Nutrition Therapy of Non-Alcoholic Fatty Liver Disease

A Most Convincing Argument for Low-Carb Eating

Nicolai Worm (PhD)

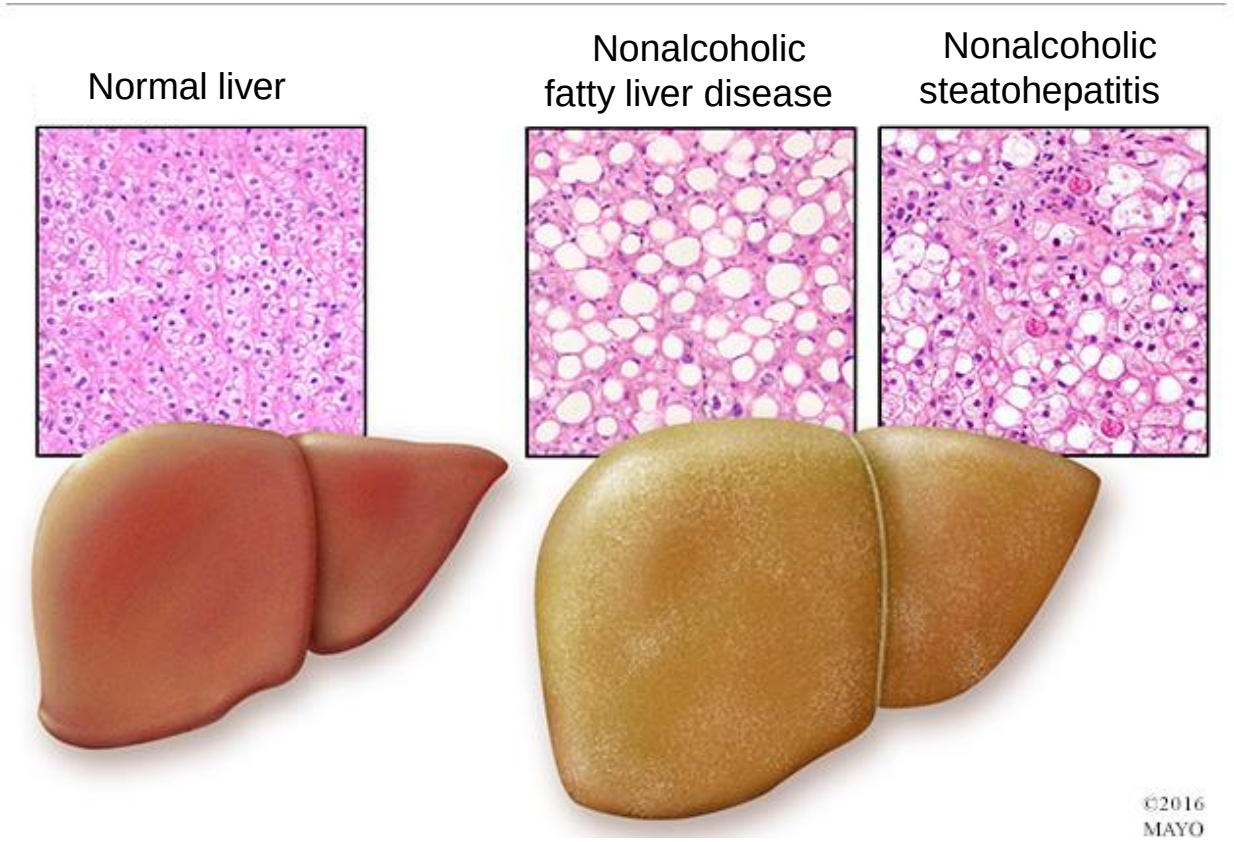
Munich/Germany

Conflict of Interest

- Author of 3 books on NAFLD (in German only)
- Creator of *Hepafast ® („Liver Fasting“)* – a liver-specific diet program (meal replacement + low-carb diet) for the treatment of NAFLD (available in Germany, Austria and Switzerland)

Definition: Non-Alcoholic Fatty Liver

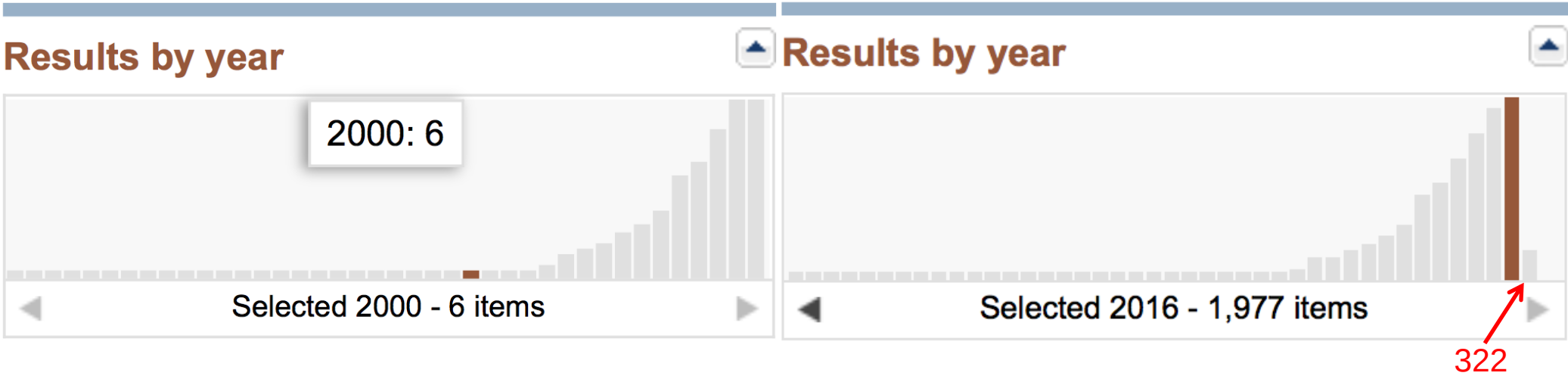
- Triglyceride content ≥ 5.5% of wet liver tissue weight
- Alcohol intake ≤ 20 g/day (women) ≤ 30 g/day (men)
- Exclusion of other causes



A New Widespread Disease:
„NAFLD“ first Entry in Pubmed in 1976

Pubmed-Search „NAFLD“ on February 18th 2017

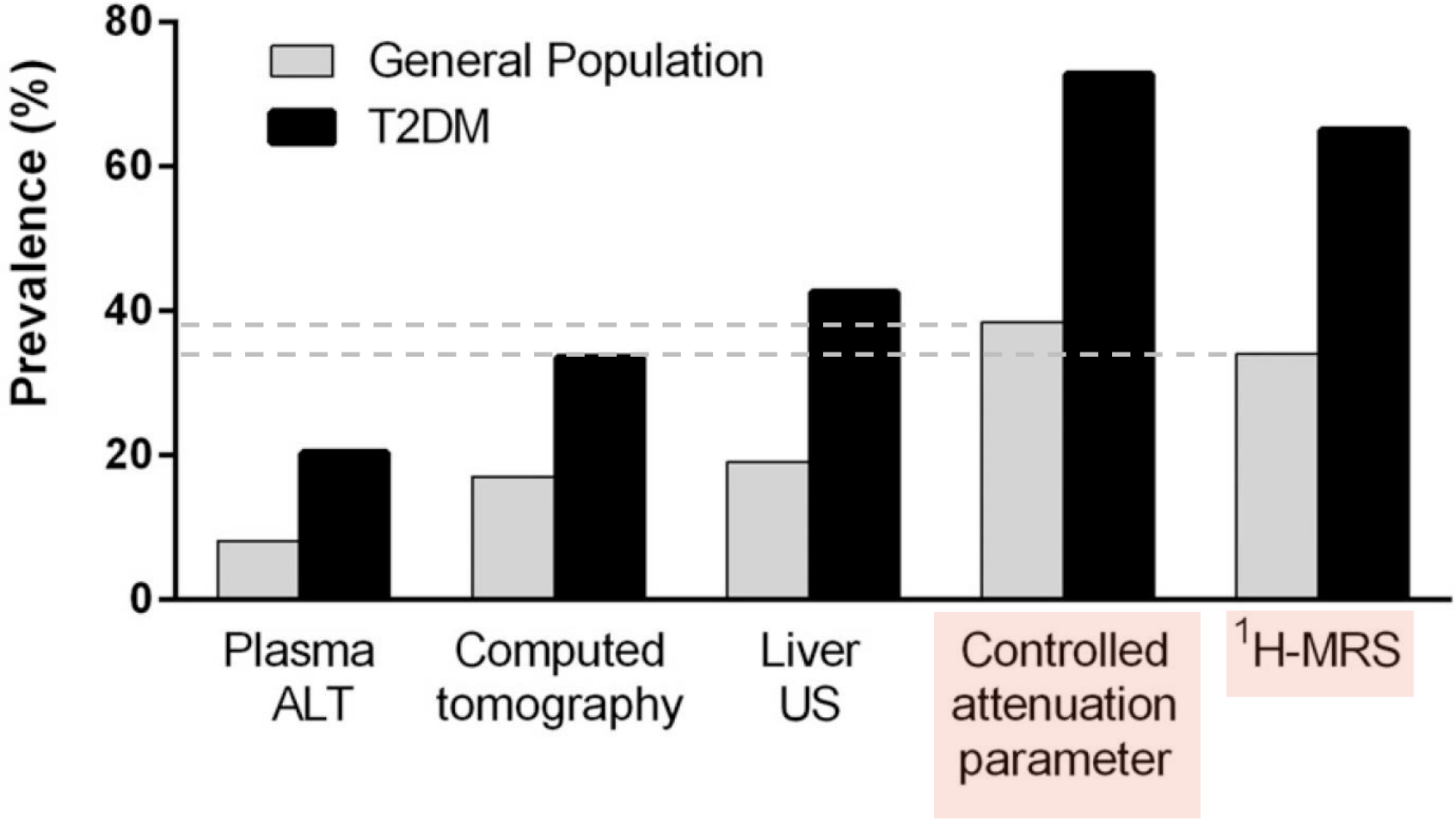
Publications per Year



Liver disease with the highest prevalence in the industrial world today!

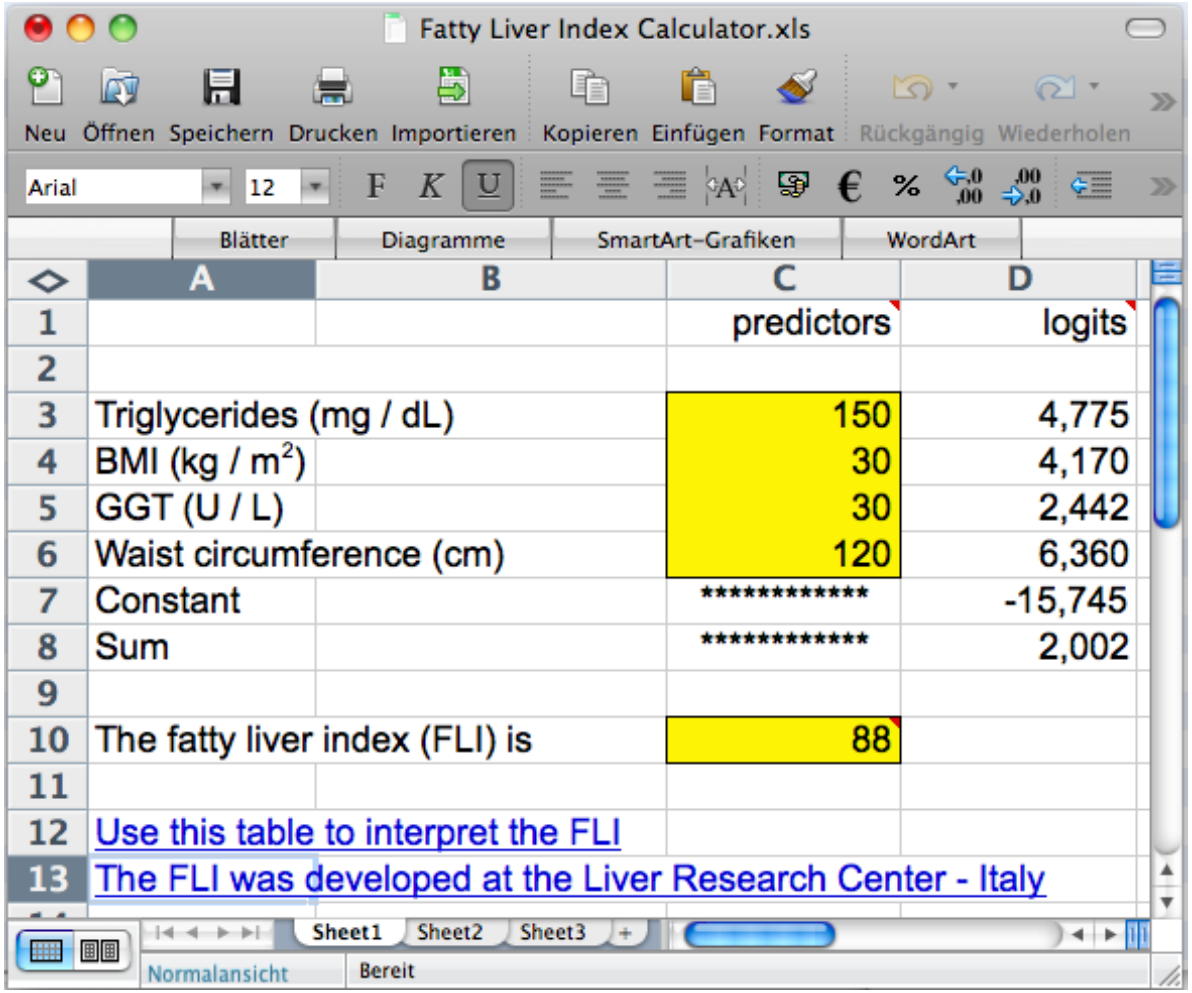
Prevalence of NAFLD in the USA

Using Different Diagnostic Tools



Bril F, et al. Diabetes Care 2017;40:419–430

Risk Calculator „Fatty Liver Index“



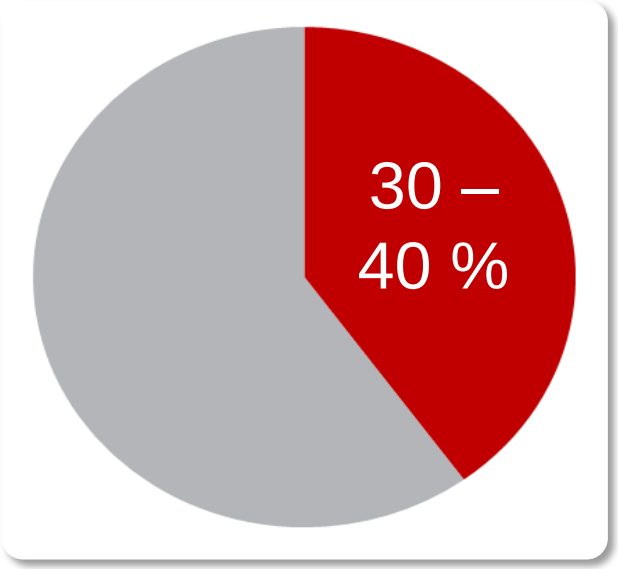
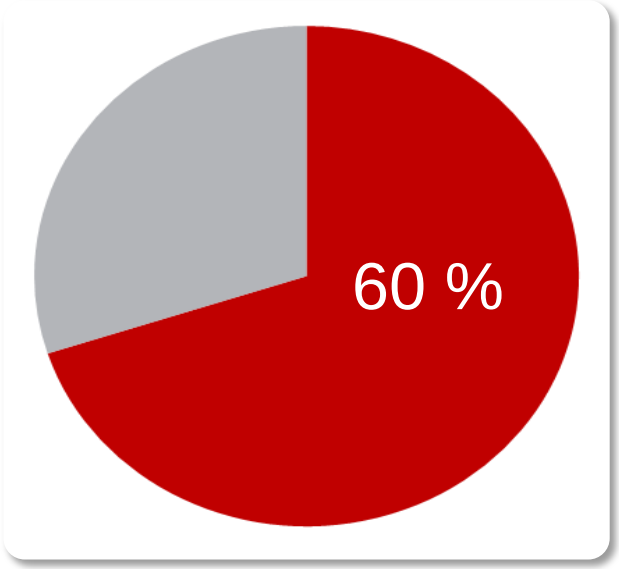
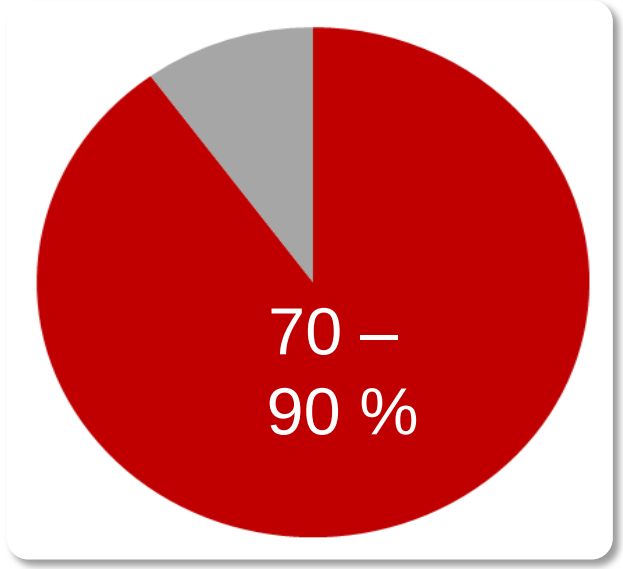
- Triglycerides
- GGT
- BMI
- Waist

FLI ≥ 60 => 78% probability of liver steatosis

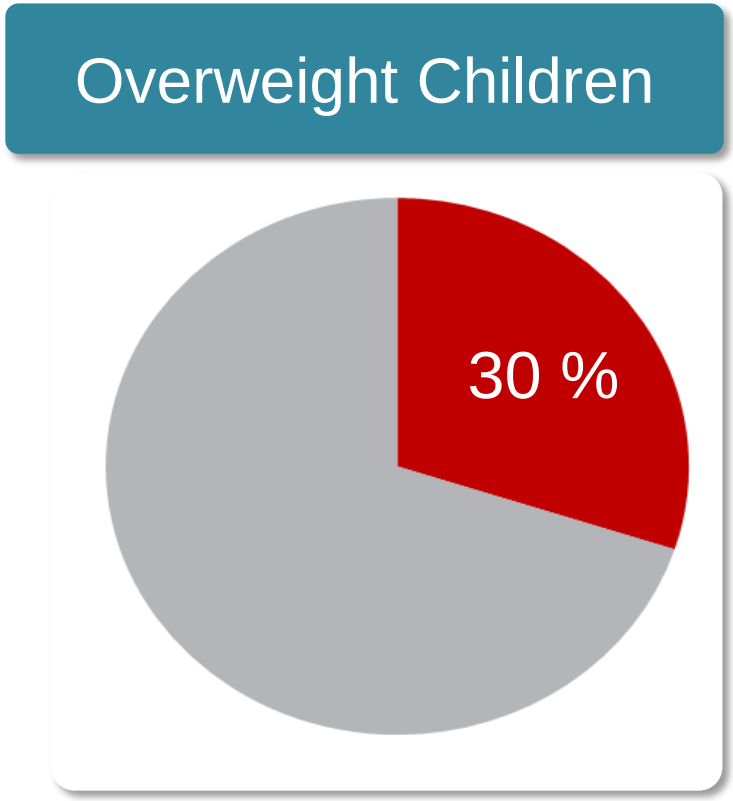
FLI < 20 => 91% probability of no liver steatosis

Prevalence of NAFLD

Nonalcoholic Fatty Liver Disease is the
most prevalent chronic liver disease in the world!

