazone	P Value*	
				Vitamin E vs. Placebo	Pioglitazone vs. Placebo
Primary outcome†					
No. of subjects randomly assigned	83	84	80		
Subjects with improvement (%)	19	43	34	0.001	0.04
Changes from baseline in histologic features					
No. of subjects with biopsy specimens at baseline and 96 wk	72	80	70		
Steatosis					
Subjects with improvement (%)	31	54	69	0.005	<0.001
Mean change in score	−0.1	−0.7	−0.8	<0.001	<0.001
Lobular inflammation					
Subjects with improvement (%)	35	54	60	0.02	0.004
Mean change in score	−0.2	−0.6	−0.7	0.008	<0.001
Hepatocellular ballooning					
Subjects with improvement (%)	29	50	44	0.01	0.08
Mean change in score	−0.2	−0.5	−0.4	0.03	0.01
Total NAFLD activity score (mean change)	−0.5	−1.9	−1.9	<0.001	<0.001
Fibrosis‡					
Subjects with improvement (%)	31	41	44	0.24	0.12
Mean change in score	−0.1	−0.3	−0.4	0.19	0.10
Resolution of definite nonalcoholic steatohepatitis (% of subjects)	21	36	47	0.05	0.001

Sanyal. NEJM , 362, 18, 2010

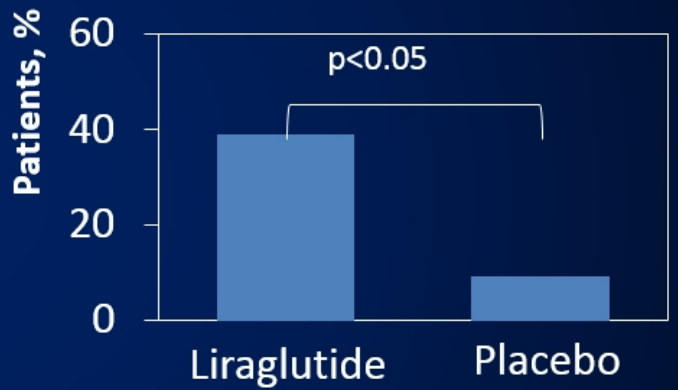
Liraglutide (Victoza®) in NASH



Baseline characteristics

Characteristics	Liraglutide (n=23)	PBO (n=22)
Mean (SD) NAS	4.9 (0.9)	4.8 (0.9)
Mean (SD) Kleiner fibrosis	2.3 (0.9)	2.3 (1.3)
F0–2, n (%)	14 (54%)	11 (42%)
F3–4, n (%)	12 (46%)	15 (58%)

Primary endpoint: NASH resolution with no worsening of fibrosis



Secondary endpoints

Endpoint	Liraglutide (n=23)	PBO (n=22)
Mean (SD) change, Kleiner fibrosis	-0.2 (0.8)	0.2 (1.0)
Improvement, n (%)	6 (26.1)	3 (13.6)
Worsening, n (%)	2 (8.7)*	8 (36.4)

*p<0.05 vs placebo

Armstrong MJ, et al. EASL 2015, Vienna. #G01

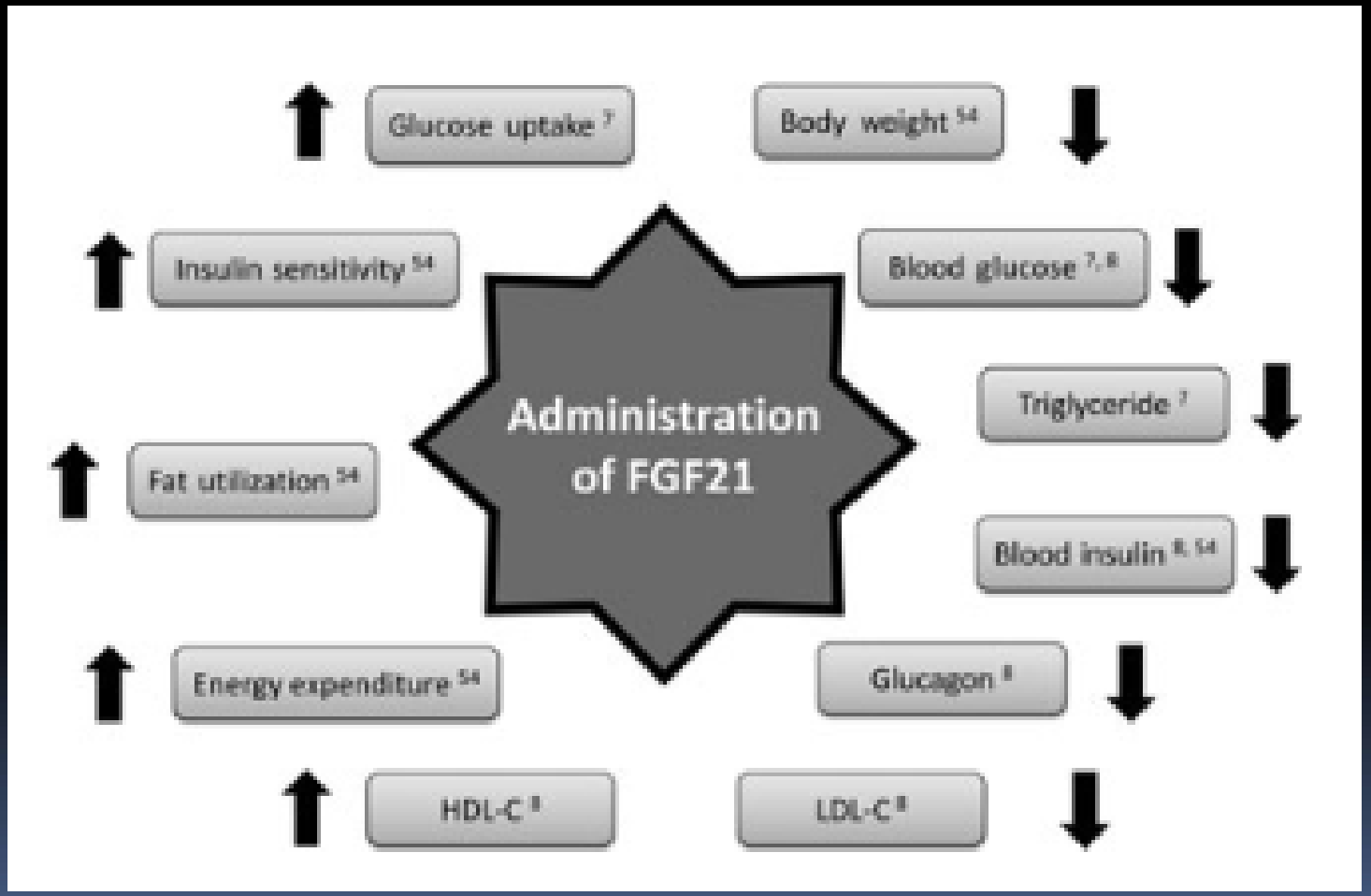
¿Qué Tratamientos Futuros Se esperan para la EHGNA?