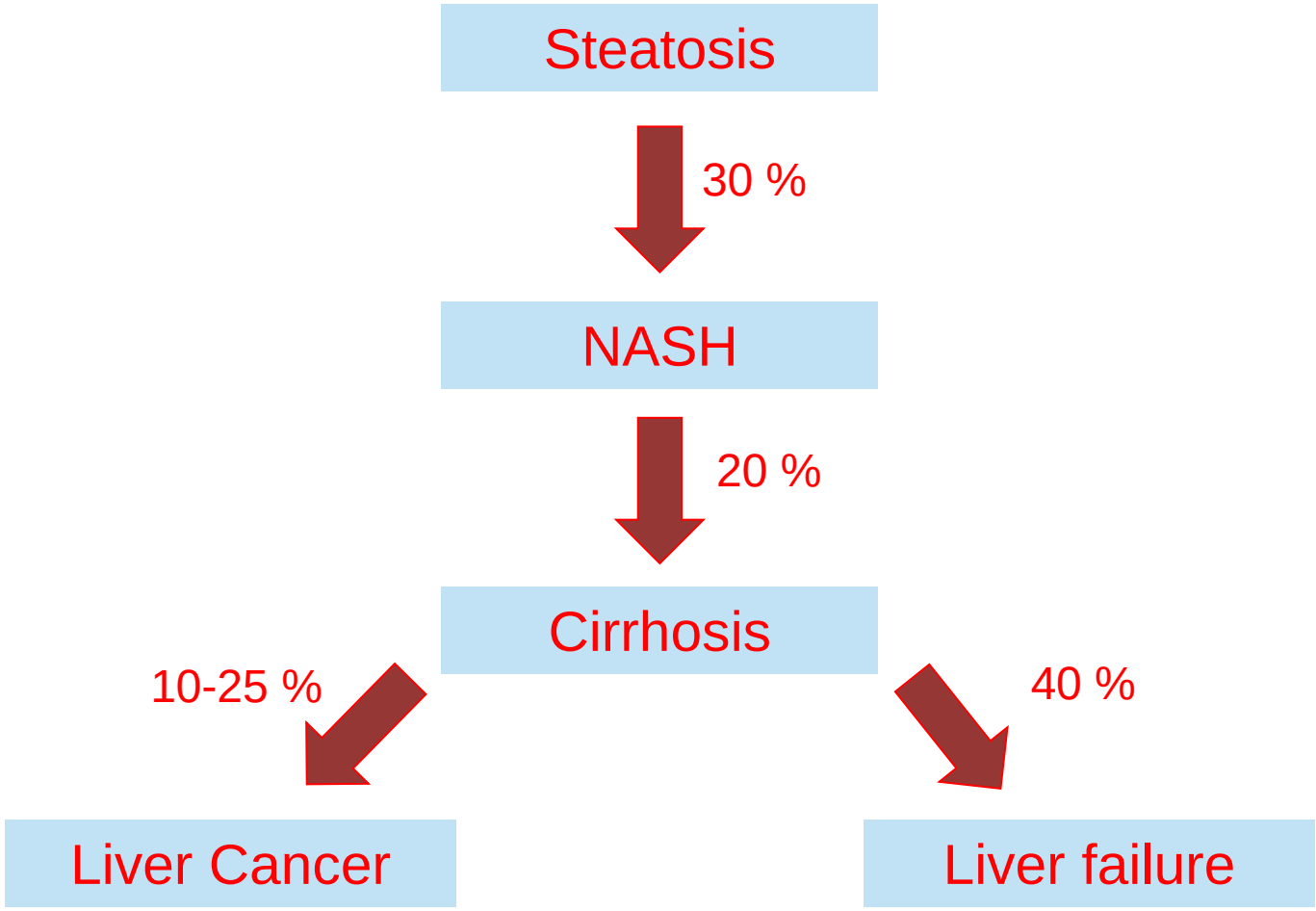
Adults	Overweight/Obese	Type-2-Diabetics
		

Prevalence of NAFLD in Overweight School Children in Germany



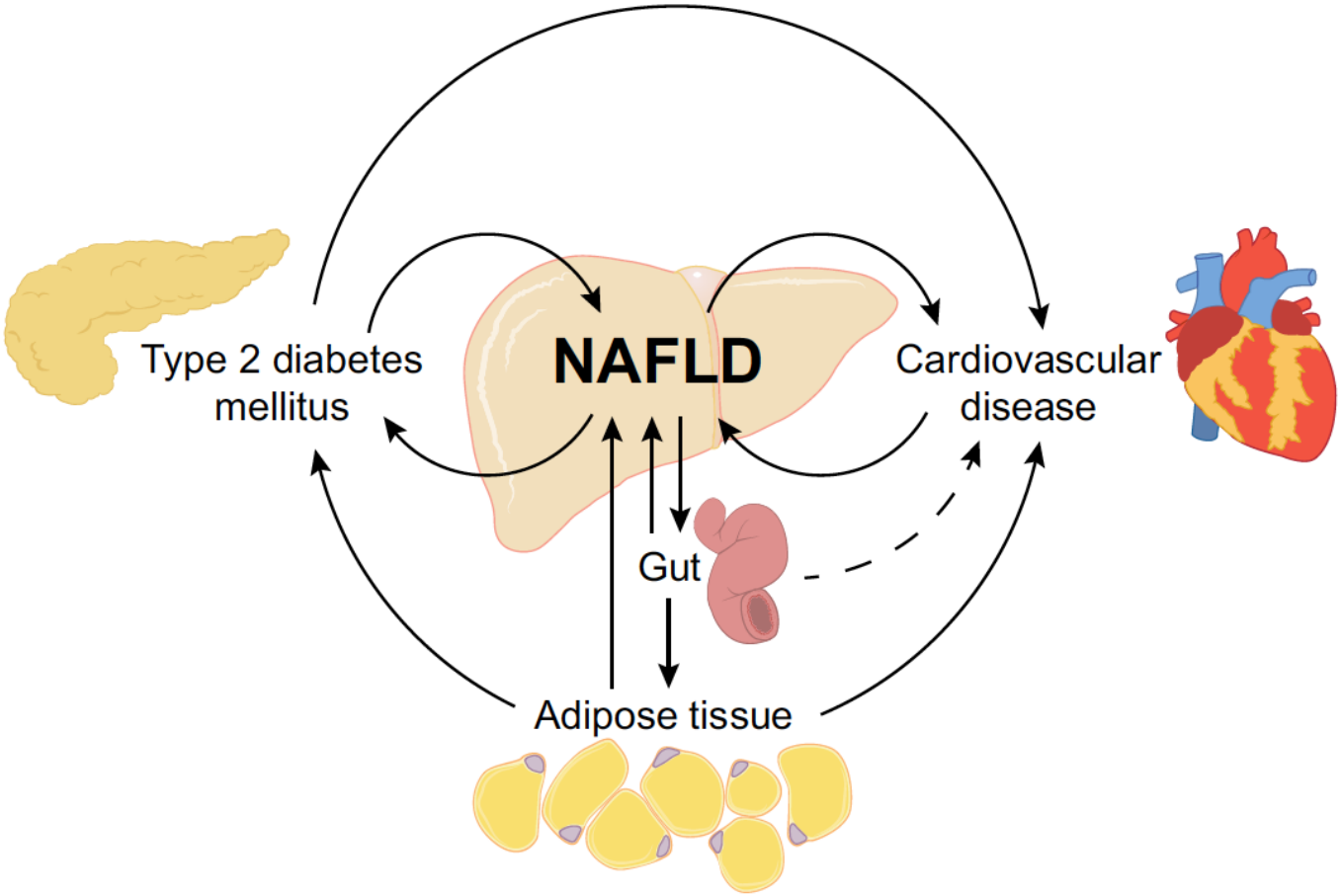
Denzer C. Deutsches Gesundheitsblatt 2013;56:517-527

Traditionally a Disease for Hepatologists: Progression of Liver Steatosis



EASL JOURNAL OF HEPATOLOGY

Non-alcoholic fatty liver disease and cardiovascular risk: Pathophysiological mechanisms and implications



Francque SM, et al. J Hepatol. 2016;65:425-43.

Atherosclerosis 239 (2015) 192–202

Review

A concise review of non-alcoholic fatty liver disease

Nwe Ni Than*, Philip N. Newsome

The Centre of Liver Research and NIHR Biomedical Research Unit in Liver Diseases, University of Birmingham and University Hospital Birmingham NHS Trust, UK

A B S T R A C T

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the met
incidence of which is rising rapidly due to the increasing epidemic
and children.
The initial accumulation of fat followed by subsequ
to the development of
liver damage, and is critically influenc
ing age, gender, presence of diabetes,
genetic polymorphisms and
microbiome. An increasing body of data suggest
that NAFLD is
factor of cardiovascular disease, which remains the commonest
patients. This review focusses on the pathogenesis of NAFLD, and the evolution
aches to the management and treatment of NAFLD.

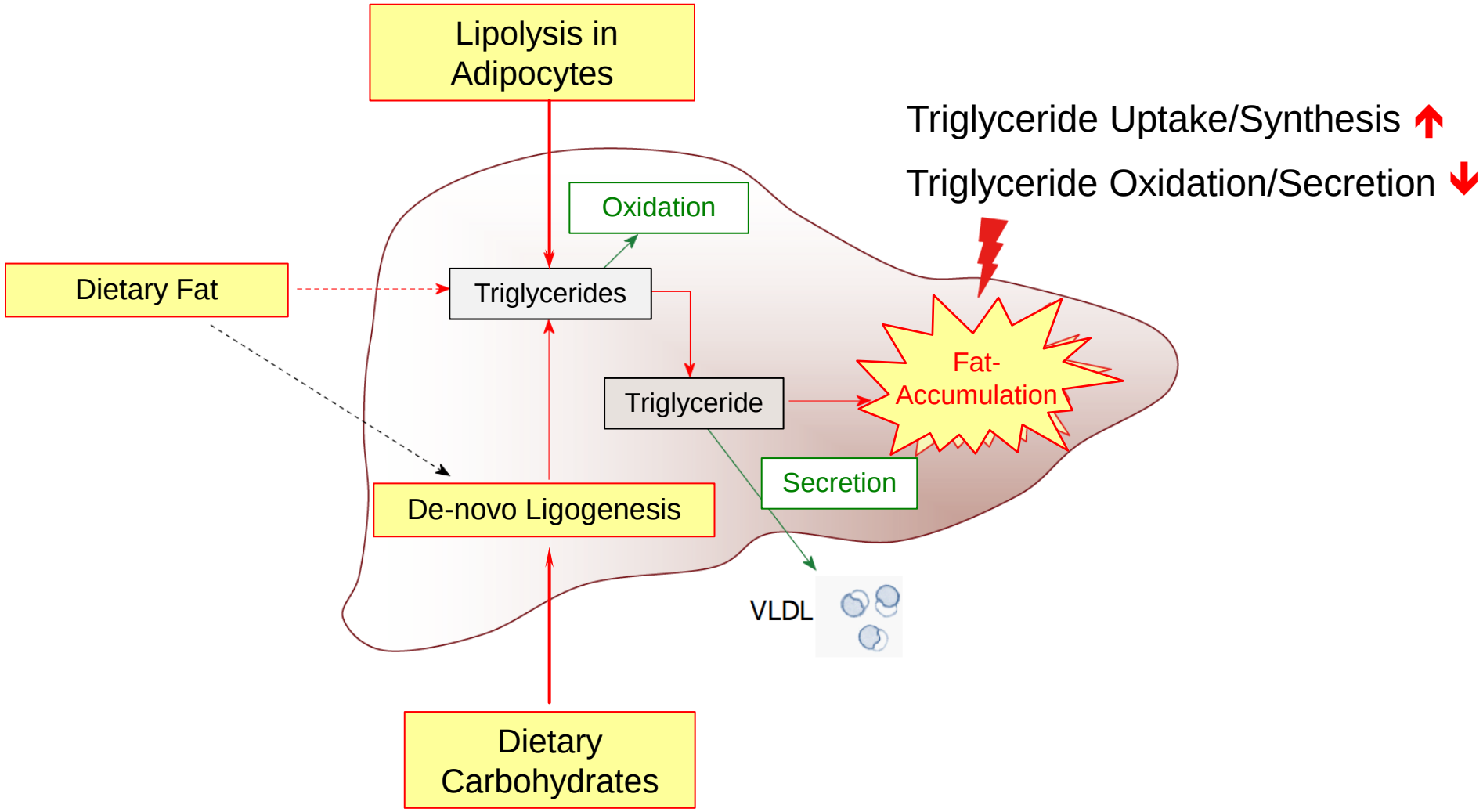
„NAFLD is …an independent risk factor of cardiovascular disease“

NAFLD – a Better Predictor for Diabetes and Cardiovascular and Kidney Disease than the Metabolic Syndrome!

„...because NAFLD predicts type 2 diabetes, even <u>independent</u> of metabolic syndrome, it might be better for predicting risk of type 2 diabetes and cardiovascular disease than is metabolic syndrome...“

Yki-Järvinen H. Lancet Diabetes Endocrinol. 2014;2(11):901-10

Development of NAFLD



Ferramosca A, et al. World J Gastroenterol 2014;20:1746-1755; Donnelly KL, et al. J Clin Invest 2005;115:1343-51.

Sources of Fat in Hepatic Steatosis

Overweight patients with NAFLD (hypertriglyceridemia and hyperinsulinemia); 4 days infusion + orally given stable isotopes

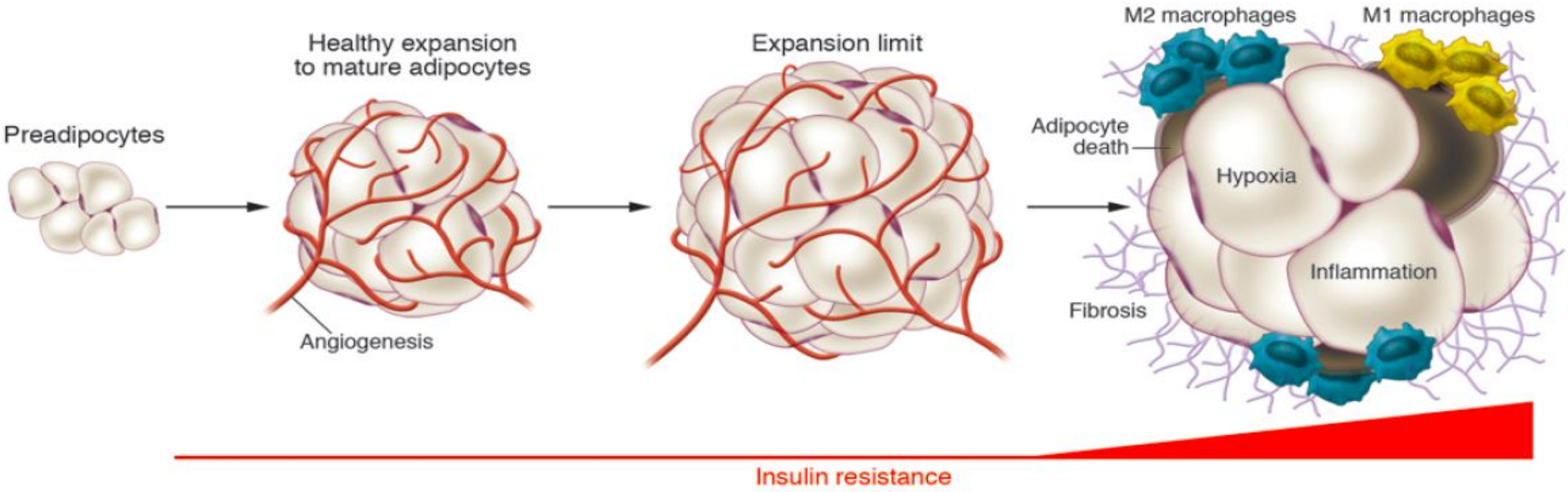
Origins of fat in the liver:

- 59 % from lipolysis of adipocytes
- 26 % from „de novo“ lipogenesis (dietary carbohydrates)
- 15 % from dietary fat

Donnelly KL, et al. J Clin Invest 2005;115:1343–1351

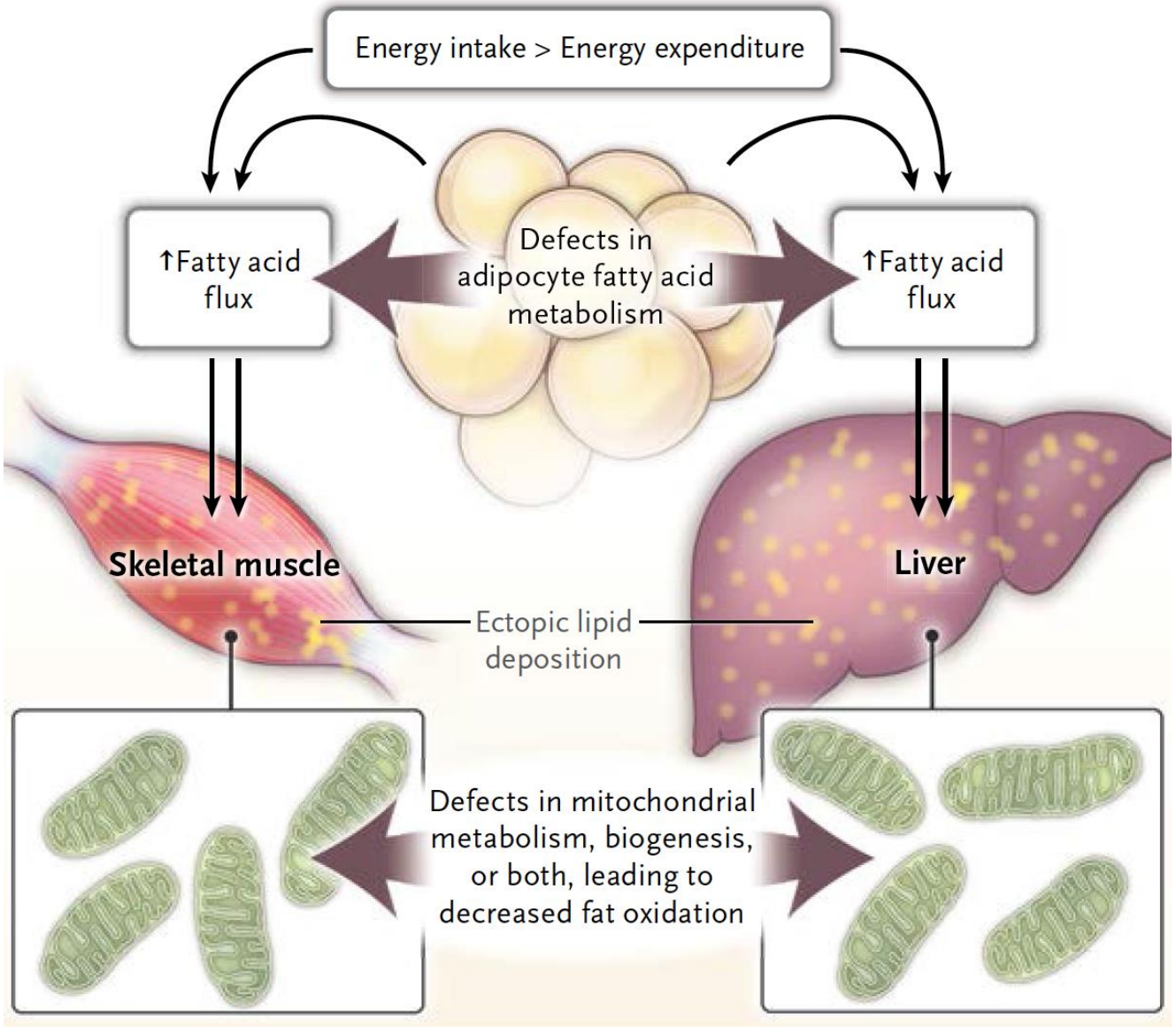
Dysfunctional Fat Storage, Ectopic Fat and NAFLD

Hypertrophy and Vascularisation of Adipose Tissue

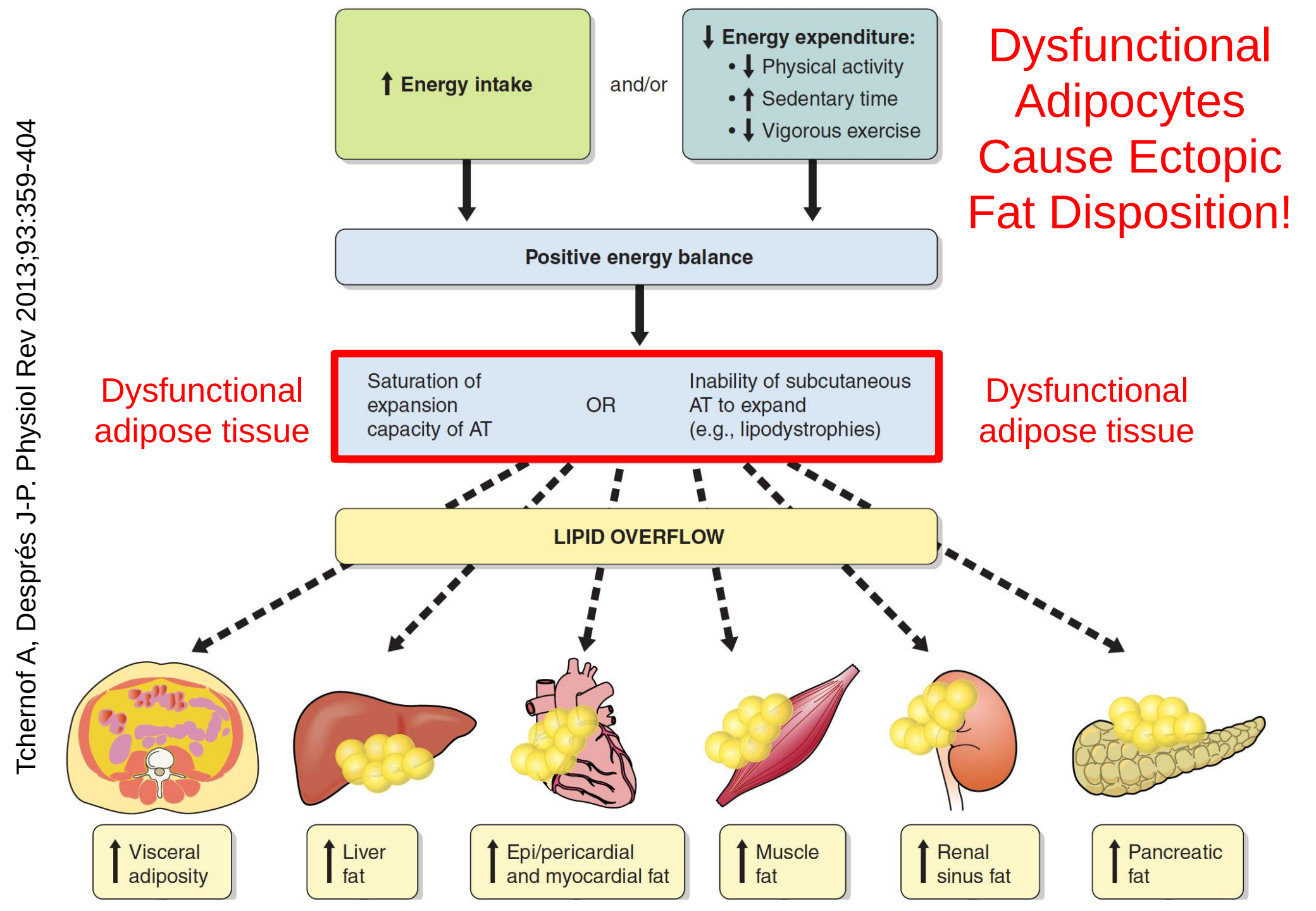


Sun K, et al. J Clin Invest. 2011;121:2094-2101.

Dysfunctional Adipocytes cause ectopic Lipid Deposition



Shulman GI. N Engl J Med 2014;371:1131-41.



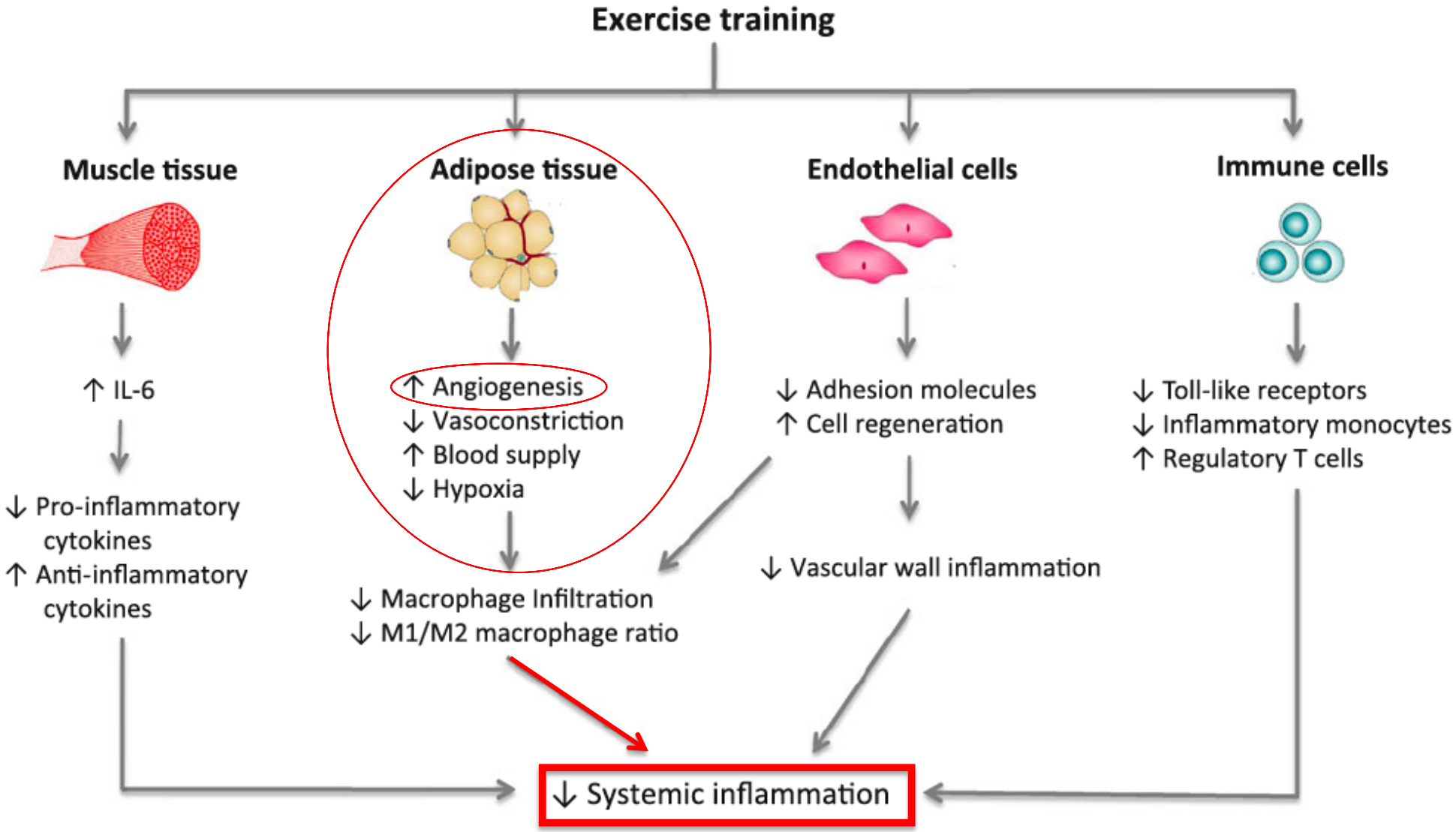
Dysfunctional Adipocytes Cause Ectopic Fat Disposition!