Nuevos Agentes en Investigación para el Tratamiento de la EHGNA

Agent	Action	Effect on NASH pathogenesis	ClinicalTrials.gov identifier
GS-9450	Caspase inhibition	Prevents apoptosis	NCT00740610 [59]
GFT-505	Dual PPARα/δ agonist	Hepatic glucose utilization, lipoprotein metabolism and anti-inflammatory effects	NCT01694849 [60]
Obeticholic acid	FXR agonist	Promotes insulin sensitivity, decreases hepatic gluconeogenesis and circulating triglycerides	NCT01265498 [61]
Cenicriviroc	CCR2/CCR5 antagonist	Interferes with recruitment of monocytes, macrophages and HSCs upon liver injury	NCT02217475 [62]
Liraglutide	GLP-1 agonist	Induces insulin secretion, reduces glucagon secretion	NCT01237119 [63]
Sitagliptin	DPP-IV inhibitors	Prevents degradation of GLP-1	NCT01963845 [64]
GS-6624 (simtuzumab)	Anti-LOXL-2 antibodies	Inhibits formation and repair of extracellular matrix	NCT01672879 [65]/ NCT01672866 [66]

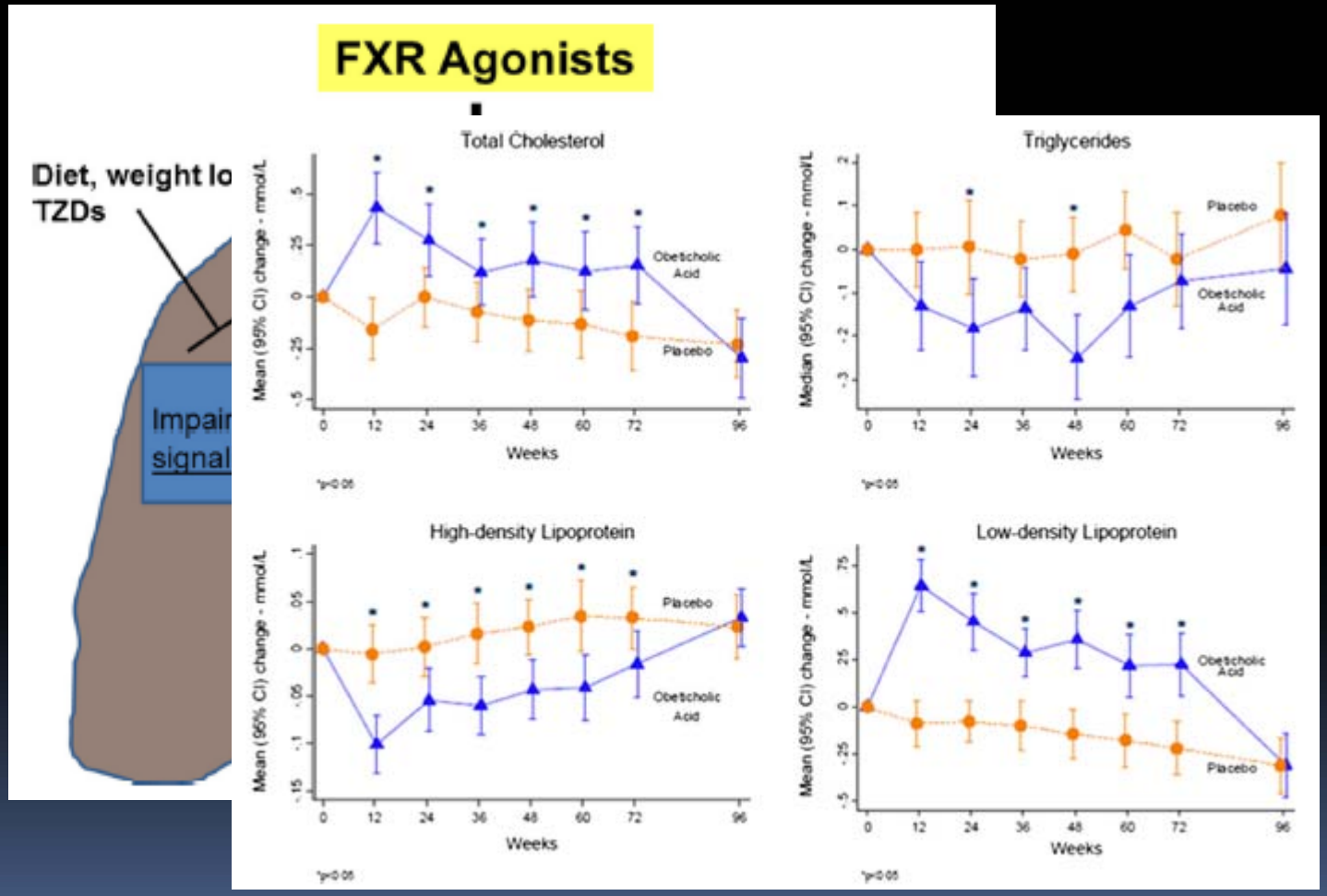
Hardy. Current Opinion of Gastroenterology, 2015