Dysfunctional adipose tissue

Dysfunctional adipose tissue

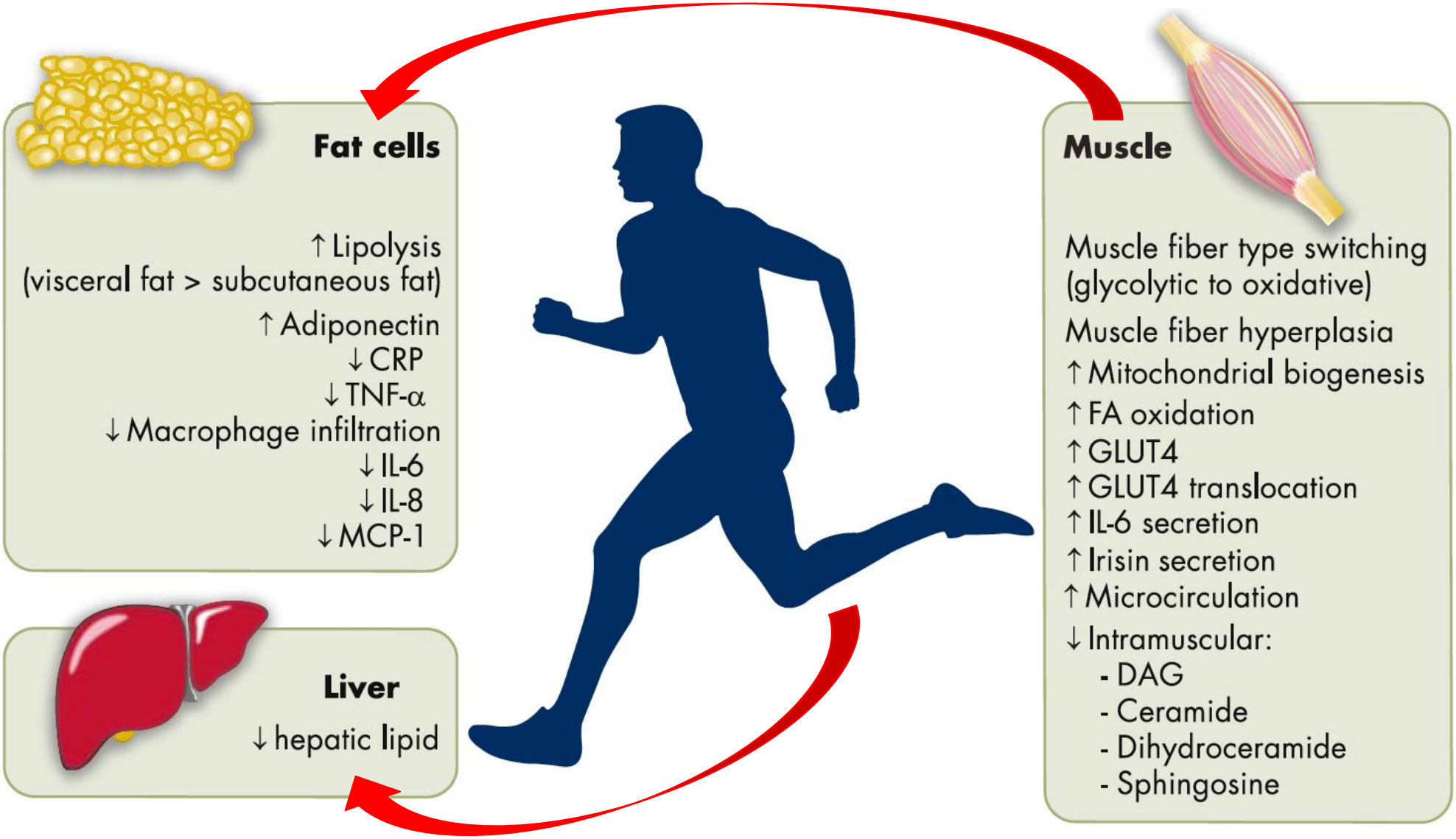
Tchernof A, Després J-P. Physiol Rev 2013;93:359-404

Adipose Tissue Function and Physical Exercise



You T, et al. Sports Med 2013;43:243-256.

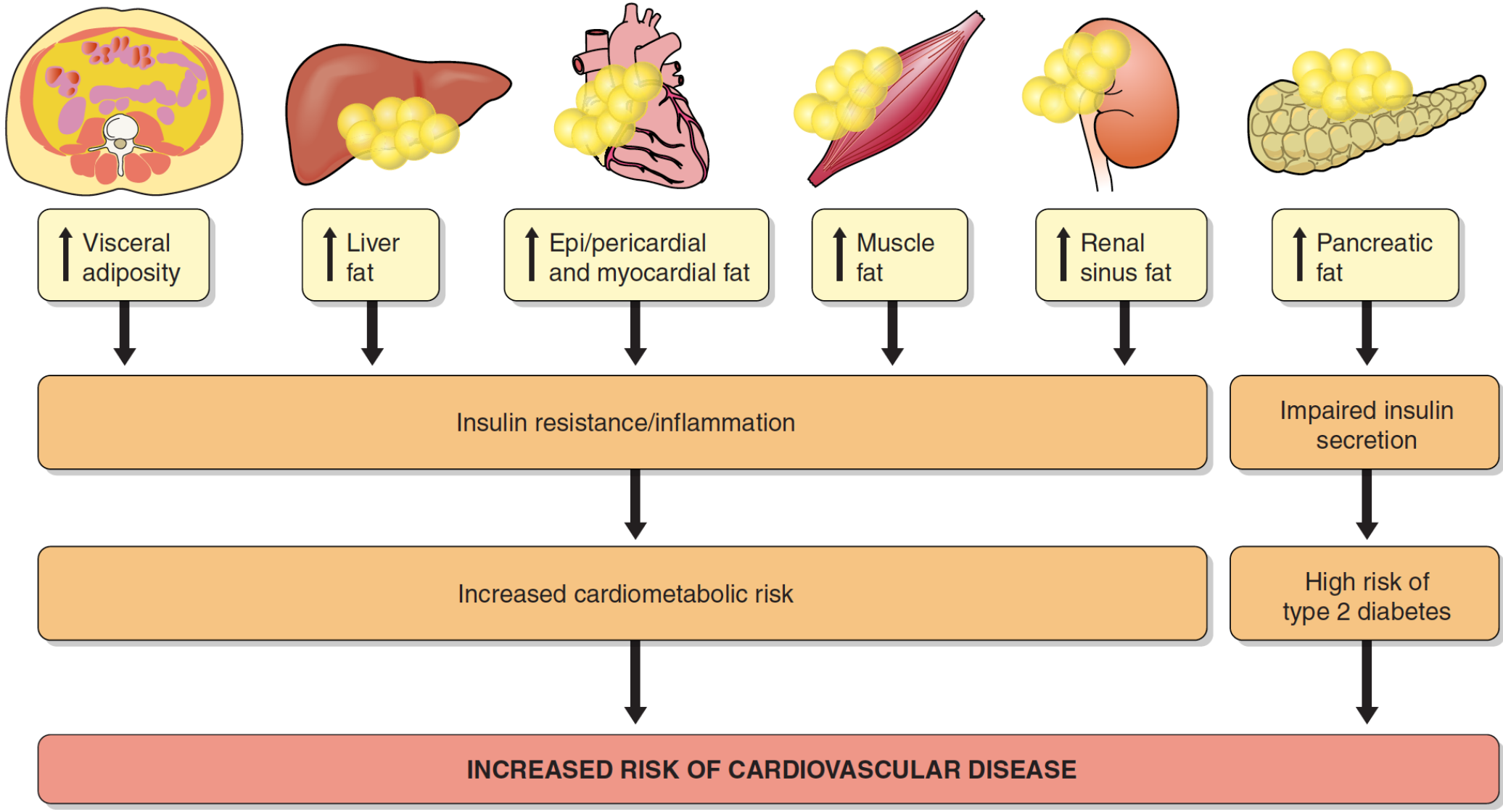
Muscles, Myocines and Metabolic Regulation



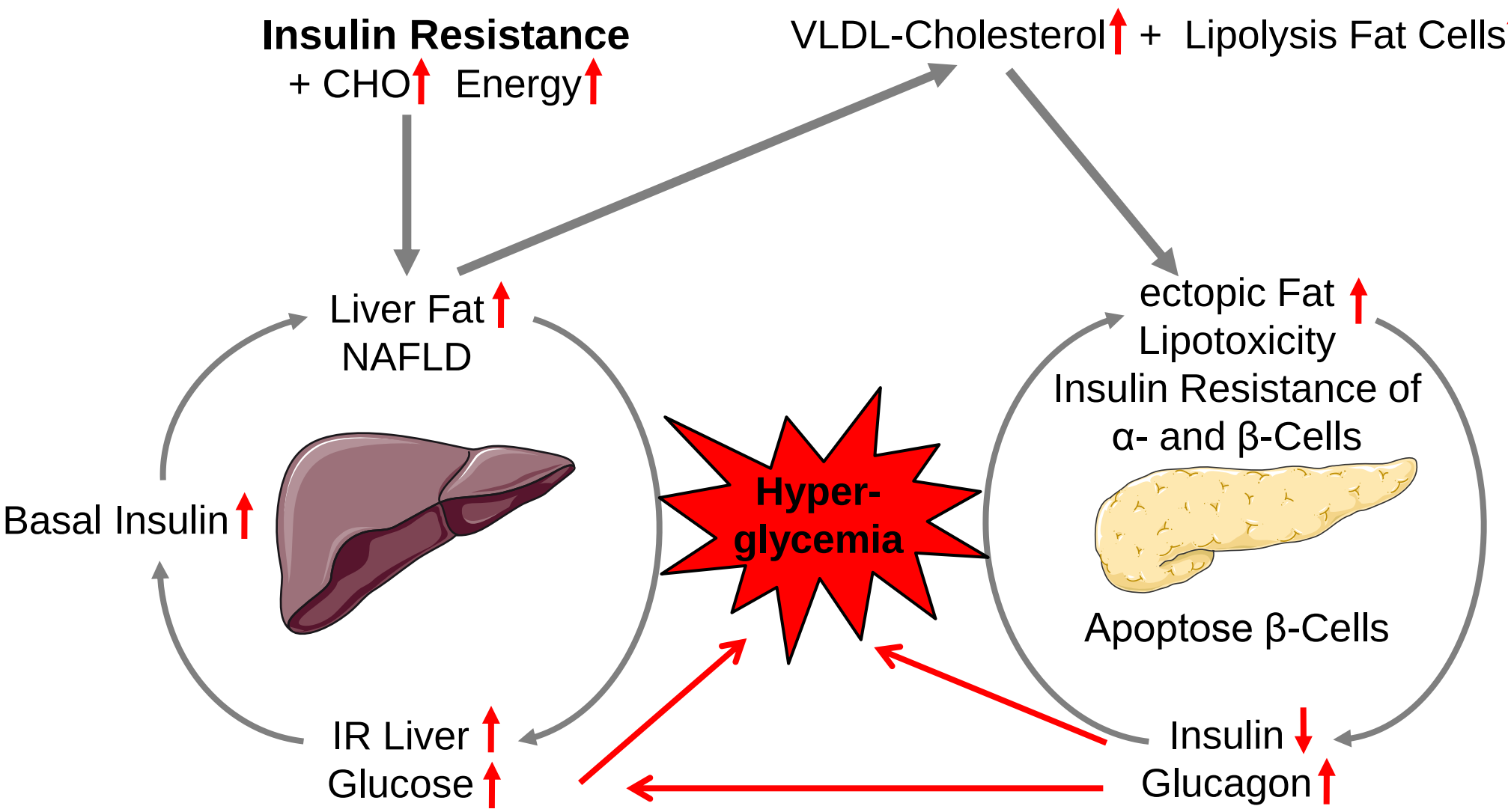
Hocking S, et al. Endocr Rev. 2013;34:463-500.

Ectopic Fat and Risk

Tchernof A, Després J-P. Physiol Rev 2013;93:359-404

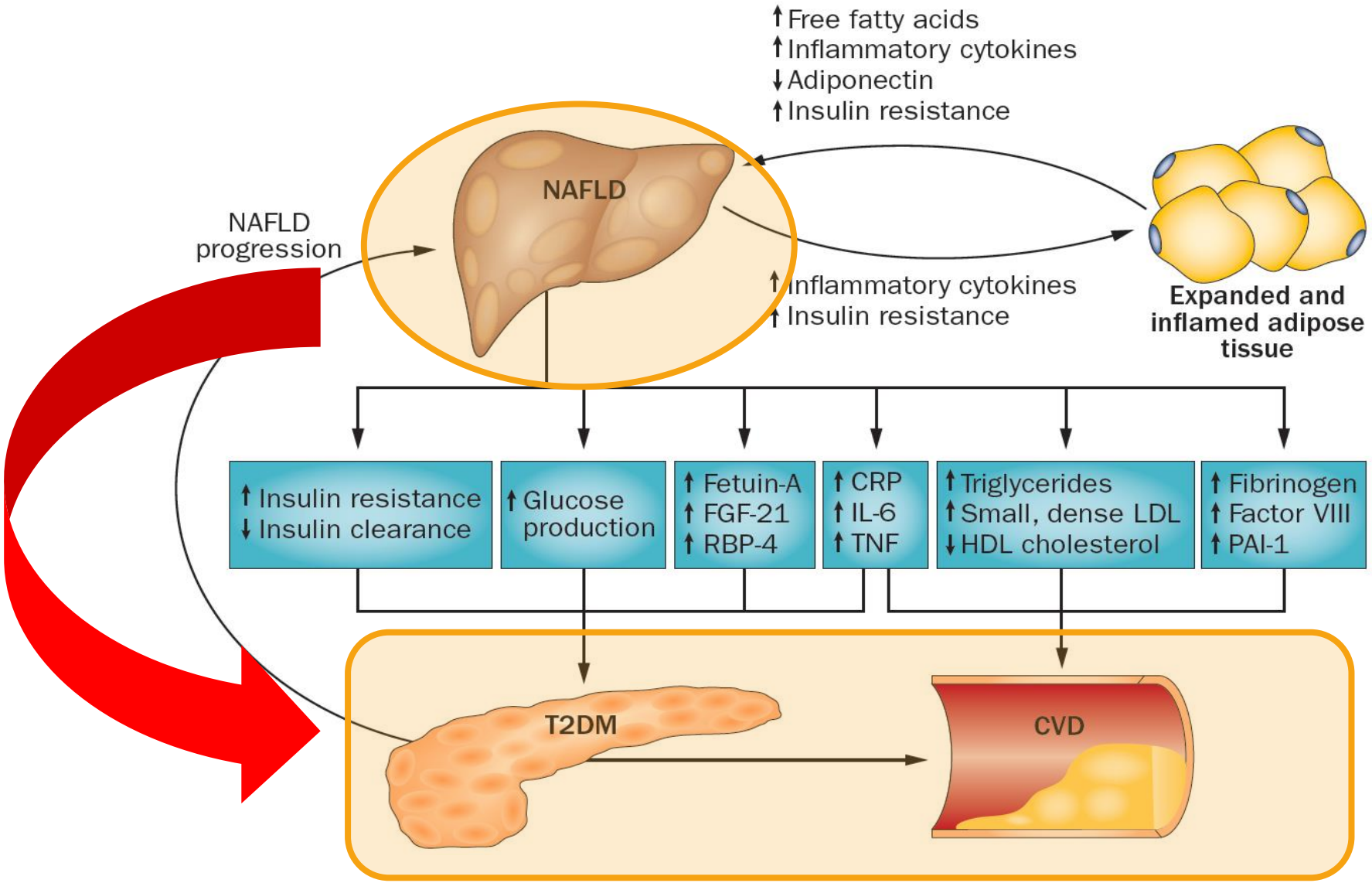


NAFLD Predisposes to Typ-2 Diabetes

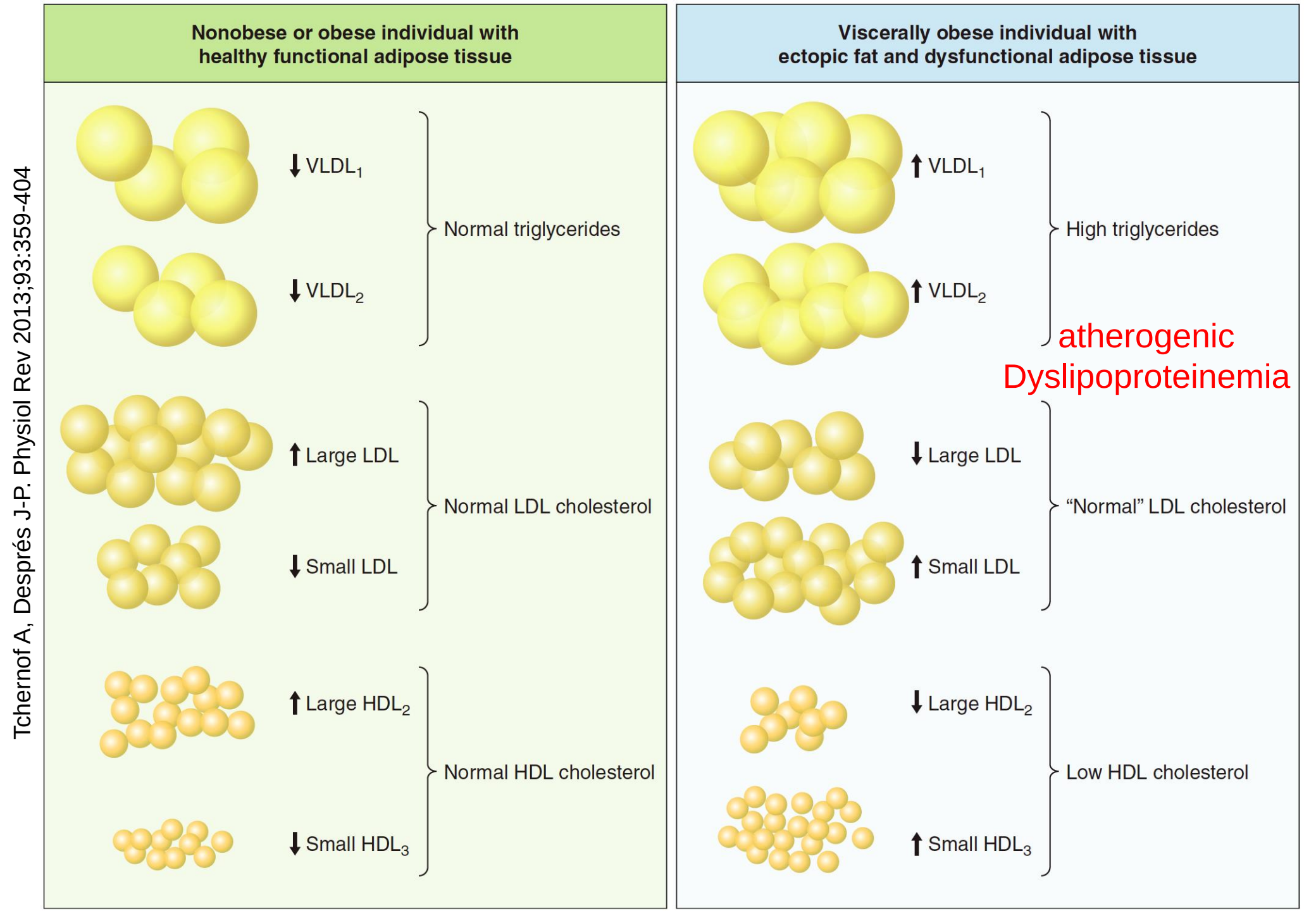


Taylor R. Reversing the Twin Cycles of Type 2 Diabetes. Diab Med 2013;30:267-275

NAFLD predisposes to T2DM and CVD



Anstee QM, et al. Nat Rev Gastroenterol Hepatol. 2013;10:330-44.



Tchernof A, Després J-P. Physiol Rev 2013;93:359-404

Review
OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

Obesity

Normal Weight Dyslipidemia: Is It All About the Liver

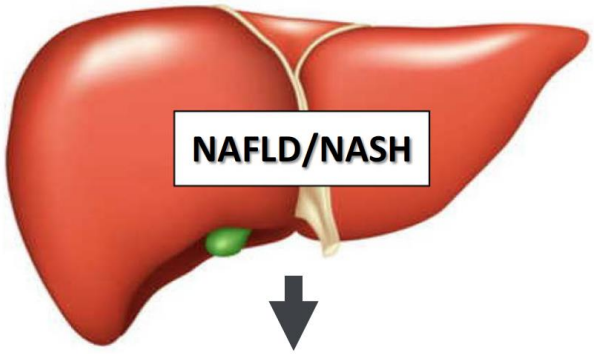
David Højland Ipsen, Pernille Tveden-Nyborg, and Jens Lykkesfeldt

Objective: The liver coordinates lipid metabolism and may play a vital role in the development of dyslipidemia, even in the absence of obesity. Normal weight dyslipidemia (NWD) and patients with nonalcoholic fatty liver disease (NAFLD) who do not have obesity constitute a unique subset of individuals characterized by dyslipidemia and metabolic deterioration. This review examined the available literature on the role of the liver in dyslipidemia and the metabolic characteristics of patients with NAFLD who do not have obesity.
Methods: PubMed was searched using the following keywords: nonobese, dyslipidemia, NAFLD, NWD, liver, and metabolically obese/unhealthy normal weight. Additionally, article bibliographies were screened, and relevant citations were retrieved. Studies were excluded if they had not measured relevant biomarkers of dyslipidemia.
Results: NWD and NAFLD without obesity share a similar abnormal metabolic profile. When compared with patients with NAFLD who have obesity, the metabolic abnormalities of NAFLD without obesity are similar or less severe. Furthermore, hepatic lesions develop independent of obesity, and the extent of dyslipidemia seems comparable.
Conclusions: NAFLD may impair hepatic lipid handling, causing faulty lipid homeostasis, and serves as a likely starting point for initiation and propagation of dyslipidemia along with associated comorbidities in patients without obesity.