Factor de Crecimiento Fibroblástico 21



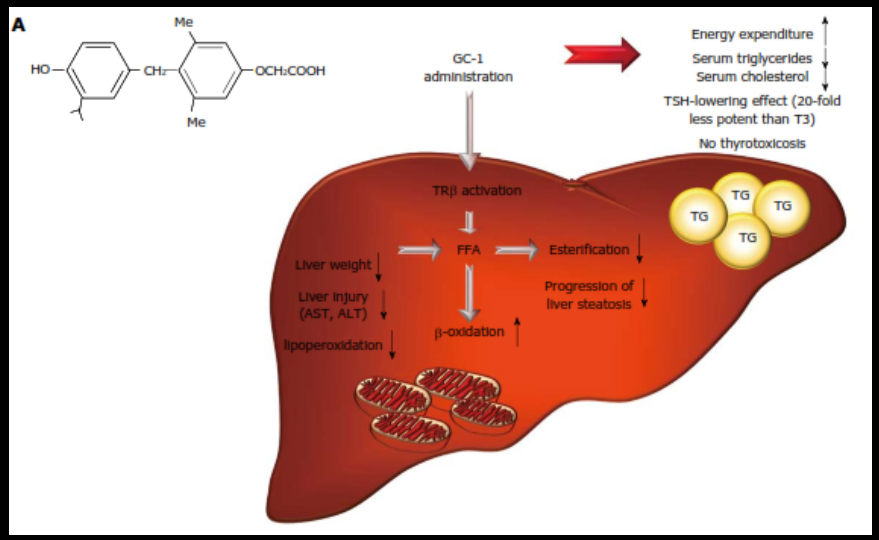
Woo Y. Clinical Endocrinology (2013) 78, 489–496

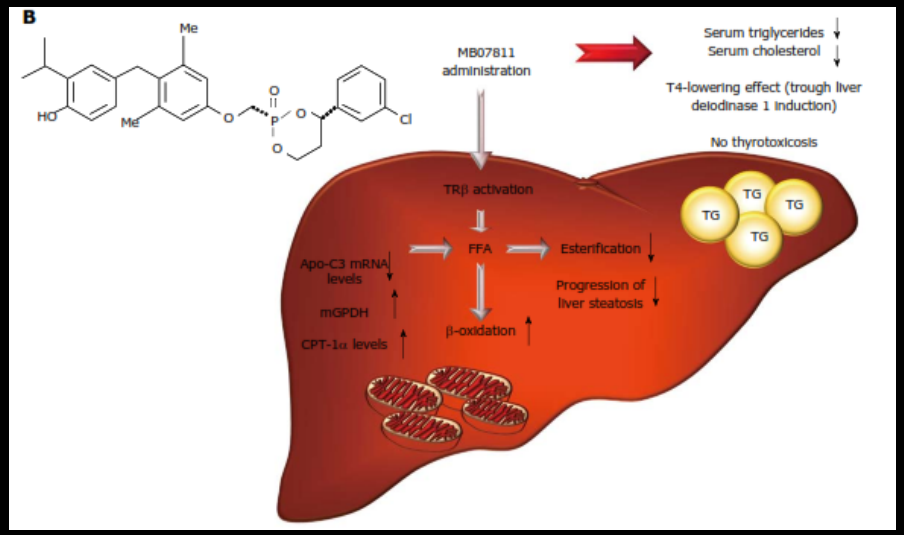
Agonistas del Receptor Farnesoide X

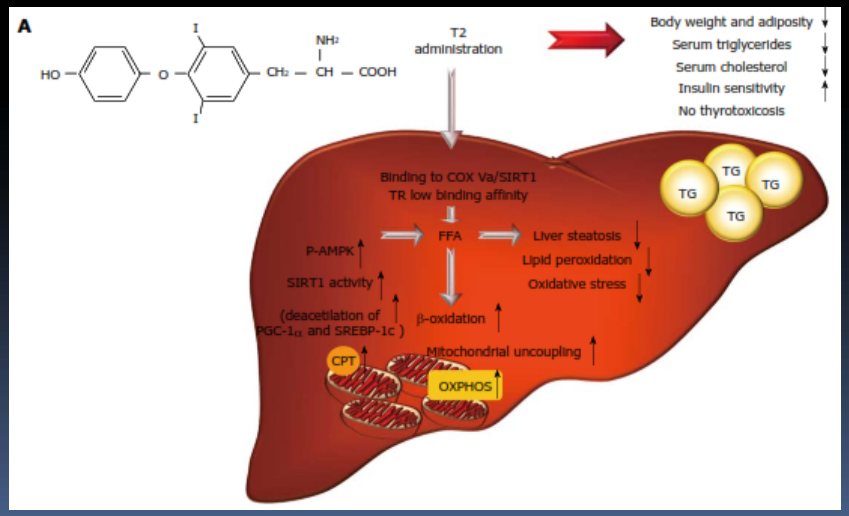


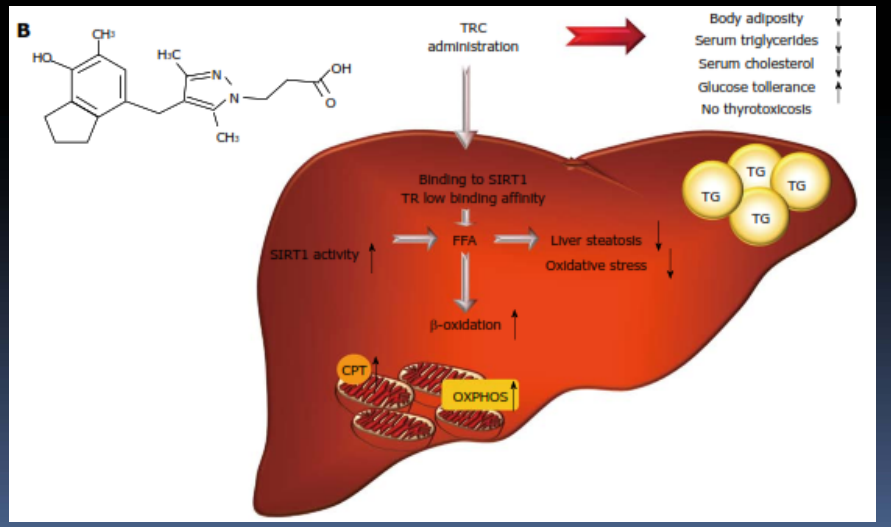
Curr Atheroscl Rep,17,16, 2015