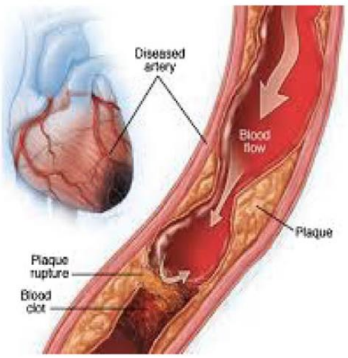
Obesity (2016) **00**, 00–00. doi:10.1002/oby.21443

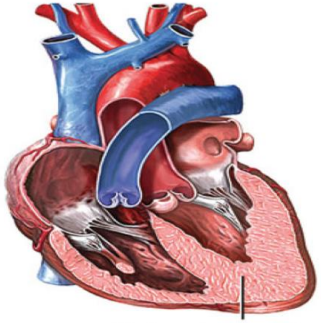
Ipsen DH, et al. Obesity 2016; online first Feb 12

NAFLD and Associated Cardiac Complications

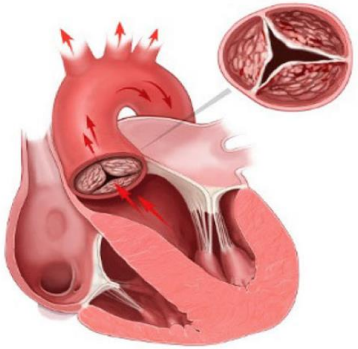


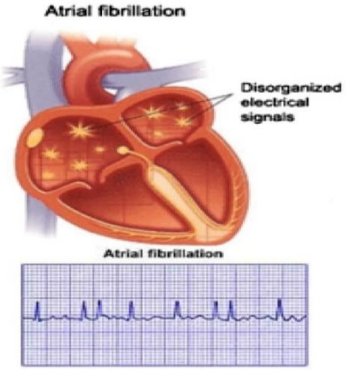
NAFLD-related cardiac complications





Enlargement of heart muscle





	Cardiac Dysfunction Cardiac Hypertrophy	Aortic-Valve Sclerosis	Atrial Fibrillation
Coronary Heart Disease	Heart Failure	Mitral Annulus Calcification	QTc Prolongation

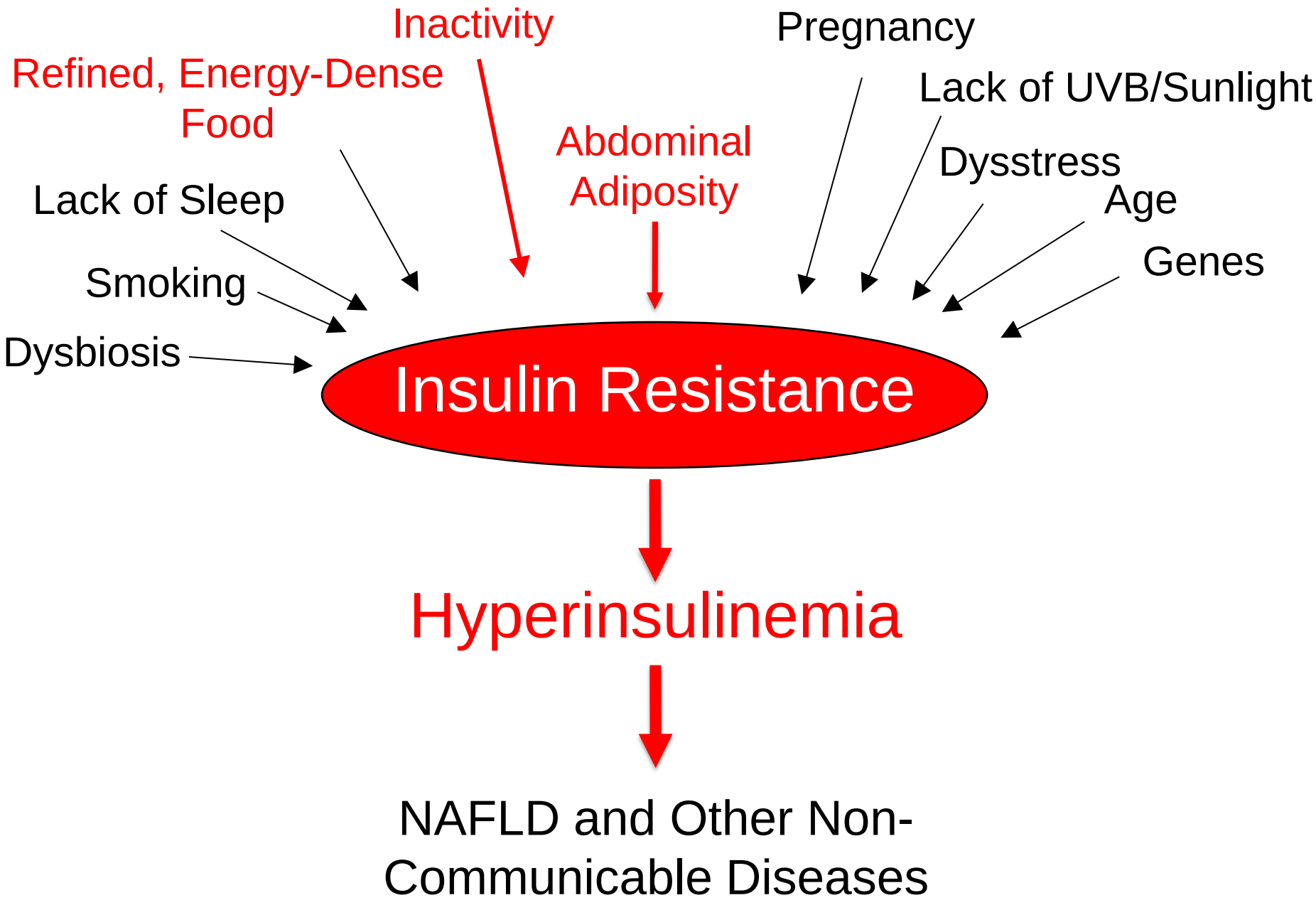
Mantovani A, et al. Clin Sci. 2013;125:301-9.

Sources of Fat in Hepatic Steatosis

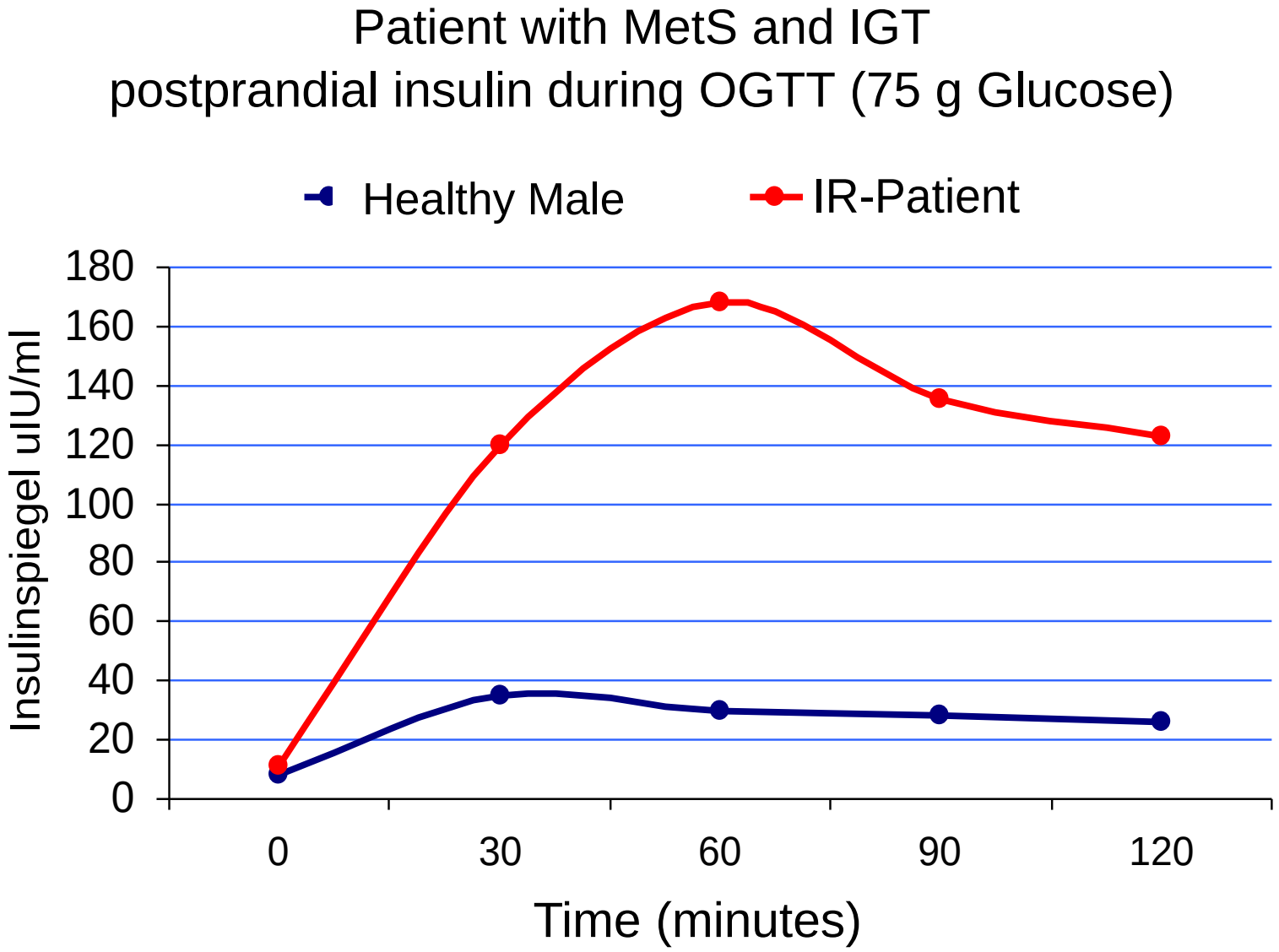
Donnelly KL, et al. J Clin Invest 2005;115:1343–1351

In overweight patients with NAFLD (Hypertriglyceridemia and Hyperinsulinemia) hepatic fat originates:

- 59 % lipolysis of adipocytes
- 26 % de novo lipogenesis (dietary carbohydrates/fructose)
- 15 % dietary fat


Inactivity
Pregnancy
Refined, Energy-Dense Food
Lack of UVB/Sunlight
Abdominal Adiposity
Dysstress
Lack of Sleep
Age
Smoking
Genes
Dysbiosis
Insulin Resistance
Hyperinsulinemia
NAFLD and Other Non-Communicable Diseases

Insulin Resistance and Hyperinsulinemia

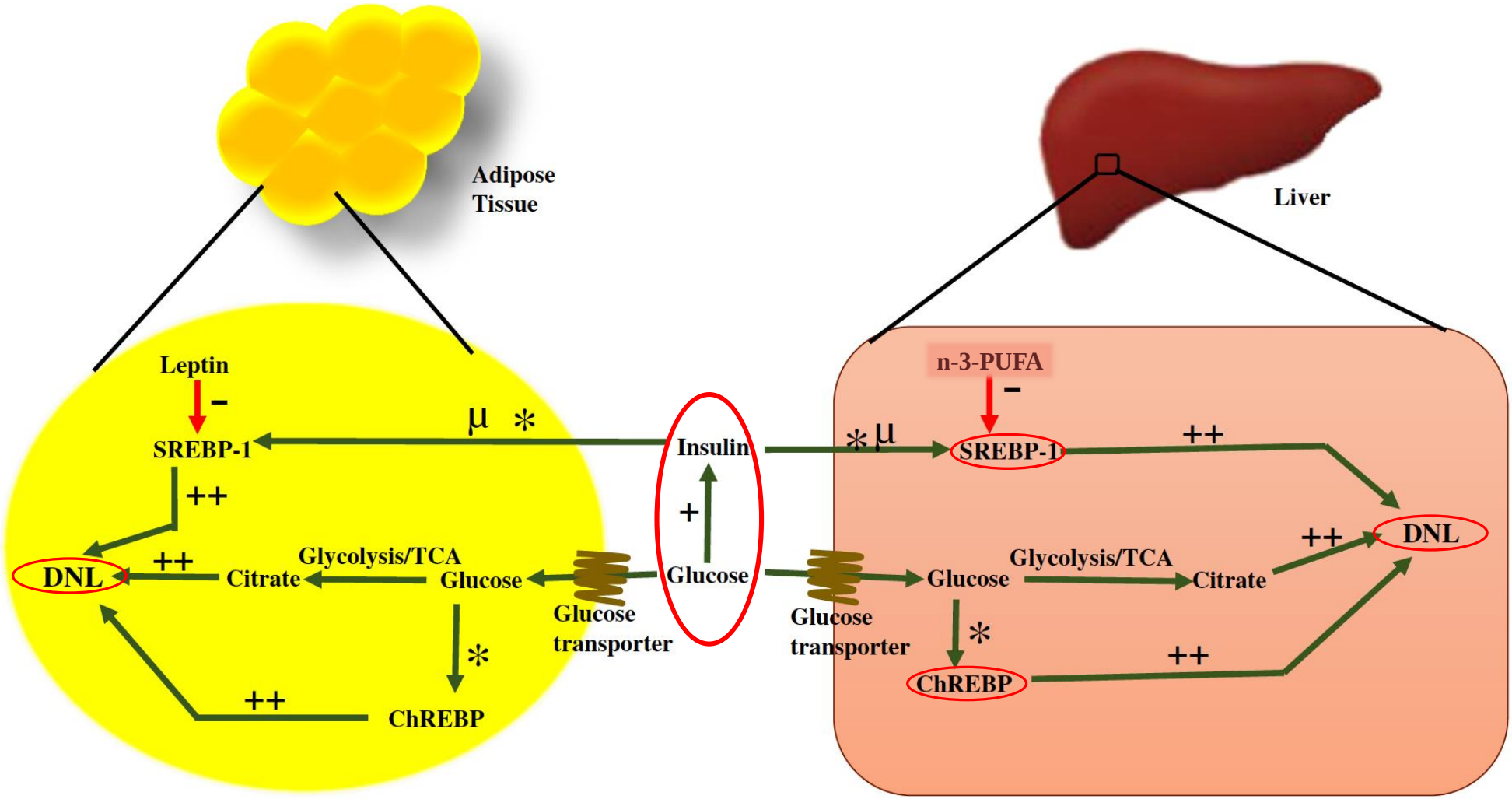


Scholl J. persönl. Mittl. 2008;

Hyperinsulinemia and de novo Lipogenesis

De-novo Lipogenesis in Liver Cells and Fat Cells

Postprandial Glucose + Hyperinsulinemia activate
the two Transcriptionsfactors ChREBP and SREBP-1



Ameer F, et al. Metabolism 2014;63:895-902.

Hepatic de novo lipogenesis in normoinsulinemic and hyperinsulinemic subjects consuming high-fat, low-carbohydrate and low-fat, high-carbohydrate isoenergetic diets[1–3]

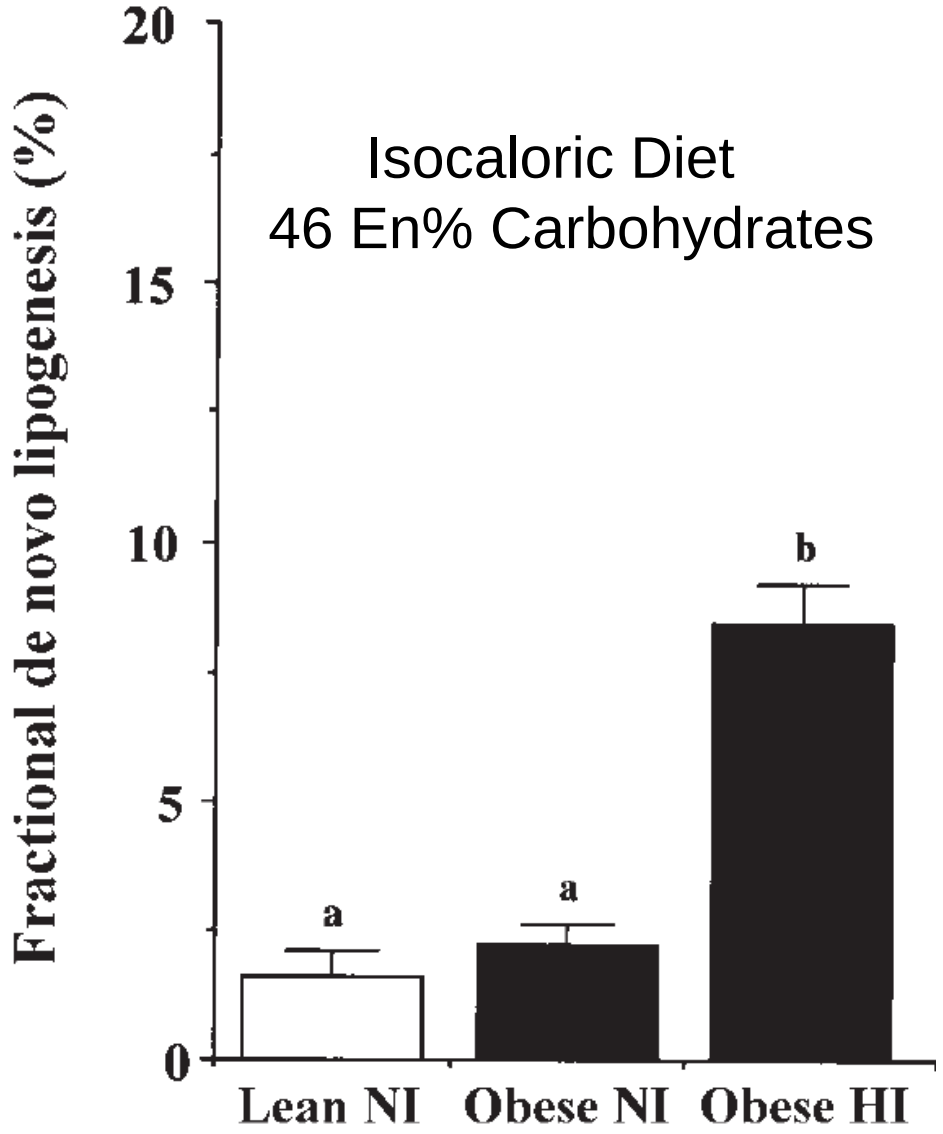
Jean-Marc Schwarz, Peter Linfoot, Doris Dare, and Karmen Aghajanian

[1] From the Department of Nutritional Sciences and Toxicology, University of California, Berkeley (J-MS and KA), and the Department of Medicine, University of California, San Francisco (J-MS, PL, and DD).

Fasting DNL was measured after a low-fat, high-carbohydrate diet in normoinsulinemic (≤ 85 pmol/L) lean (n = 9) and obese (n = 6) and hyperinsulinemic (≥ 115 pmol/L) obese (n = 8) subjects. Mass isotopomer distribution analysis was used to measure the fraction of newly synthesized fatty acids in VLDL-triacylglycerol.

Schwarz JM, et al. Am J Clin Nutr 2003;77:43–50

Hyperinsulinemia and de novo Lipogenesis



Schwarz JM, et al. Am J Clin Nutr 2003;77:43–50

Cave!

Insulin resistant people already show a signifianctly elevated de novo lipogenesis with a „normal“ carbohydrate intake!

Gastroenterology 2014;146:726–735

CLINICAL—LIVER

Increased De Novo Lipogenesis Is a Distinct Characteristic of Individuals With Nonalcoholic Fatty Liver Disease

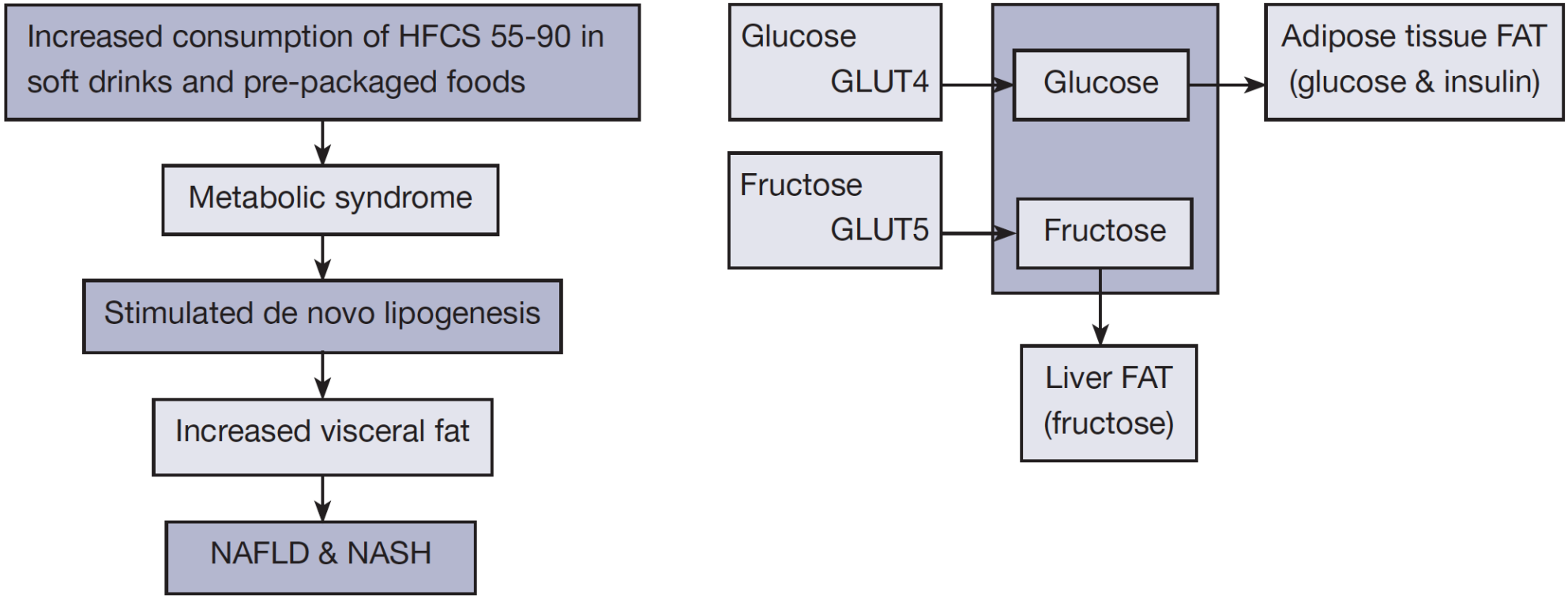
Jennifer E. Lambert,[1] Maria A. Ramos–Roman,[2] Jeffrey D. Browning,[3] and Elizabeth J. Parks[1]

[1]Center for Human Nutrition, Divisions of [2]Endocrinology and [3]Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, Texas

Carbohydrate intake and nonalcoholic fatty liver disease: fructose as a weapon of mass destruction

Metin Basaranoglu[1], Gokcen Basaranoglu[2], Elisabetta Bugianesi[3]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, [2]Department of Anaesthesiology, Bezmialem Vakif University Faculty Hospital, Istanbul, Turkey; [3]Division of Gastroenterology and Hepatology, Department of Medical Sciences, University of Torino, Turin, Italy
Correspondence to: Metin Basaranoglu, MD, PhD. Division of Gastroenterology and Hepatology, Department of Internal Medicine, Bezmialem Vakif University Faculty Hospital, Istanbul, Turkey. Email: metin_basaranoglu@yahoo.com.