Análogos de HT en Esteatosis Hepática



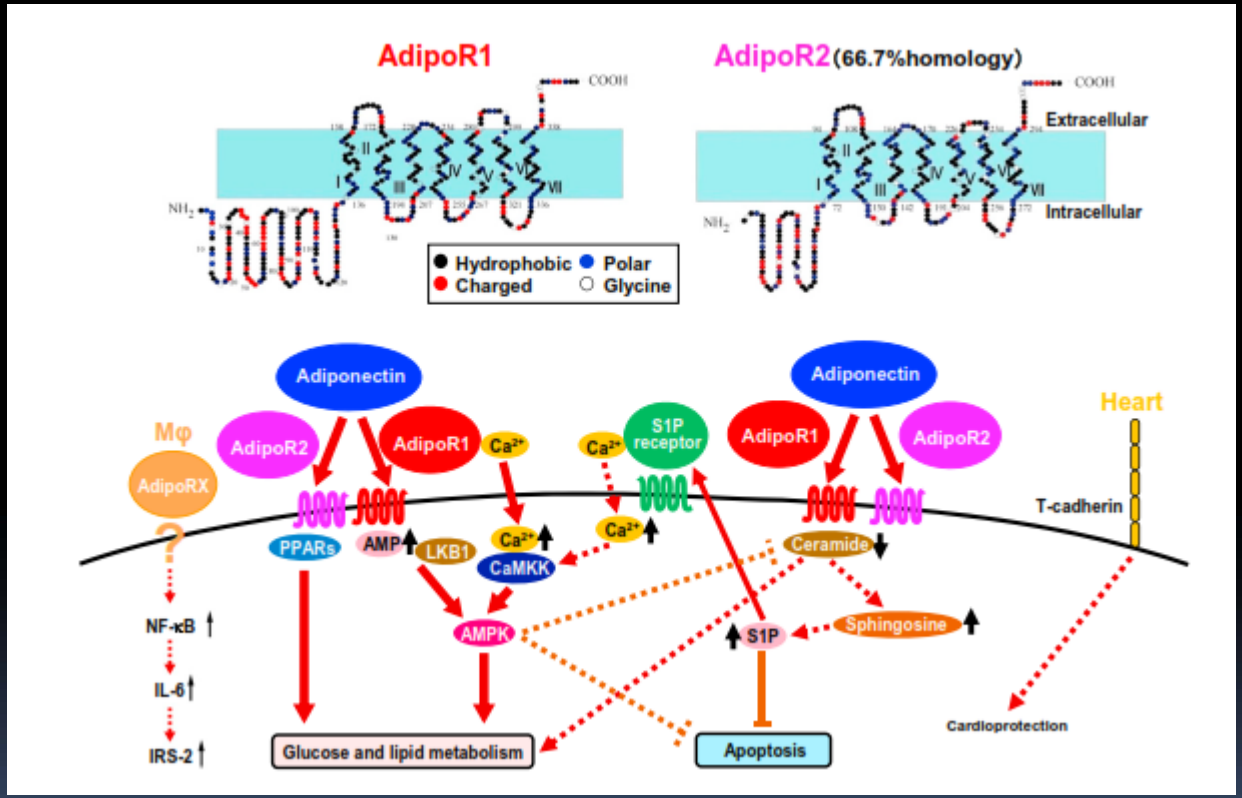






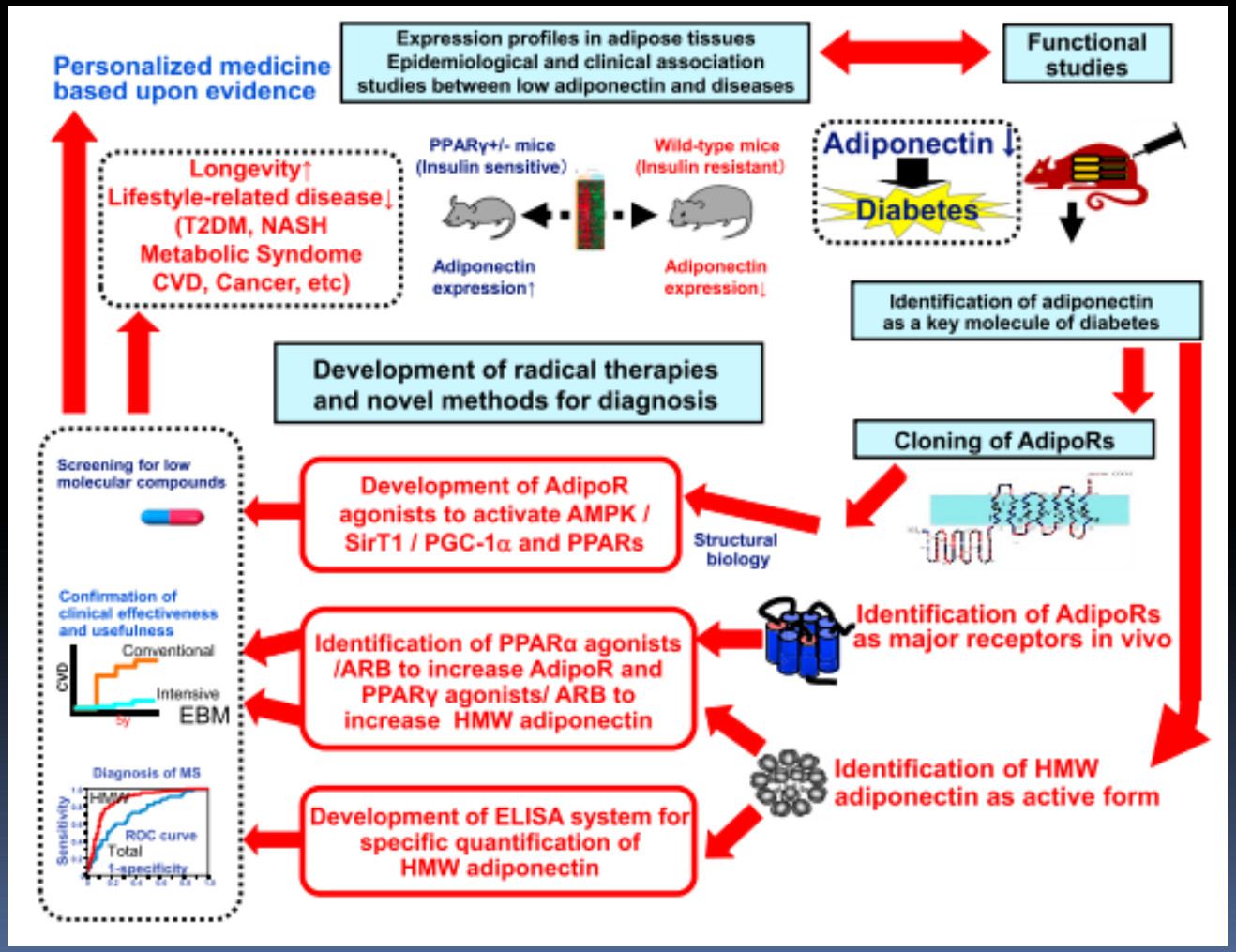
Coppola M. World J Hepatol 2014 March 27; 6(3): 114-129