Basaranoglu M, et al. Hepato Biliary Surg Nutr 2015;4:109-116

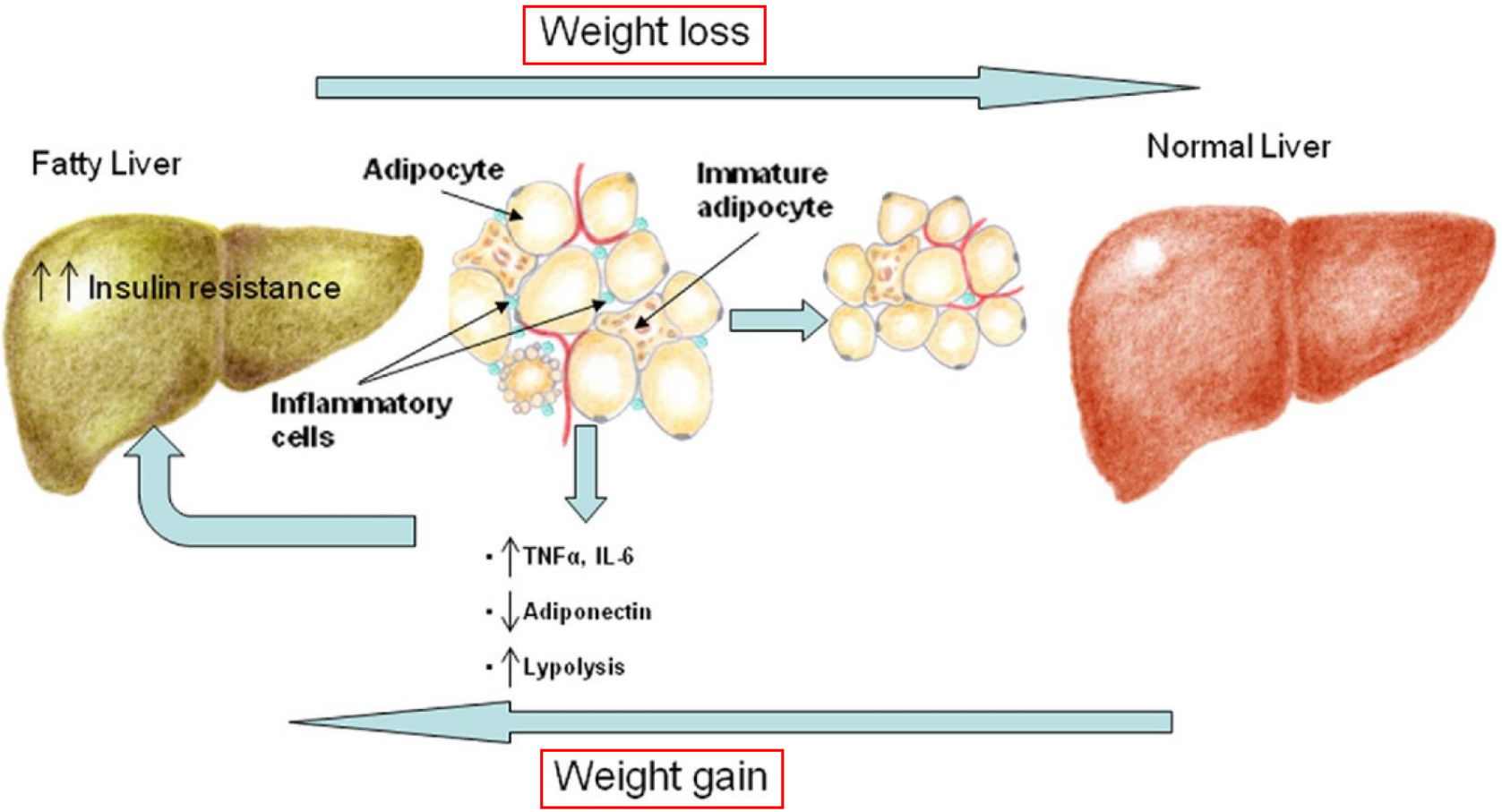
How to Produce Foie Gras?

You have to „noodle“ the goose!

Therapy of NAFLD

There are no approved drugs for the treatment of NAFLD, and the main clinical recommendation is lifestyle modification, including increase of physical activity and the adoption of a healthy eating behavior!

Energy Restriction – Effective Decrease of Ectopic Fat in Liver and Pancreas



McCarthy EM, et al. J Acad Nutr Diet 2012;112:401-409

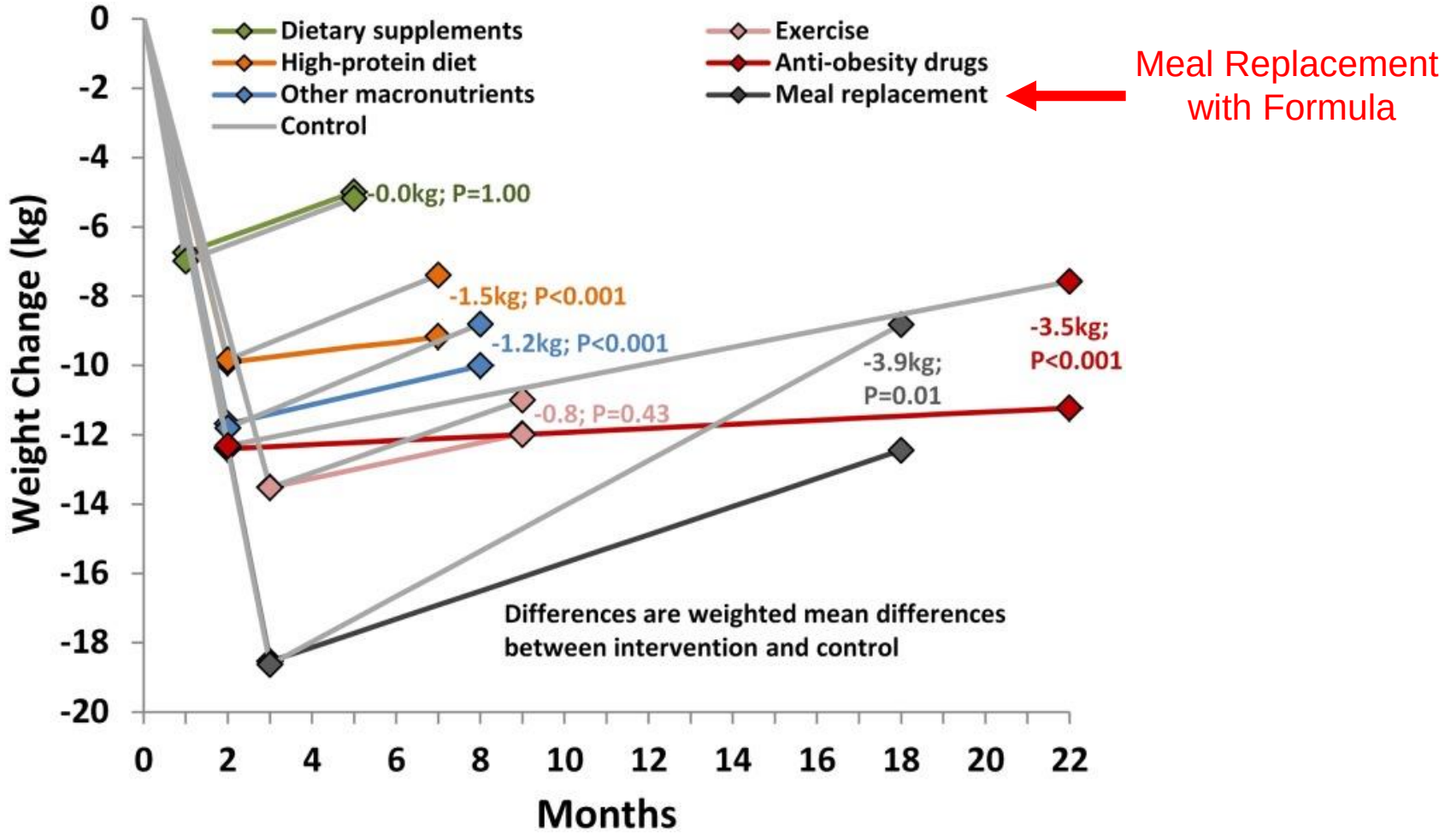
Treatment of NAFLD/NASH

Together, it appears that a weight reduction in the magnitude range of ~5–7% may clearly decrease steatosis but that more weight loss is needed (~8–10% reduction) to reverse steatohepatitis. Weight reductions of ≥10% may also cause a significant regression of fibrosis (65).

Bril F, et al. Diabetes Care 2017;40:419–430

Very-Low-Calorie-Diets/Meal-Replacements: Superior

Meta-Analysis: 20 randomized-controlled Studies; n = 3,017;



Johansson K, et al. Am J Clin Nutr 2014;99:14–23.

Newcastle University

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Magnetic Resonance Centre
Newcastle University
Campus for Ageing and Vitality
Newcastle upon Tyne
NE4 5PL

The DiRECT study

What is the background to this research?

Not everyone with Type 2 diabetes is overweight, but weight gain and obesity are the most important risk factors for Type 2 diabetes and the reason why Type 2 has become a global epidemic that affects overweight people of all ages.

Eight weeks using the diet helped those who took part to lose weight and reduced the amount of fat in their liver and pancreas. Doing so helped to restore their insulin production and put their Type 2 diabetes into remission. Three months later, some had put weight back on, but most still had normal blood glucose control.

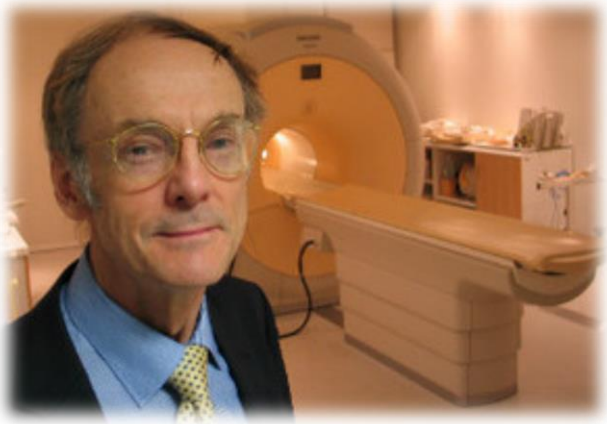
Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol

E. L. Lim • K. G. Hollingsworth • B. S. Aribisala •
M. J. Chen • J. C. Mathers • R. Taylor

- 11 Patients with Type-2-Diabetes < 4 Years, 104 kg, BMI 34, HbA1c 7,4%, fasting-Glucose 166 mg/dl
- 8 Weeks VLCD: 3 x Formula (600 kcal) + Vegetables ad-libitum (200 kcal) Meal Replacement (46 % CH, 33 % P, 20% F); 60 g CH/d
- Medication: oral antidiabetics (no Glitazones)

Lim EL, et al. Diabetologia 2011:54:2506–2514

Formula-Diet, Ectopic Fat and Diabetes-Remission



End of Week 1 with Diet

Body Weight: - 4,0 kg (- 4 %)
Fatmass: - 2,4 kg (- 6 %)
Waist: - 3,0 cm (- 3 %)

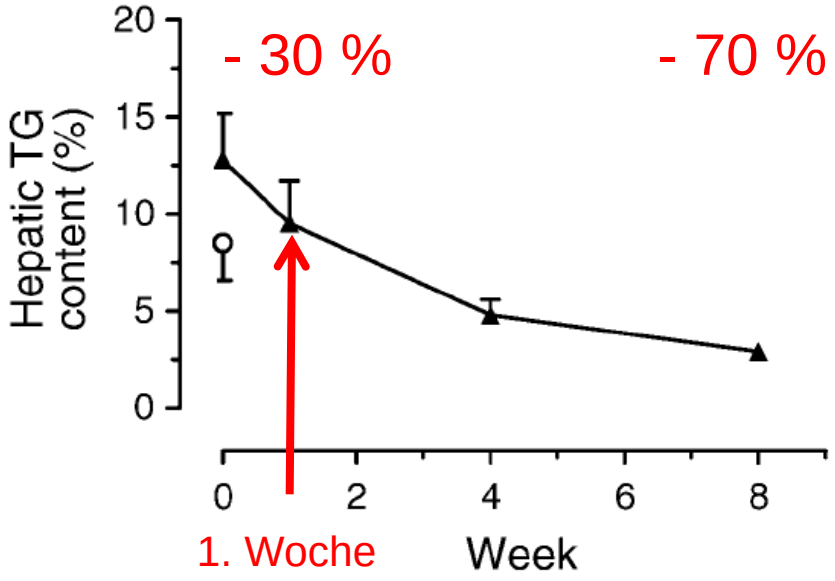
Variable	Controls	Baseline	Week 1	Week 4	Week 8
Weight (kg)	101.5±3.4	103.7±4.5	99.7±4.5*	94.1±4.3*	88.4±4.3*†
BMI (kg/m^2)	33.4±0.9	33.6±1.2	32.3±1.2*	30.5±1.2*	28.7±1.3*†
Fat mass (kg)	36.2±2.7	39.0±3.5	36.6±3.6*	31.7±3.7*	26.3±4.0*
ffm (kg)	64.7±3.8	64.7±3.0	63.2±3.1	62.4±3.0*	62.1±3.0*
Waist circumference (cm)	105.0±1.5	107.4±2.2	104.4±2.2*	99.7±2.4*	94.2±2.5*†
Hip circumference (cm)	109.8±2.4	109.5±2.9	108.3±2.7*	105.0±2.6*	99.5±2.6*†
WHR	0.96±0.02	0.98±0.02	0.97±0.02	0.95±0.01	0.95±0.01

Lim EL, et al. Diabetologia 2011:54:2506–2514

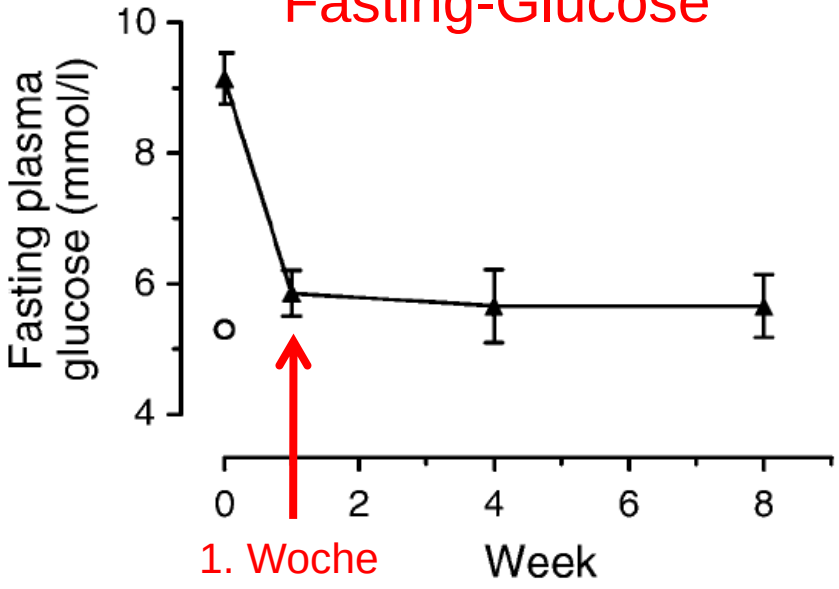
Formula-Diet, Fat Removal and Diabetes-Remission

Lim EL, et al. Diabetologia 2011:54:2506-2514

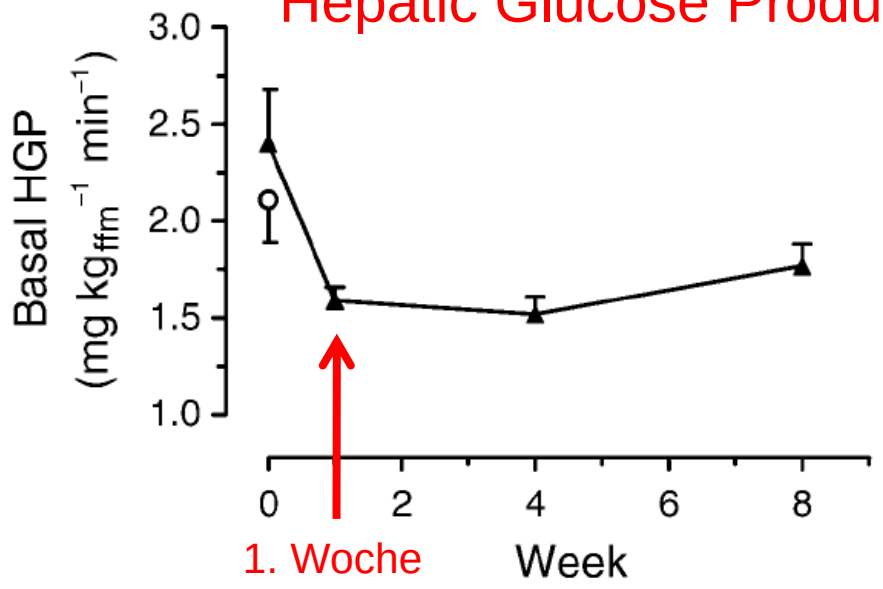
Liver-Fat



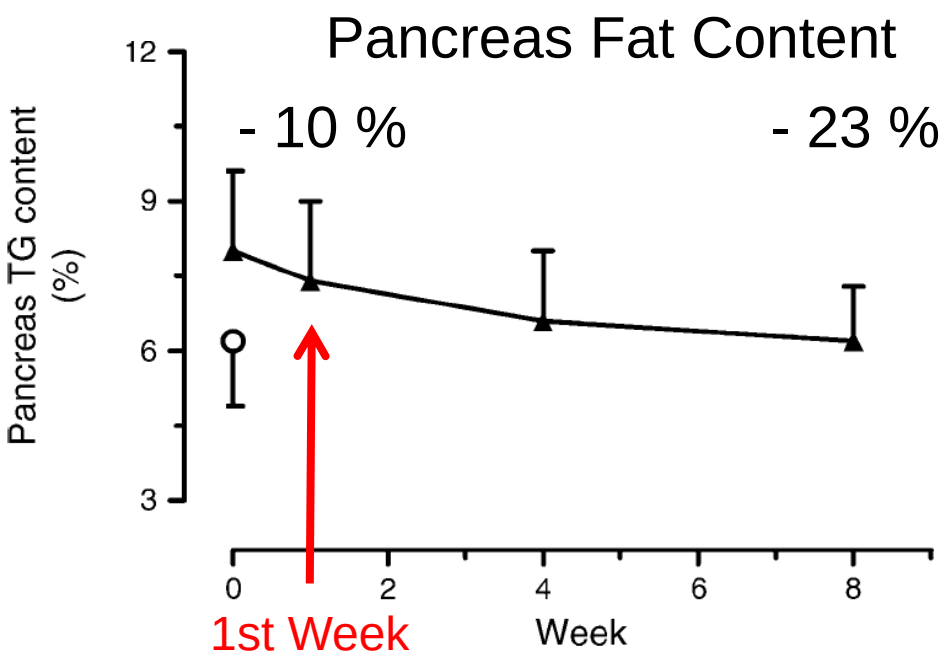
Fasting-Glucose

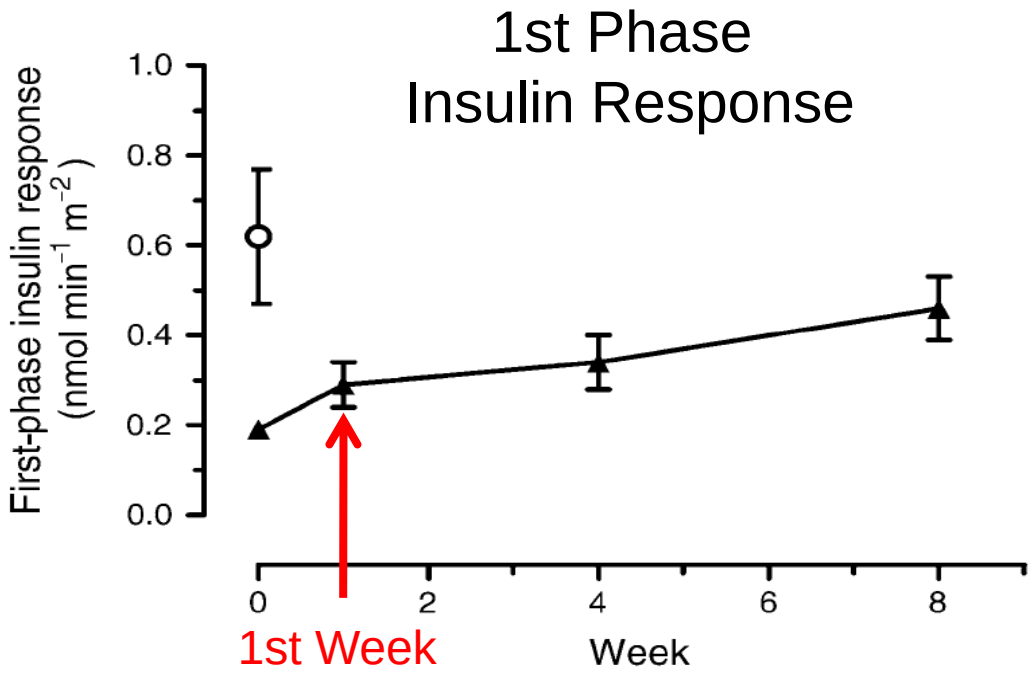


Hepatic Glucose Production



VLED (Meal-Replacement), Fat-Reduction and Diabetes-Remission

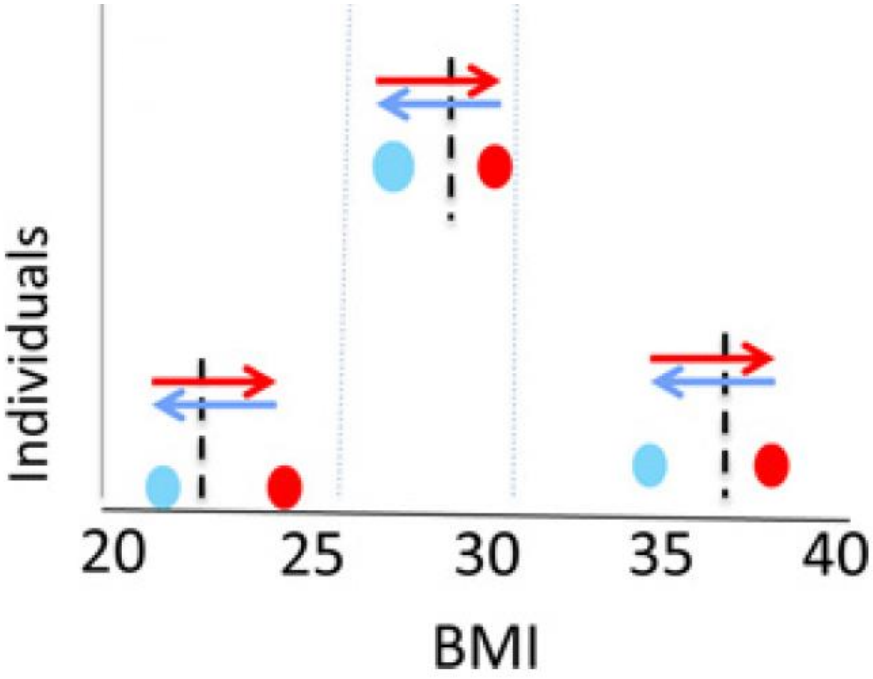




Lim EL, et al. Diabetologia 2011:54:2506–2514

Diabetes-Remission with Formula-Diet

DiRECT-Studie (Diabetes Remission Clinical Trial) Newcastle, UK



Patients must shift their body fat to the left of their personal fat threshold (PFT) to reach their endocrinologic and metabolic competence. PFT is independent of BMI!