Efectos Benéficos de la Adiponectina

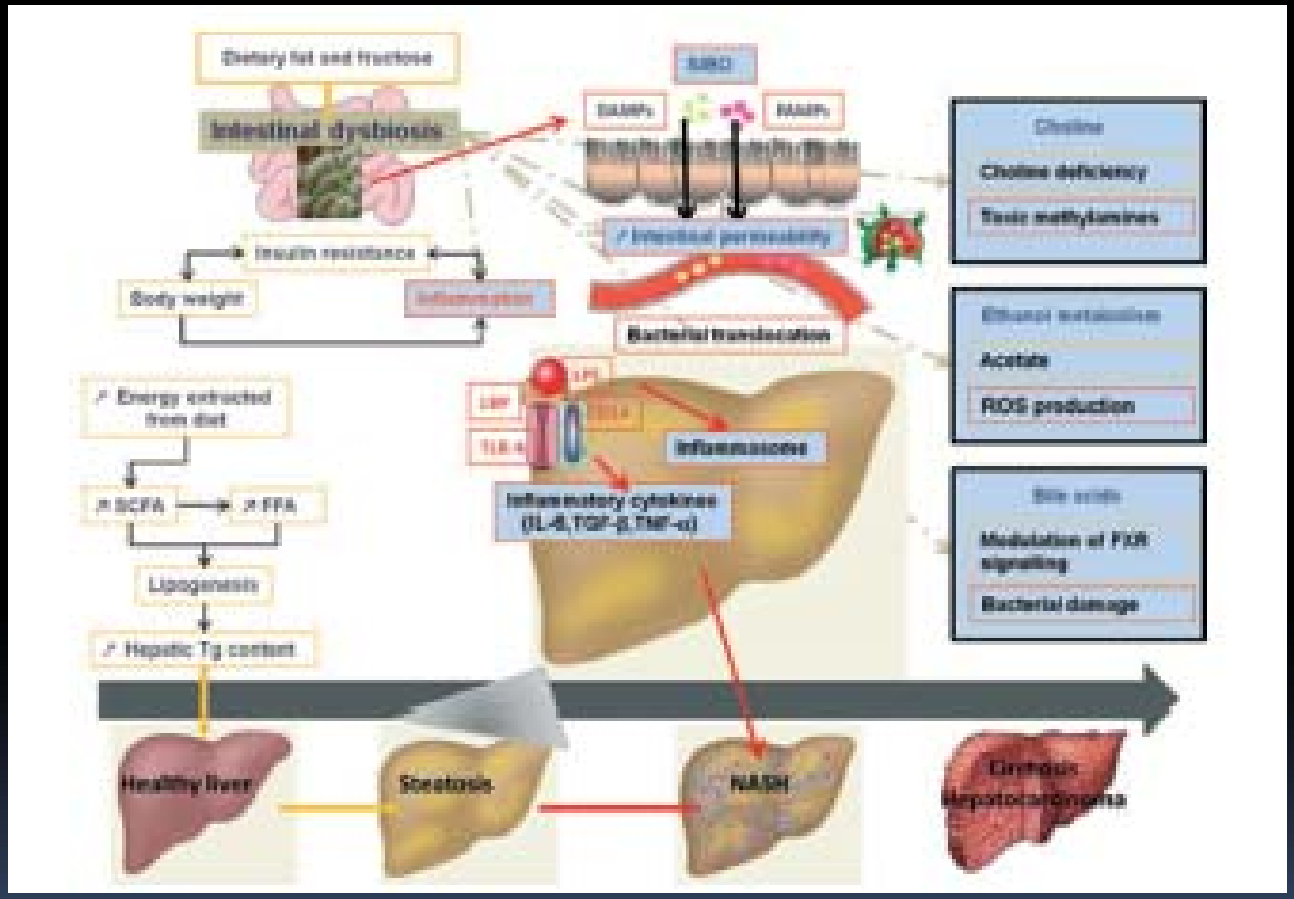


Yamauchi T. Cell Metabolism 17, February 5, 2013

Efectos Benéficos Potenciales de la Adiponectina

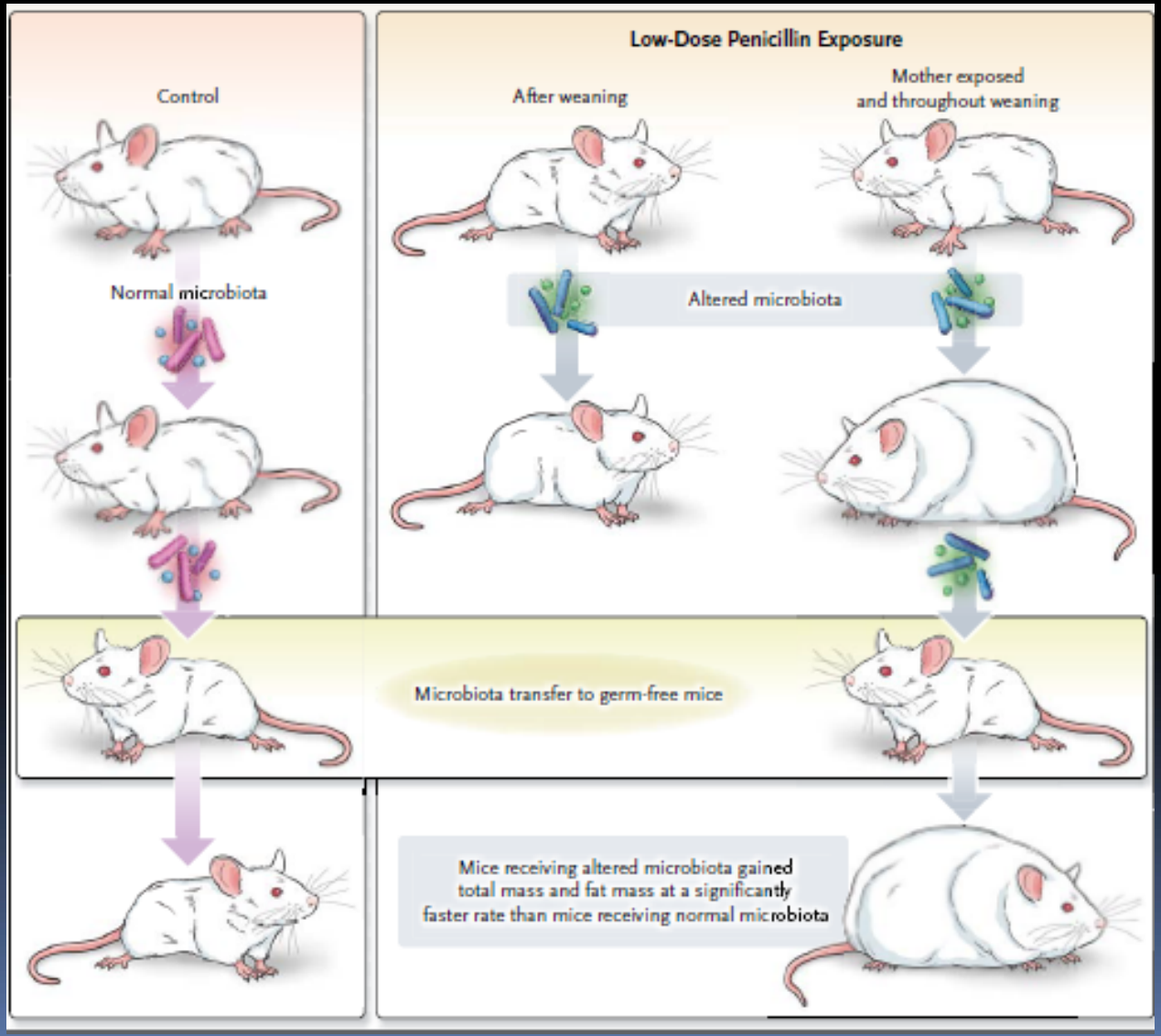


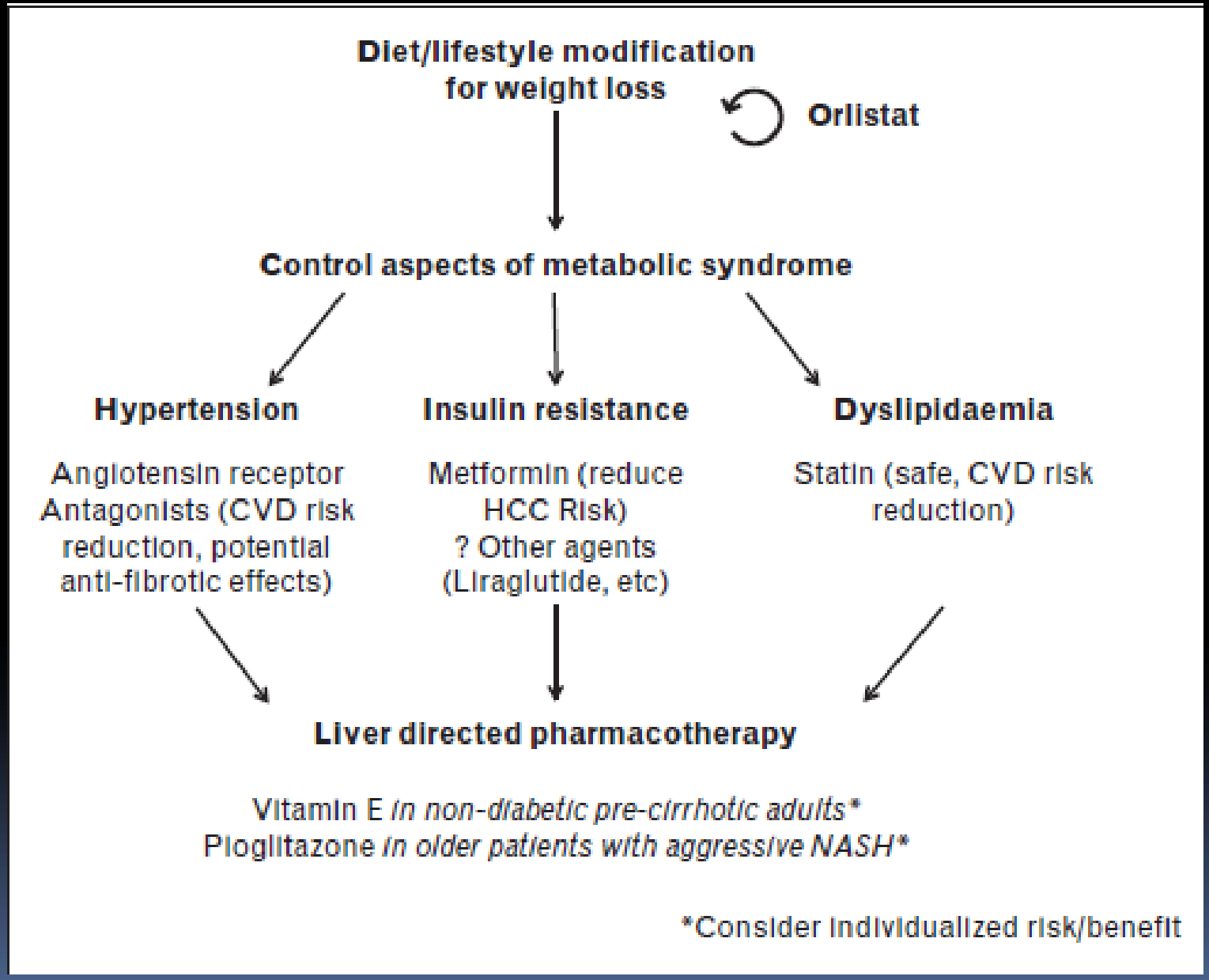
Microbiota Intestinal y NASH



Wisnewky A. Clin Microbiol Infect 2013; 19: 338–348

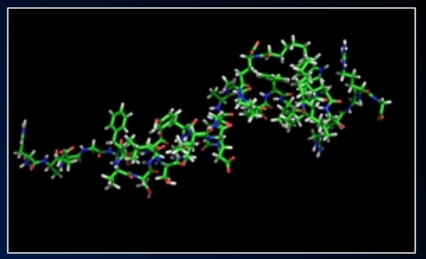
Efecto de la administracion de Penicilina sobre la microbiota intestinal antes y despues del destete. Efectos Potenciales sobre el Peso Corporal