Taylor R, et al. Clinical Science 2015;128:405–410

Calorie-Reduced Low-Carb/Ketogenic Diet: in the Treatment of NAFLD

Very-low-carbohydrate ketogenic diet *v.* low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials

In conclusion, the present meta-analysis demonstrates that individuals assigned to a VLCKD achieve significantly greater long-term reductions in body weight, diastolic blood pressure and TAG, as well as greater LDL and HDL increases when compared with individuals assigned to a LFD; hence, the VLCKD may be an alternative tool against obesity. Investigations beyond that of blood cardiovascular risk factors merit further study.

Bezerra Bueno N, et al. Br J Nutr. 2013;110:1178-87

The Effect of a Low-Carbohydrate, Ketogenic Diet on Nonalcoholic Fatty Liver Disease: A Pilot Study

David Tendler · Sauyu Lin · William S. Yancy Jr. · John Mavropoulos · Pam Sylvestre · Don C. Rockey · Eric C. Westman

Tendler D, et al. Dig Dis Sci 2007;52:589–593.

Abstract Nonalcoholic fatty liver disease is an increasingly common condition that may progress to hepatic cirrhosis. This pilot study evaluated the effects of a low-carbohydrate, ketogenic diet on obesity-associated fatty liver disease. Five patients with a mean body mass index of 36.4 kg/m^2 and biopsy evidence of fatty liver disease were instructed to follow the diet (<20 g/d of carbohydrate) with nutritional supplementation for 6 months. Patients returned for group meetings biweekly for 3 months, then monthly for the second 3 months. The mean weight change was −12.8 kg (range 0 to −25.9 kg). Four of 5 posttreatment liver biopsies showed histologic improvements in steatosis ($P = .02$) inflammatory grade ($P = .02$), and fibrosis ($P = .07$). Six months of a low-carbohydrate, ketogenic diet led to significant weight loss and histologic improvement of fatty liver disease. Further research is into this approach is warranted.

The Effect of the Spanish Ketogenic Mediterranean Diet on Nonalcoholic Fatty Liver Disease: A Pilot Study

12 week diet in 14 obese men; average BMI = 37 m^2, average age = 41 years

In conclusion, treatment of NAFLD associated with MS with SKMD seems to be safe and efficacious, improving levels of transaminases, especially ALT, the severity of steatosis, and all the parameters associated with MS. Further study is needed to confirm these results.

Pérez-Guisado J, et al. J Med Food 2011;14:677–680

Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction[1–3]

Jeffrey D Browning, Jonathan A Baker, Thomas Rogers, Jeannie Davis, Santhosh Satapati, and Shawn C Burgess

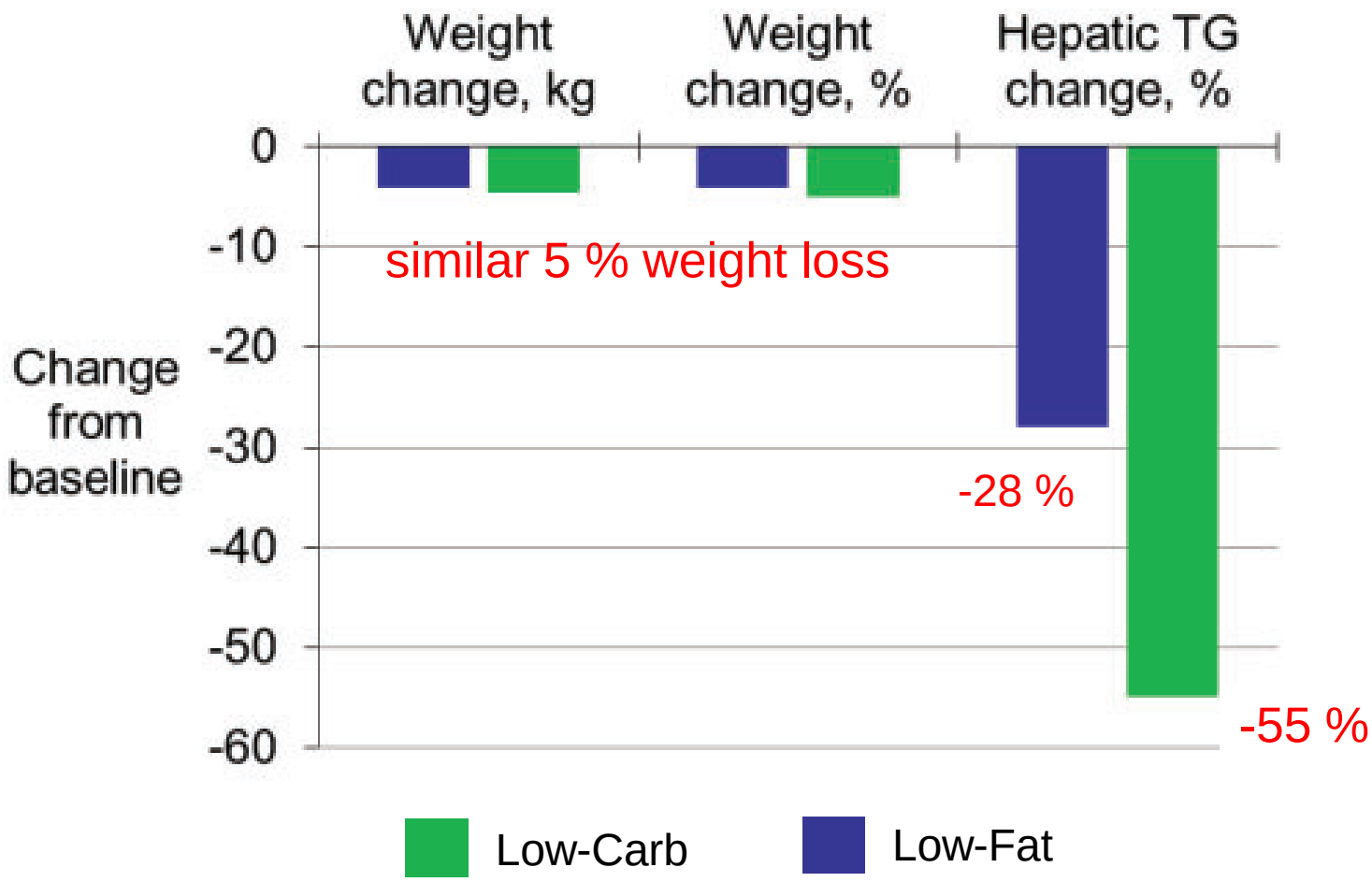
2 weeks low-caloric high-carb diet vs low-carb diet

	Low-calorie diet (n = 9)	Low-carbohydrate diet (n = 9)	P value[2]
Energy intake (kcal/d)	1325 ± 180	1553 ± 517	0.229
Diet composition			
Protein (%)	16 ± 3	33 ± 4	<0.001
Fat (%)	34 ± 6	59 ± 7	<0.001
Carbohydrate (%)	50 ± 4	8 ± 5	<0.001
Protein (g/d)	53 ± 12	121 ± 34	<0.001
Fat (g/d)	49 ± 9	105 ± 44	0.002
Carbohydrate (g/d)	169 ± 33	26 ± 8	<0.001
Fat intake (%)			
Saturated	42 ± 8	37 ± 4	0.134
Monounsaturated	37 ± 2	38 ± 6	0.634
Polyunsaturated	18 ± 7	15 ± 4	0.221

Browning JD, et al. Am J Clin Nutr 2011;93:1048–52

Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction[1–3]

Jeffrey D Browning, Jonathan A Baker, Thomas Rogers, Jeannie Davis, Santhosh Satapati, and Shawn C Burgess



Browning JD, et al. Am J Clin Nutr 2011;93:1048–52

Dietary Fat and Carbohydrates Differentially Alter Insulin Sensitivity During Caloric Restriction

ERIK KIRK, DOMINIC N. REEDS, BRIAN N. FINCK, MITRA S. MAYURRANJAN, BRUCE W. PATTERSON, and SAMUEL KLEIN

Center for Human Nutrition and Division of Geriatrics and Nutritional Science, Washington University School of Medicine, St Louis, Missouri

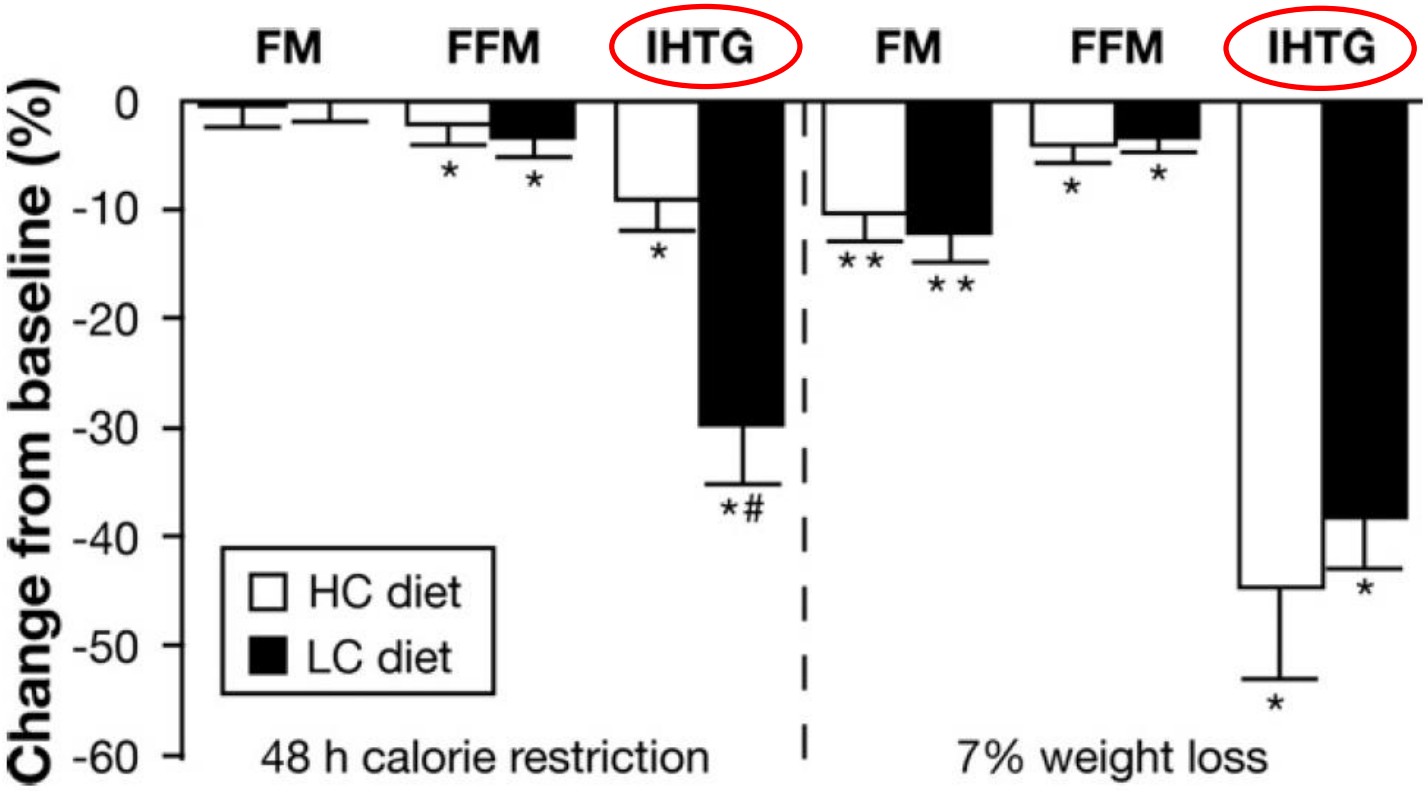
22 Obese patients (BMI = 37), randomized to 2 groups with hypocaloric diät: ≈ 1100 kcal/day;

- Low-Fat/High-Carb: > 180 g CHO/d vs Low-Carb: < 50 g CHO/d
  - Low-Fat/High-Carb: 65 En% CHO, 20 EN% F, 15 En% P;
  - Low-Carb/High-Fat: 10 EN% CHO, 75 EN% F, 15 En% P;

Kirk E, et al. Gastroenterology 2009;136:1552-1560

High-Carb- vs Low-Carb-Low-Calorie Diet and Liver Fat

Kirk E, et al. Gastroenterology 2009;136:1552-1560

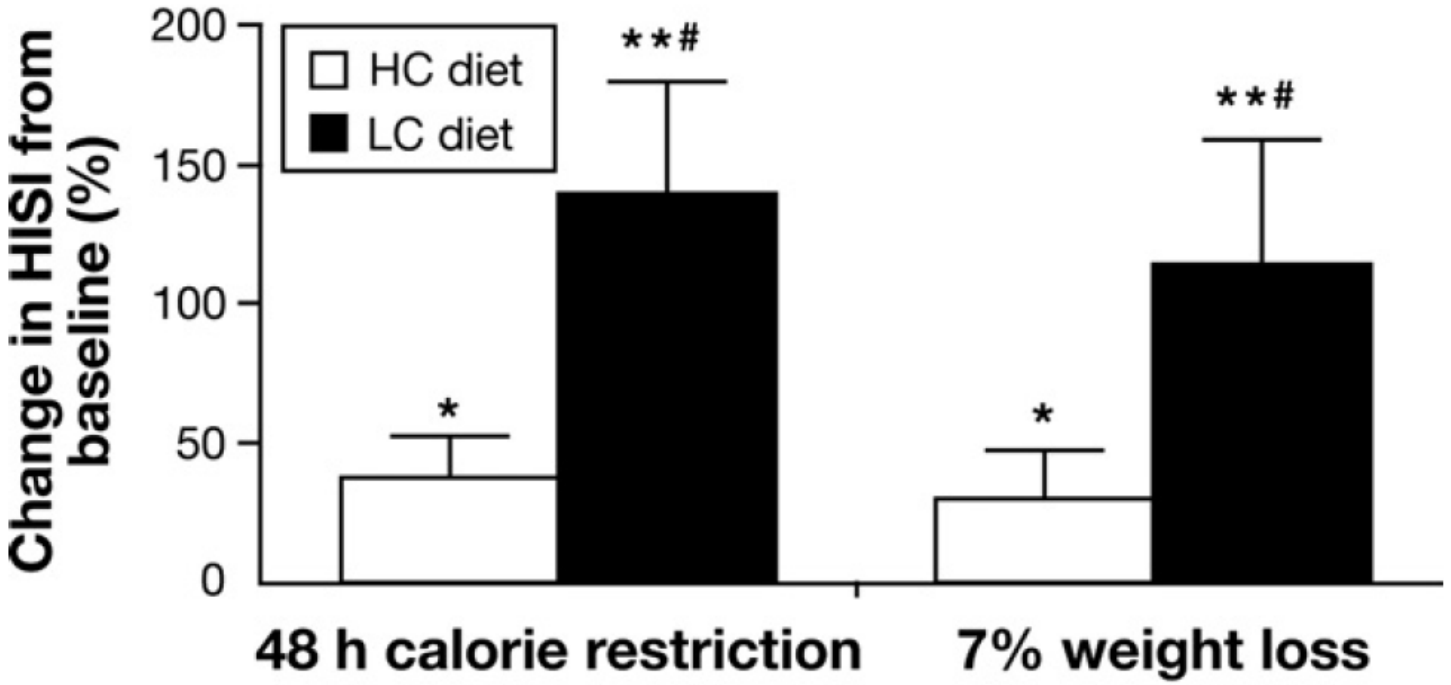


IHTG = intrahepatischer Fettgehalt

High-Carb- vs Low-Carb-Low-Calorie Diet and Liver Fat

Kirk E, et al. Gastroenterology 2009;136:1552-1560

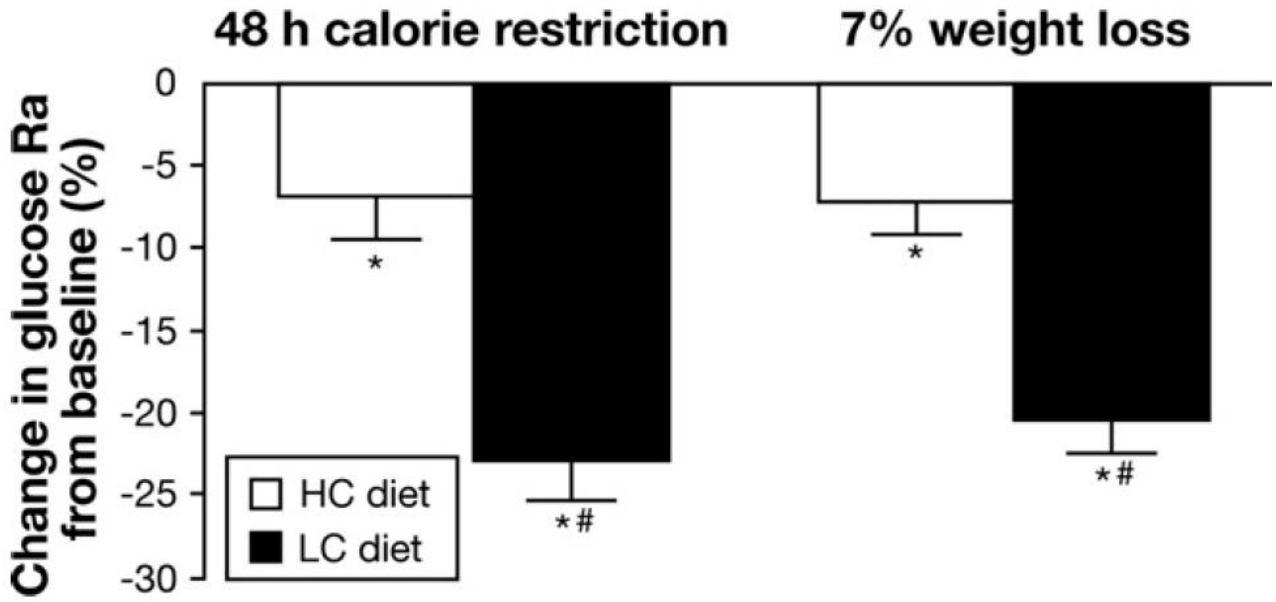
Hepatic Insulin Sensitivity



High-Carb- vs Low-Carb-Low-Calorie Diet and Liver Fat

Kirk E, et al. Gastroenterology 2009;136:1552-1560

Hepatic Glucose Secretion



Macronutrients and Liver Fat Without Calorie Reduction

Whey Protein and NAFLD

Effects of a whey protein supplementation on intrahepatocellular lipids in obese female patients

Murielle Bortolotti [a,d], Elena Maiolo [a,d], Mattia Corazza [a,d], Eveline Van Dijke [a,d], Philippe Schneiter [a,e], Andreas Boss [b,f], Guillaume Carrel [a,e], Vittorio Giusti [c,g], Kim-Anne Lê [a,h], Daniel Guae Quo Chong [b,f], Tania Buehler [b,f], Roland Kreis [b,f], Chris Boesch [b,f], Luc Tappy [a,c,*]

[a] *Department of Physiology, University of Lausanne, 7, rue du Bugnon, 1005 Lausanne, Switzerland*
[b] *Department of Clinical Research/AMSM, University of Bern, Pavilion 52A, Inselspital, P.O. Box 35, 3010 Bern, Switzerland*
[c] *Service of Endocrinology, Diabetes and Metabolism, CHUV, 1011 Lausanne, Switzerland*

- 11 obese women with 60 g whey protein/day for 4 weeks in addition to their regualar diet
- after 4 weeks of whey supplementation:

- liver fat:	- 21 %
- serum triglycerides:	- 15 %
- serum cholesterol:	- 7 %
- fat-free body mass:	+ 4 %

Bortolotti M, et al. Clinical Nutrition 2011;30:494-498

Isocaloric Diets High in Animal or Plant Protein Reduce Liver Fat and Inflammation in Individuals With Type 2 Diabetes

[1]German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany; [2]German Center for Diabetes Research, Germany; [3]Department of Endocrinology, Diabetes and Nutrition, Campus Benjamin Franklin, Charité University Medicine,

n = 18 on diet high in animal protein (AP rich in meat and dairy foods);
n = 19 on diet high in plant protein (PP mainly legume protein)

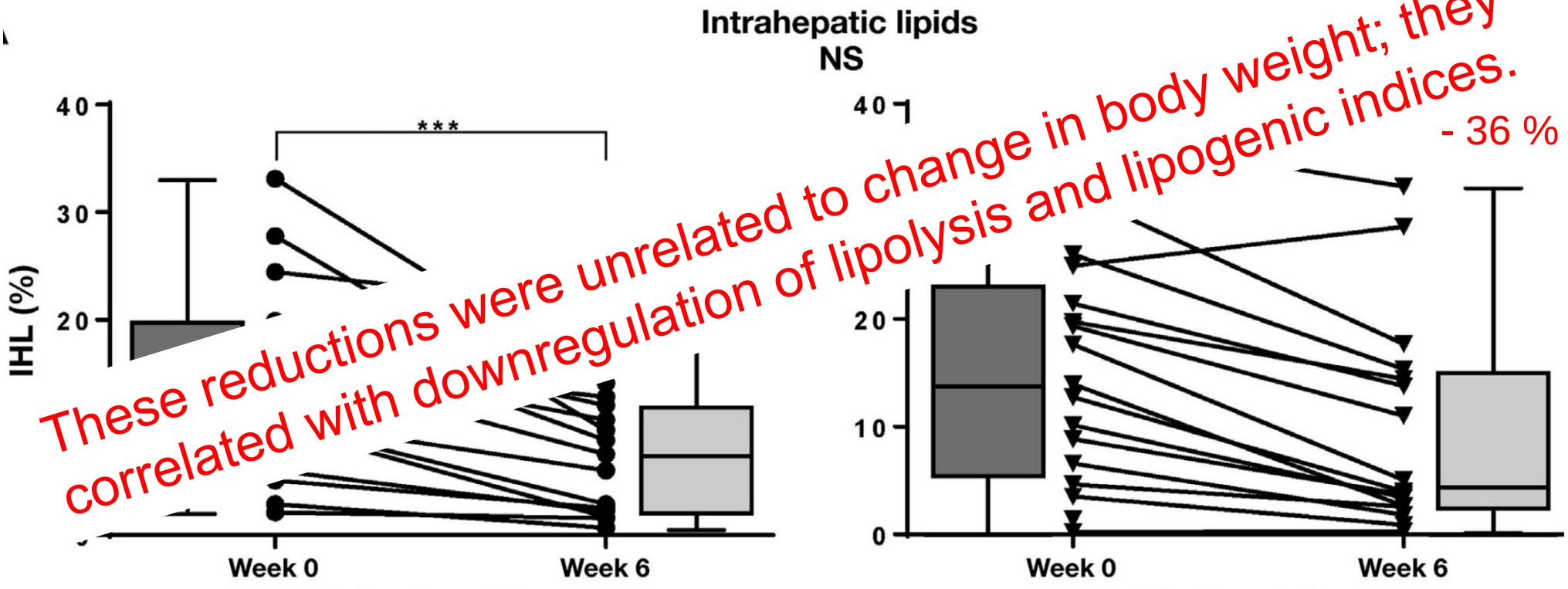
Diets without calorie restriction for 6 weeks. Isocaloric with the same composition (30% protein, 40% carbohydrates, and 30% fat).

Markova M, et al. Gastroenterology 2017;152:571–585e8

High-Protein Diet and Intrahepatic Lipids

Animal vs Plant Protein

n = 18 on diet high in animal protein (AP rich in meat and dairy foods); n = 19 on diet high in plant protein (PP mainly legume protein); Diets without calorie restriction for 6 weeks. Isocaloric with the same composition (30% protein, 40% carbohydrates, and 30% fat).



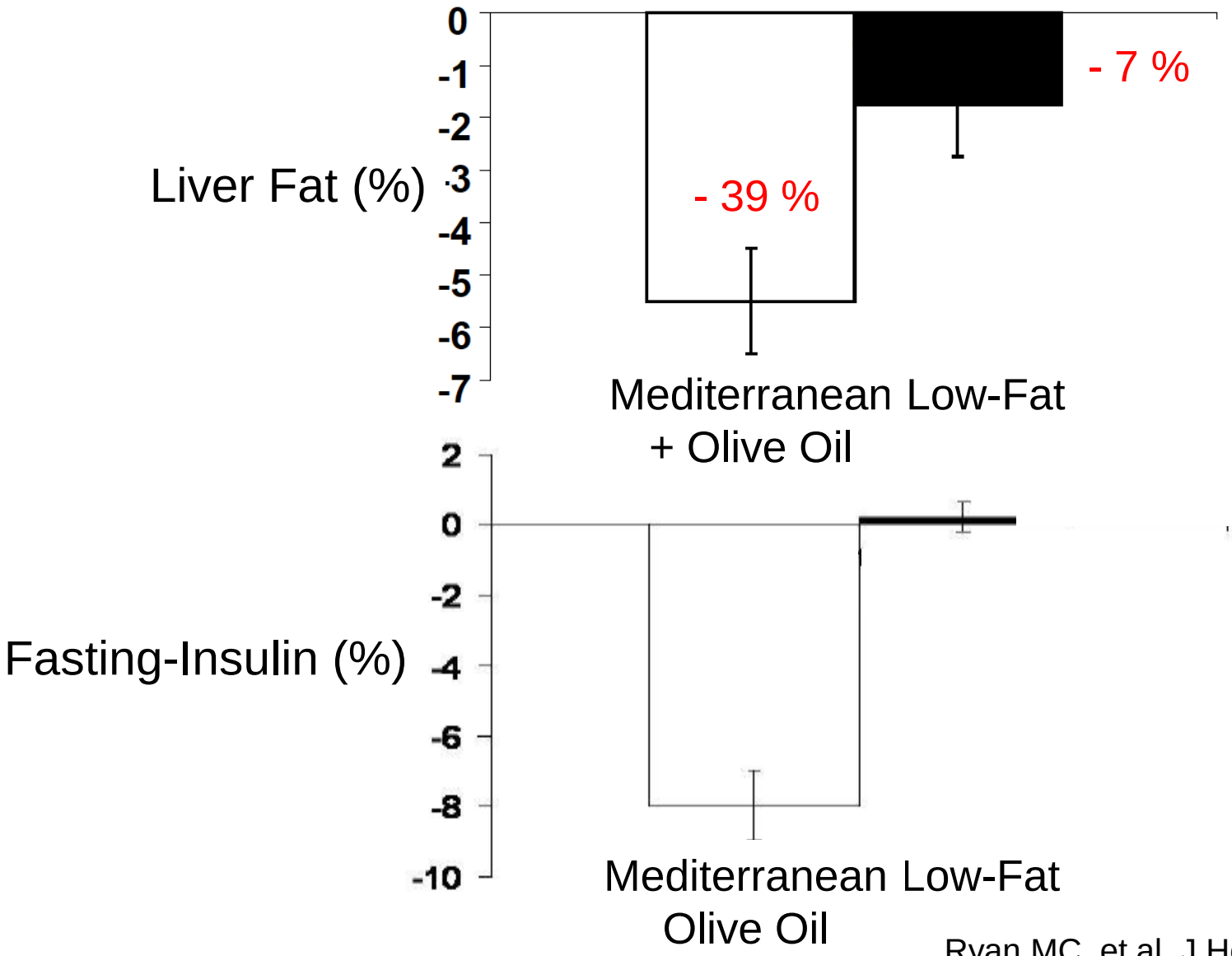
These reductions were unrelated to change in body weight; they correlated with downregulation of lipolysis and lipogenic indices.

Markova M, et al. Gastroenterology 2017;152:571–585e8

Mediterranean diets rich in virgine olive oil lowers liver fat!

High-Fat Mediterranean Diet for Treatment of NAFLD

n = 12; Cross-over 6 weeks isocaloric, stable weight



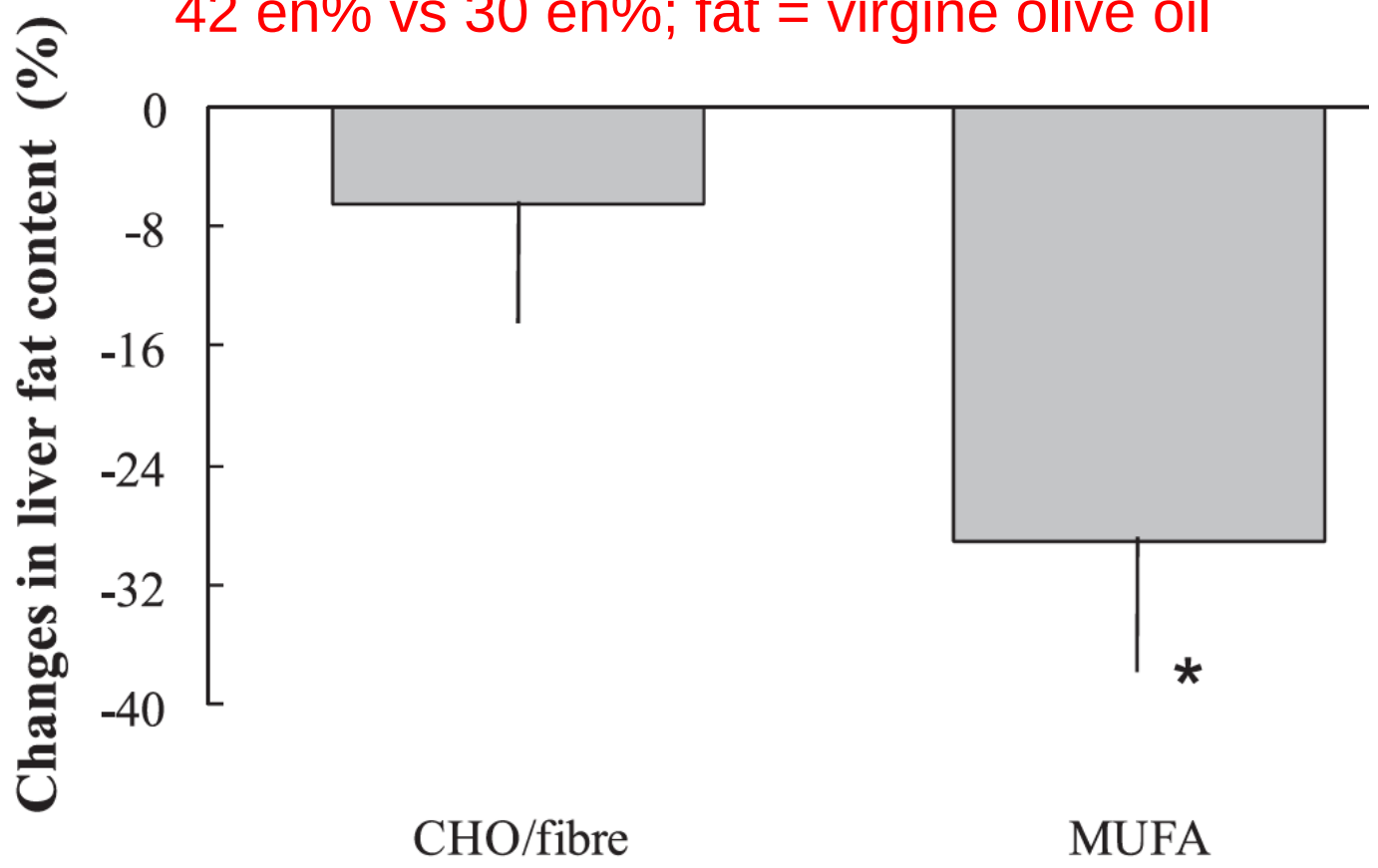
Ryan MC, et al. J Hepatol 2013;59:138-43

High-Fat Mediterranean Diet for Treatment of NAFLD

n = 45; randomized cross-over à 8 weeks;

isocaloric: CHO-rich + fibre-rich vs MUFA-rich mediterranean diet

42 en% vs 30 en%; fat = virgine olive oil



Bozzetto L, et al. Diabetes Care 2012;35:1429–1435

Reduction in liver fat by dietary MUFA in type 2 diabetes is helped by enhanced hepatic fat oxidation

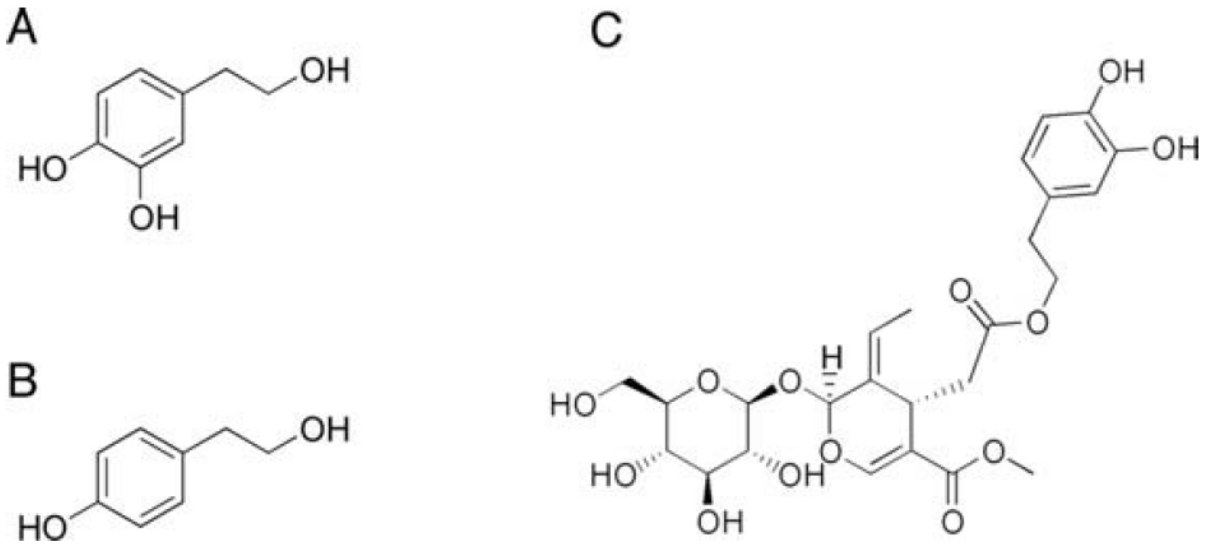
Isocaloric exchange: 30 en% vs 42 en% fat: virgine olive oil

In this study, postprandial hepatic fat oxidation was enhanced by an 8 week MUFA-rich diet resulting in significantly reduced LF, compared with a CHO/fibre diet. The postprandial suppression of β-oxidation was associated with a greater reduction in LF induced by the MUFA diet.

Bozzetto L, et al. Diabetologia 2016;59(12):2697-2701

Critical Review

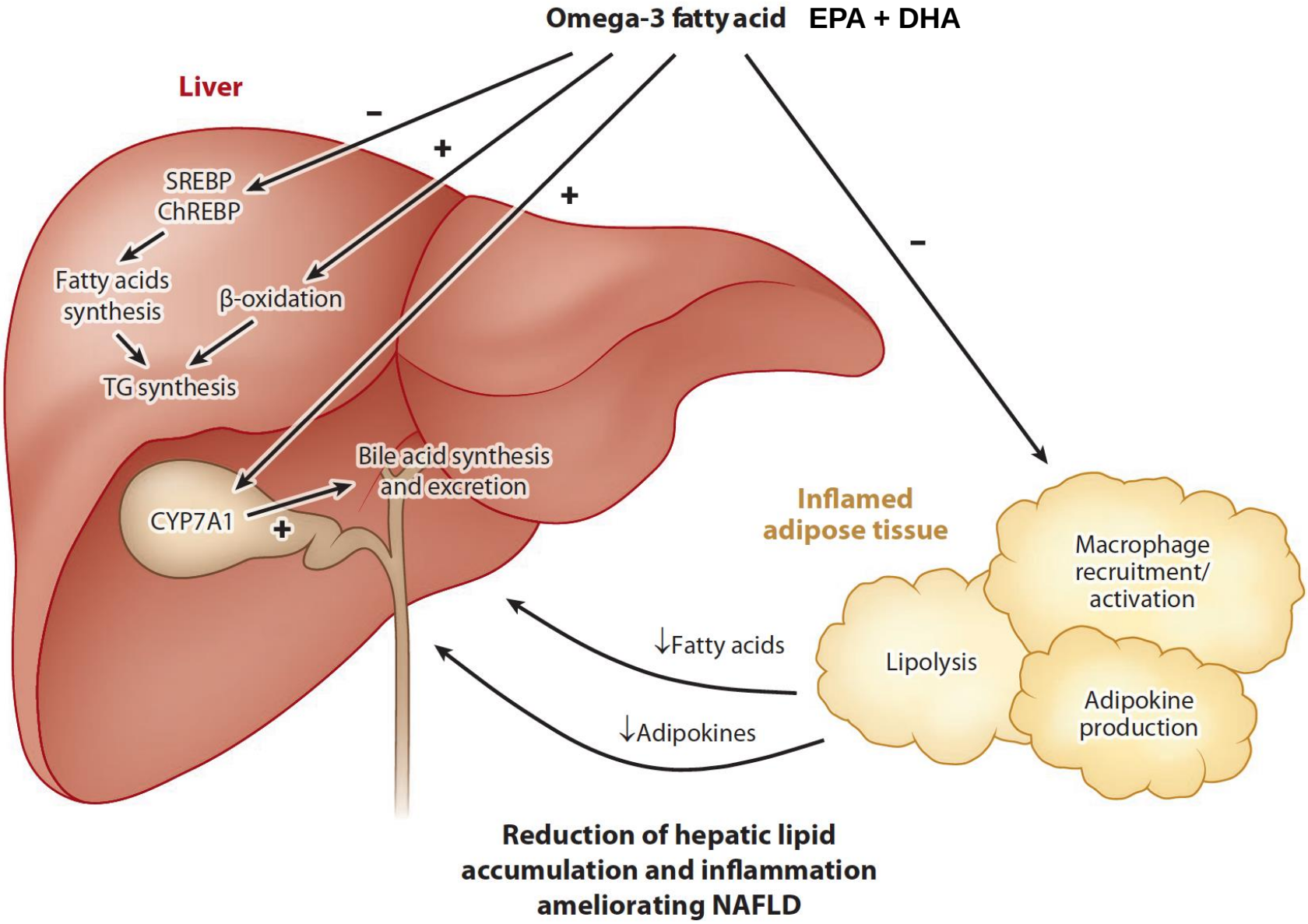
Modulation of Hepatic Lipid Metabolism by Olive Oil and its Phenols in Nonalcoholic Fatty Liver Disease



Chemical structures of EVOO phenols. Chemical structures of hydroxtyrosol (A), tyrosol (B), and oleuropein (C).

Priore P, et al. IUBMB Life. 2015 Jan;67(1):9-17.

Omega-3-Fatty Acids in the Therapy of NALFD

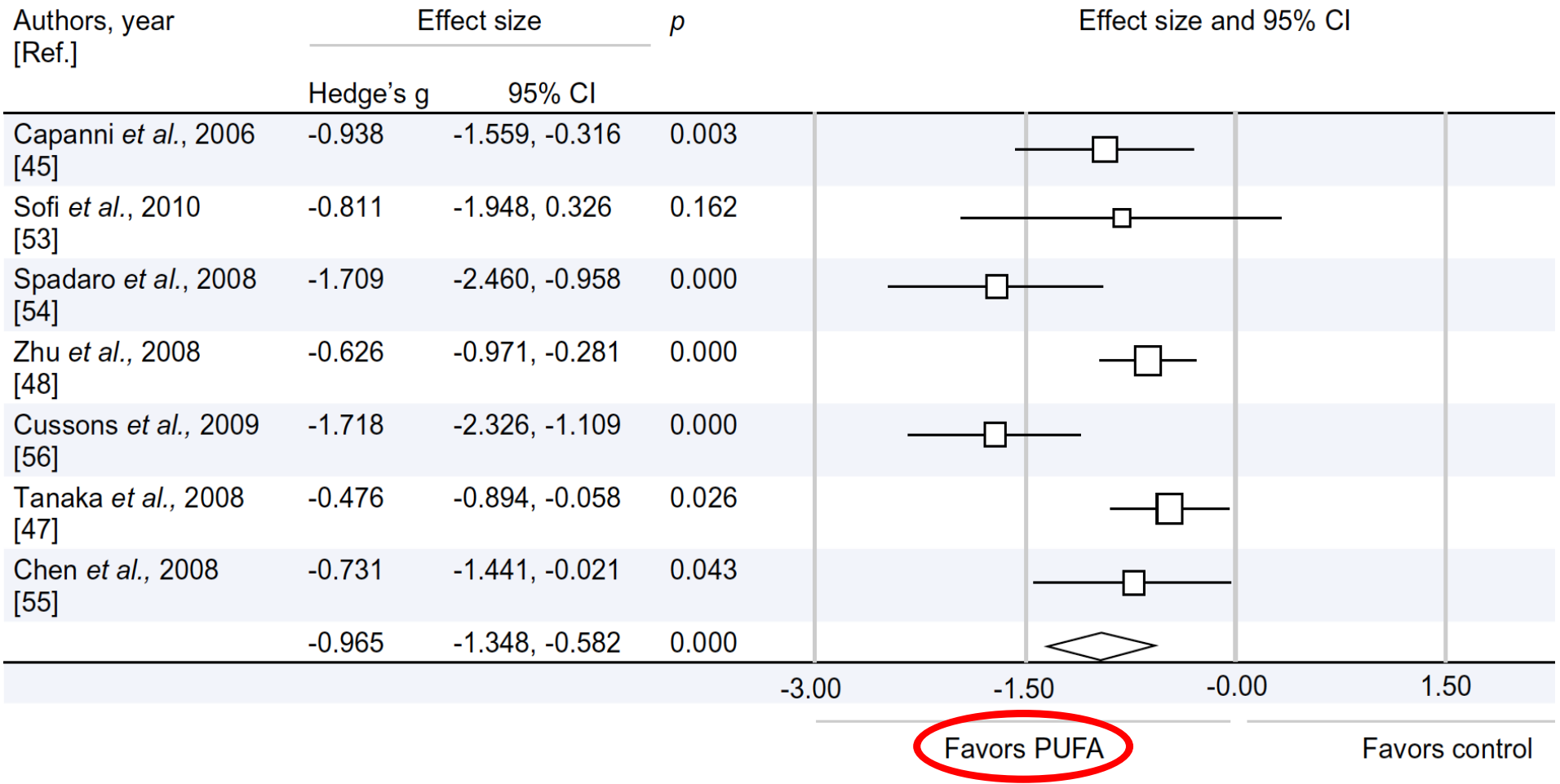


Scorletti E, Byrne CD. Annu Rev Nutr 2013;33:231–48

Omega-3 supplementation and non-alcoholic fatty liver disease: A systematic review and meta-analysis

Helen M. Parker[1], Nathan A. Johnson[1,3], Catriona A. Burdon[1], Jeffrey S. Cohn[2], Helen T. O'Connor[1,3], Jacob George[4,*]

[1]*Discipline of Exercise and Sport Science, University of Sydney, Australia;* [2]*Nutrition and Metabolism Group, Heart Research Institute, Sydney, Australia;* [3]*Boden Institute of Obesity, Nutrition and Exercise, University of Sydney, Australia;* [4]*Storr Liver Unit, Westmead Millennium Institute and Westmead Hospital, University of Sydney, Australia*



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Nutrient-Specific Effects for the Redcution of Liver Fat

Treatment of NAFLD: Nutrient Specific Effects

- Protein
- Olive oil (Hydroxytyrosol)
- n-3-PUFA (EPA+DHA)
- β-Glucan
- Inulin
- Carnitine
- Vitamin E
- Choline
- Taurine
- Resveratrol
- Quercitine
- Coffein