Diet/lifestyle modification for weight loss
Orlistat
Control aspects of metabolic syndrome
Hypertension
Angiotensin receptor Antagonists (CVD risk reduction, potential anti-fibrotic effects)
Insulin resistance
Metformin (reduce HCC Risk)
? Other agents (Liraglutide, etc)
Dyslipidaemia
Statin (safe, CVD risk reduction)
Liver directed pharmacotherapy
Vitamin E *in non-diabetic pre-cirrhotic adults**
Pioglitazone *in older patients with aggressive NASH**
*Consider individualized risk/benefit

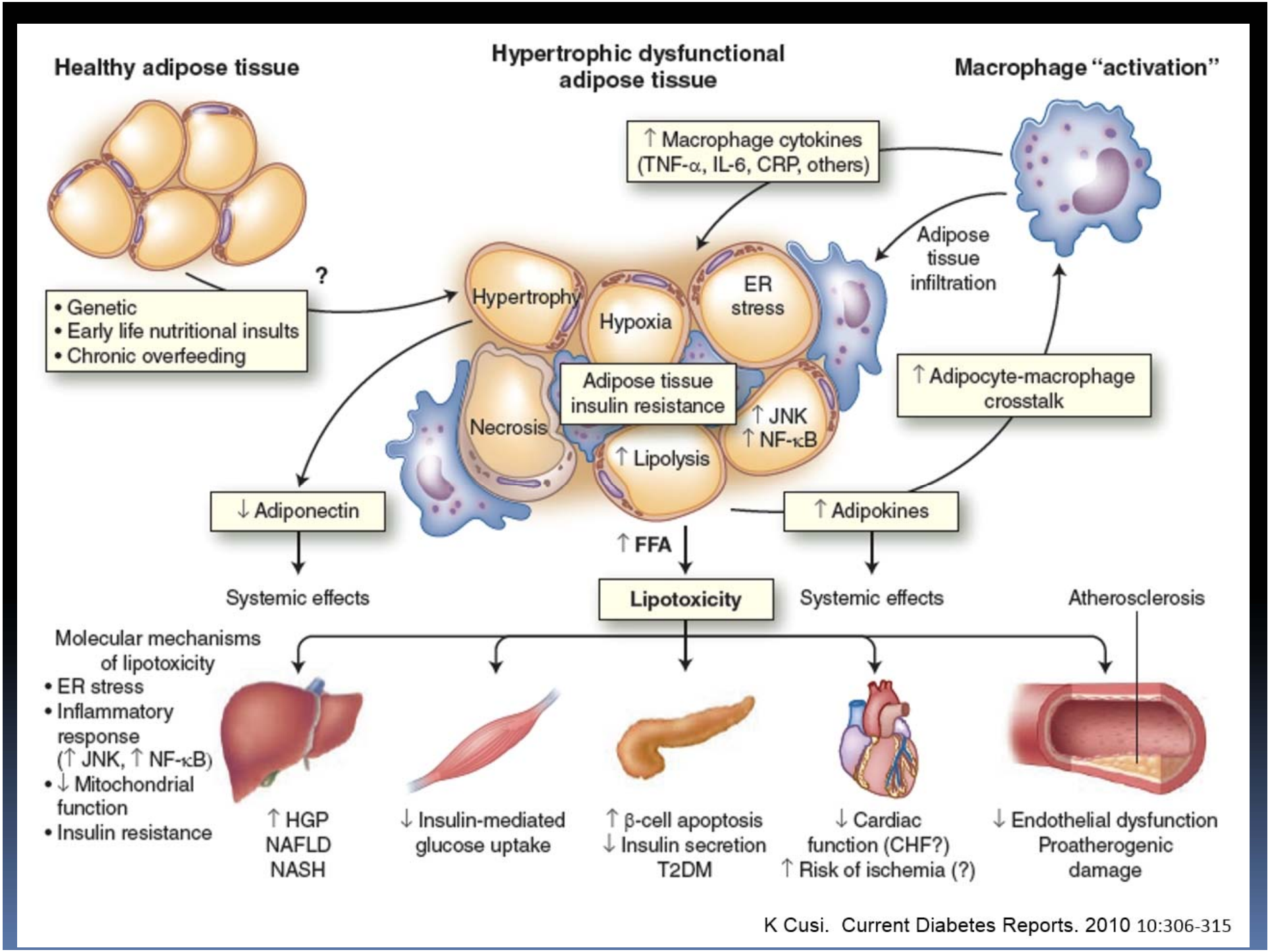
Muchas Gracias

Liraglutide (Victoza®) in NASH



- GLP-1 RA that lowers plasma glucose by ↑ insulin secretion, and ↓ appetite and stomach emptying.
- Controversial GLP-1 signaling in hepatocytes (Gupta et al, Hepatology 2010; Svegliati-Baroni et al, Liver Intern 2011).
- A 48-week Phase 2 RCT in 52 patients with biopsy-proven NASH, A1c <9%; patient characteristics well matched.
- Intervention: liraglutide or placebo (for up to 1.8 mg QD) for 48 weeks (follow-up at 72 weeks).

Armstrong MJ, et al. EASL 2015, Vienna. #G01



K Cusi. Current Diabetes Reports. 2010 10:306-315