Nutritional Therapy of NAFLD

4 Basic Principles:

- calorie-reduced diet
- low-carbohydrate diet
- protein-rich diet
- fat-modified diet

Nutrient Specific Effects:

- n-3-PUFA (EPA+DHA)
- Hydroxytyrosol
- β-Glucan
- Inulin
- Carnitine
- Vitamin E
- Choline
- Taurine
- Resveratrol
- Quercitine
- Coffeine

Liver-Fasting with *Hepafast*®

Very-Low-Energy Diet

High-Protein/Low-Carb Meal Replacement with liver-active nutrients:

- Omega-3-Fatty Acids
- Vitamin E
- Choline
- β-Glucan
- Inulin
- Carnitine
- Taurin

Liver-Fasting with *Hepafast*®

- 2 weeks VLCD 3 x *Hepafast*® per day (protein-rich, low-carb, fiber-rich meal replacement) + 200 kcal low-starch vegetables/day + 1 table spoon native olive oil;
- 800 kcal / day

Breakfast

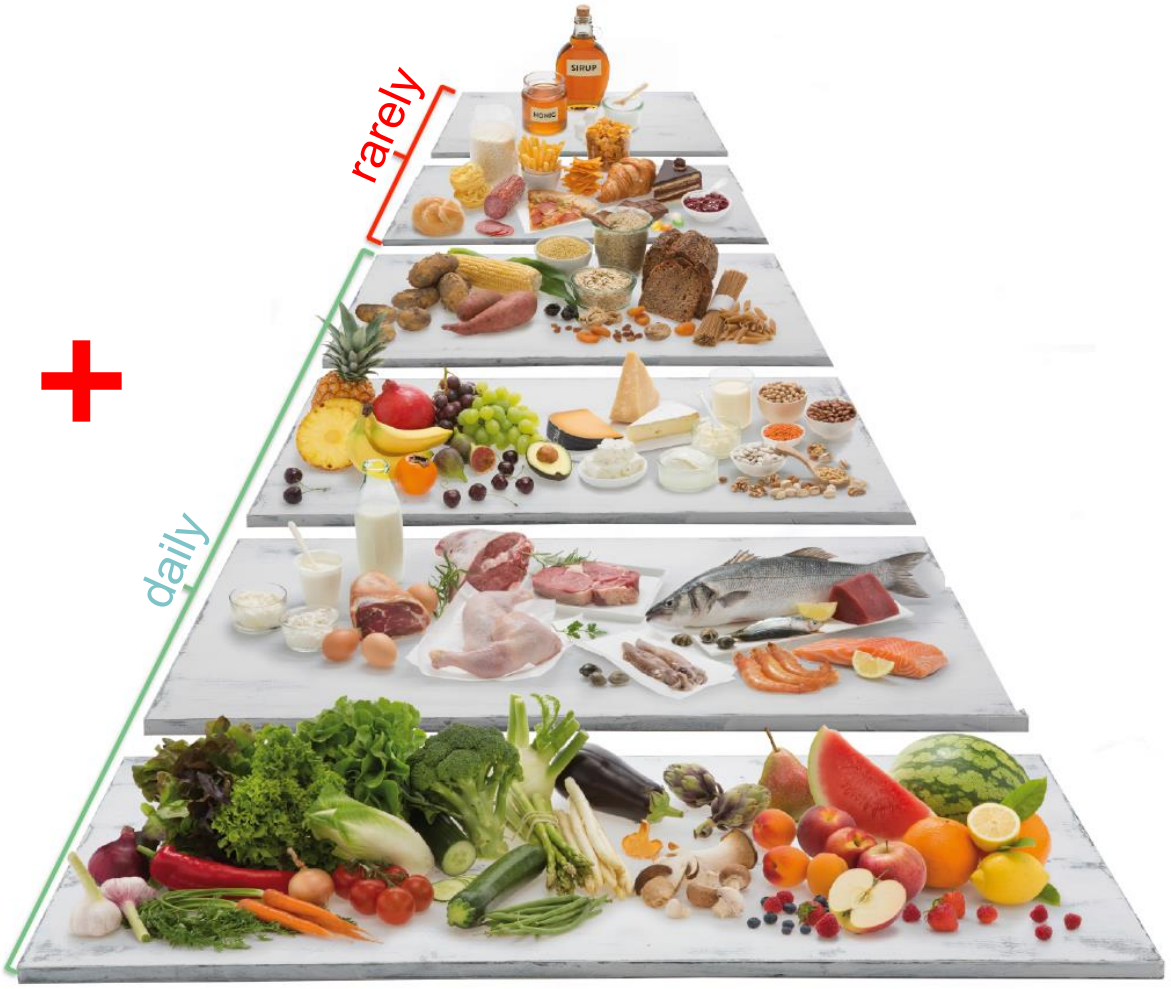
Lunch

Dinner

Liver-Fasting

with/without Meal Replacement (*Hepafast®*)

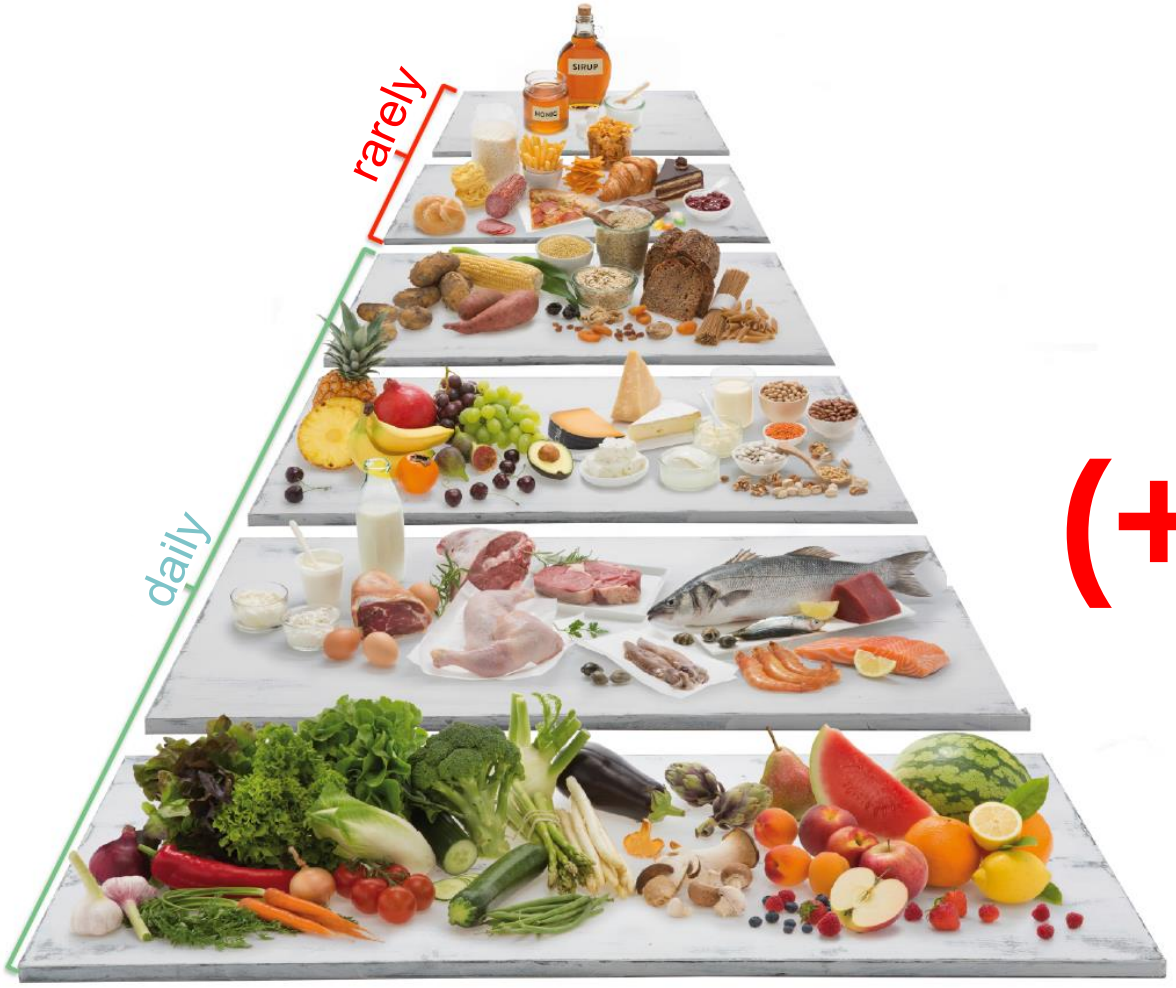
+



Mediterranean Low-Carb Diet

Liver-Healthy Diet

with/without Meal Replacement (*Hepafast®*)



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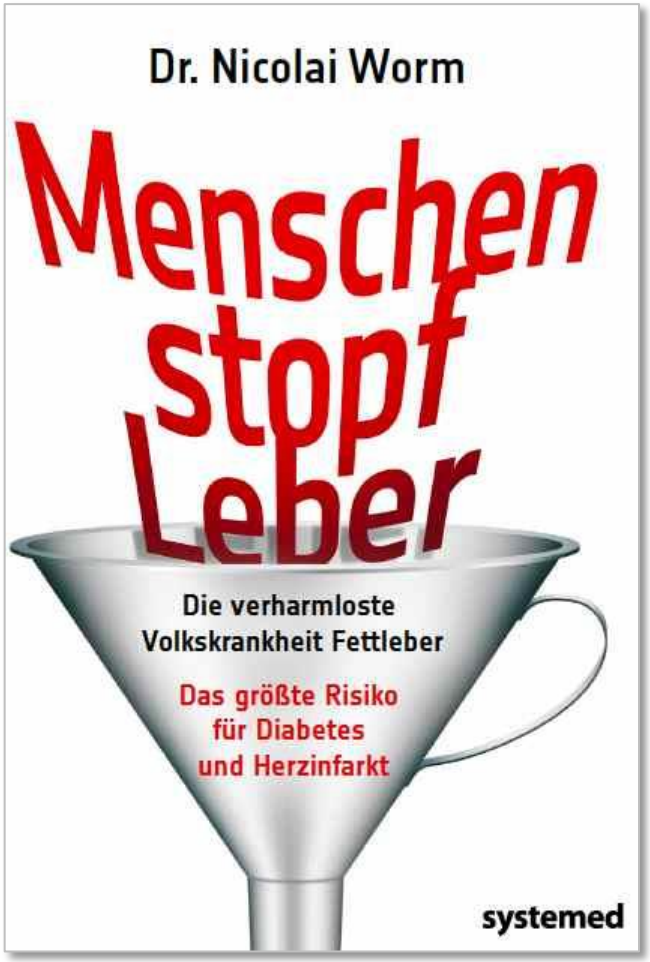
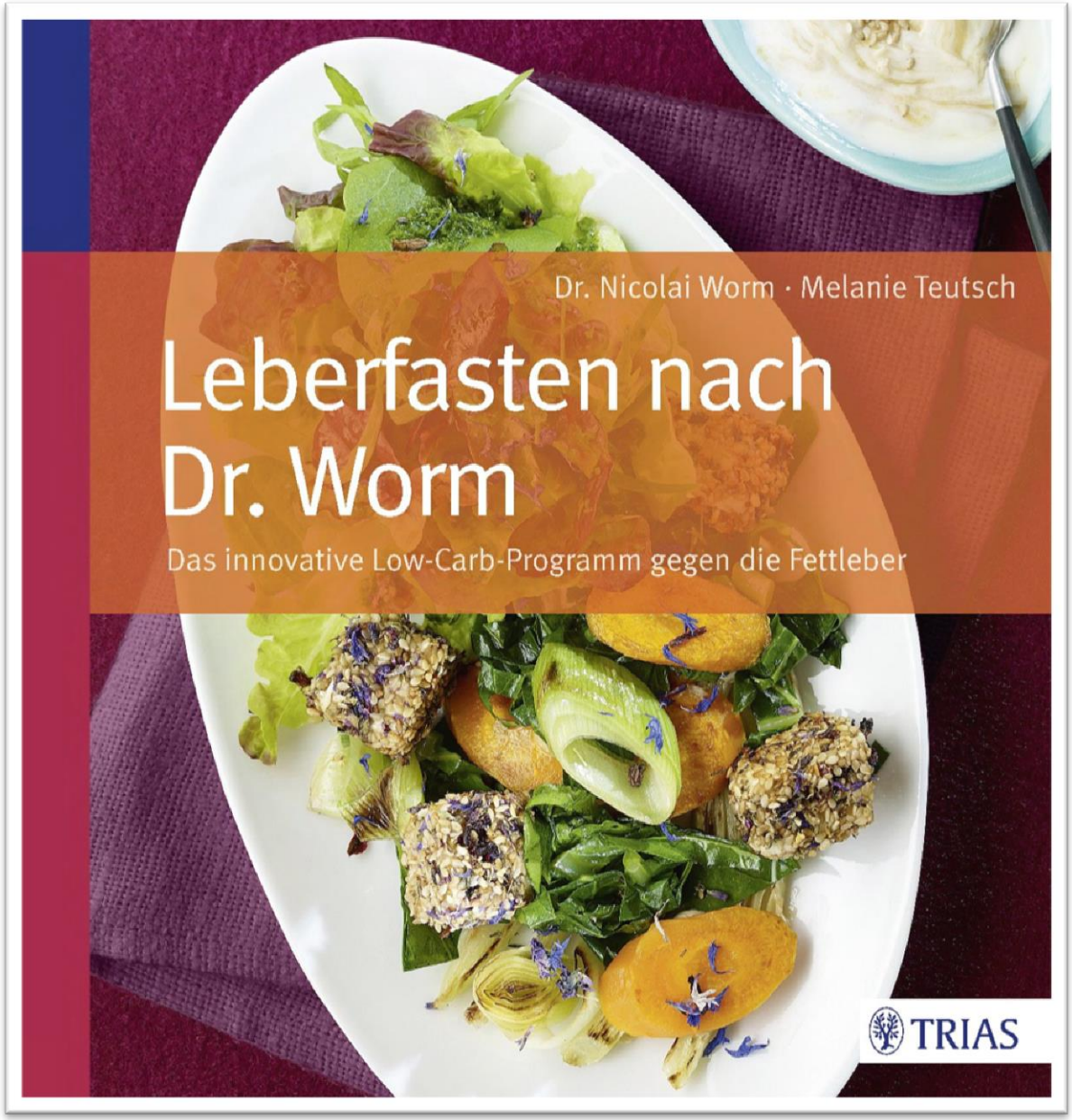
Mediterranean Low-Carb Diet


Dr. Nicolai Worm
Menschen stopf Leber
Die verharmloste Volkskrankheit Fettleber
Das größte Risiko für Diabetes und Herzinfarkt
systemed


Dr. Nicolai Worm · Kirsten Segler
VOLKS KRANKHEIT FETT LEBER
VERKANNT VERHARMLOST HEILBAR
systemed

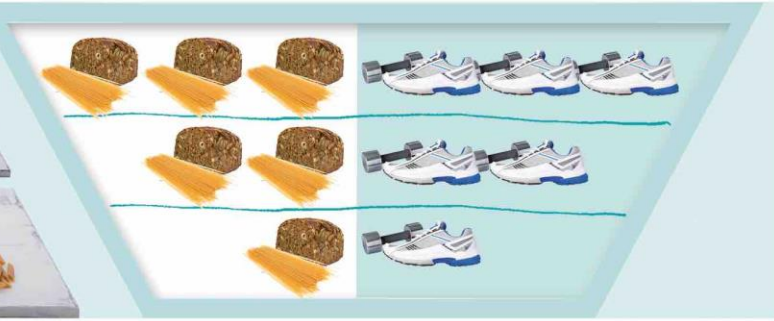

Dr. Nicolai Worm · Melanie Teutsch
Leberfasten nach Dr. Worm
Das innovative Low-Carb-Programm gegen die Fettleber
TRIAS

The *Flexi*-CARB-PYRAMID

Rarely

Daily

Your Earned Extra-Carbs



Moderate Wine Consumption

Sufficient Sleep

Recommended Fats

Sufficient Sunlight Exposure

The Flexi-Carb-Pyramid is weighted according to energy density, nutrient density, carbohydrate content, and degree of processing; by Worm/Lemberger/Mangiameli © riva Verlag, 2015

Fruit Juices, Soft Drinks

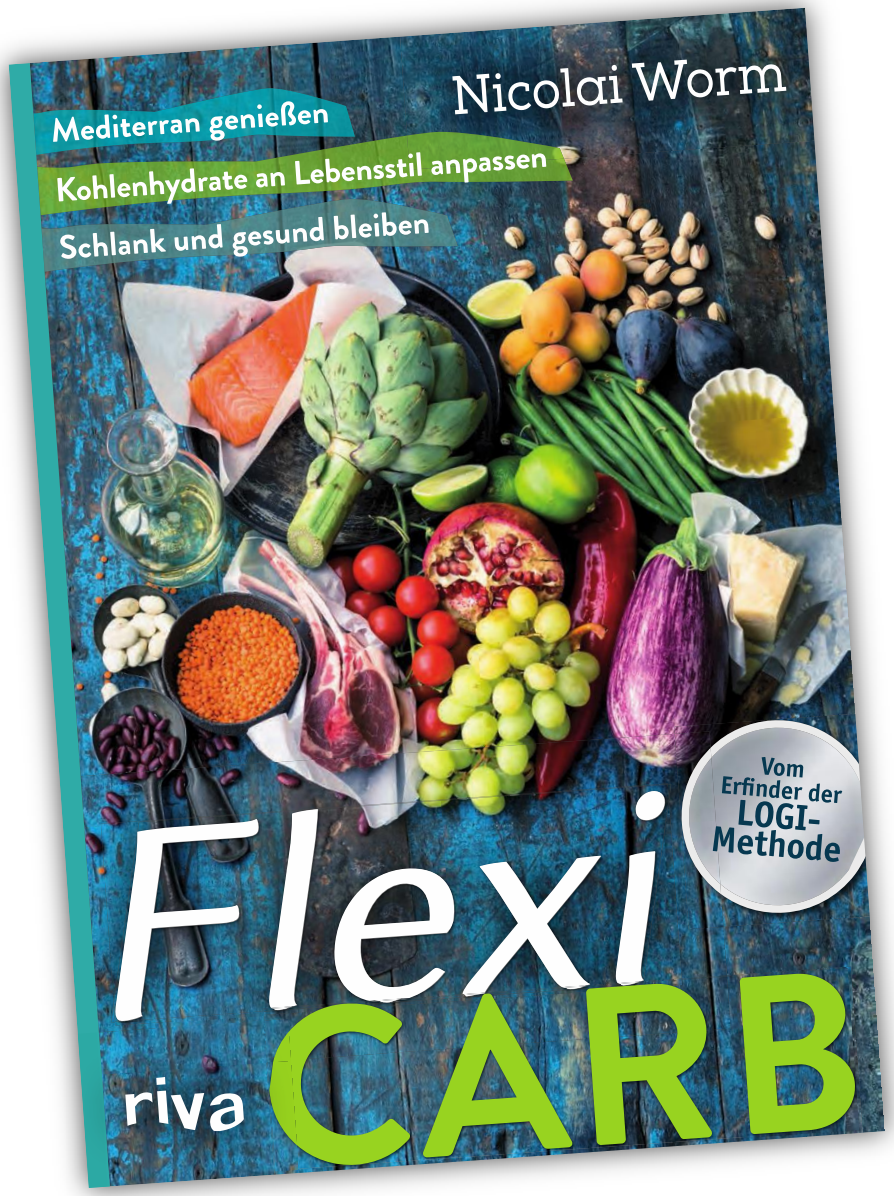
Diet Sodas,
Fruit Smoothies

Wellness Water,
Fruit Spritzers

Vegetable Juice

Black/Green Tea, Coffee

Water,
Fruit and Herbal Tea



www.flexi-carb.de

Liver-fastig – Study at the Universitäty Hospital Homburg with FibroScan® 522

we did not specifically assess the effect of the diet on insulin resistance.

Shen *et al.*[47] studied the effect of a lifestyle modification program in NAFLD patients and observed that patients who carry the *PNPLA3* mutation p.I148M showed a better response as compared to patients with wild-type alleles.[47] Although, the current data on genetic associations in our study are hampered by sample size, we also note that hepatic response was observed in all homozygous carriers of the *PNPLA3* risk allele, which should be further evaluated as personalized biomarker for a response to the dietary regimen.

Recent recommendations from a joint AASLD–FDA workshop pointed out that the use of elastography in subjects with NASH has not been explored in great detail, and that non-invasive measures should be included as secondary or exploratory endpoints in current trials.[48] Our study results illustrate that CAP might represent a reliable alternative for monitoring hepatic steatosis in research and clinical settings.[23,49]

In conclusion, the 14-day hypocaloric high-fiber, high-protein diet reduced CAP, and hence hepatic steatosis simultaneously to improvements in parameters of the metabolic syndrome. We demonstrated that improvements in hepatic fat contents can be observed after a couple of weeks only, which highlights the possibility for dynamic short-term modulation of liver fat. Whether such a program provides long-term benefits for these patients should be substantiated, but extent and rate of liver fat reduction set the benchmark for pharmacological treatment. Regardless, CAP provides a convenient and patient-friendly method to assess lipid turnover during lifestyle and dietary interventions to combat

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Non-alcoholic fatty liver disease (NAFLD) is a global rapidly growing health problem.
- ✓ Non-inasive methods are increasingly being used to evaluate hepatic steatosis.

WHAT IS NEW HERE

- ✓ Profound reduction of hepatic steatosis can be detected after only 14 days of dietary intervention using the controlled attenuation parameter.
- ✓ Calorie reduced high-fiber and high-protein diet causes dynamic short-term changes of hepatic and systemic lipids.
- ✓ These can be simultaneously and non-invasively assessed by the combination of transient elastography and bioelectrical impedance analysis.

1. Chalasani N, Younossi Z, Lavine JE *et al.* The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 2012; **55**: 2005–2023.
2. Than NN, Newsome PN. A concise review of non-alcoholic fatty liver disease. *Atherosclerosis* 2015; **239**: 192–202.
3. Adams LA, Lymp JF, St Sauver J *et al.* The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; **129**: 113–121.
4. Blachier M, Leleu H, Peck-Radosavljevic M *et al.* The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol* 2013; **58**: 593–608.
5. Ratziu V, Bellentani S, Cortez-Pinto H *et al.* A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol* 2010; **53**: 372–384.
6. Loomba R, Schork N, Chen CH *et al.* Heritability of hepatic fibrosis and steatosis based on a prospective twin study. *Gastroenterology* 2015; **149**: 1784–1793.
7. Loria P, Lonardo A, Anania F. Liver and diabetes. A vicious circle. *Hepatol Res* 2013; **43**: 51–64.

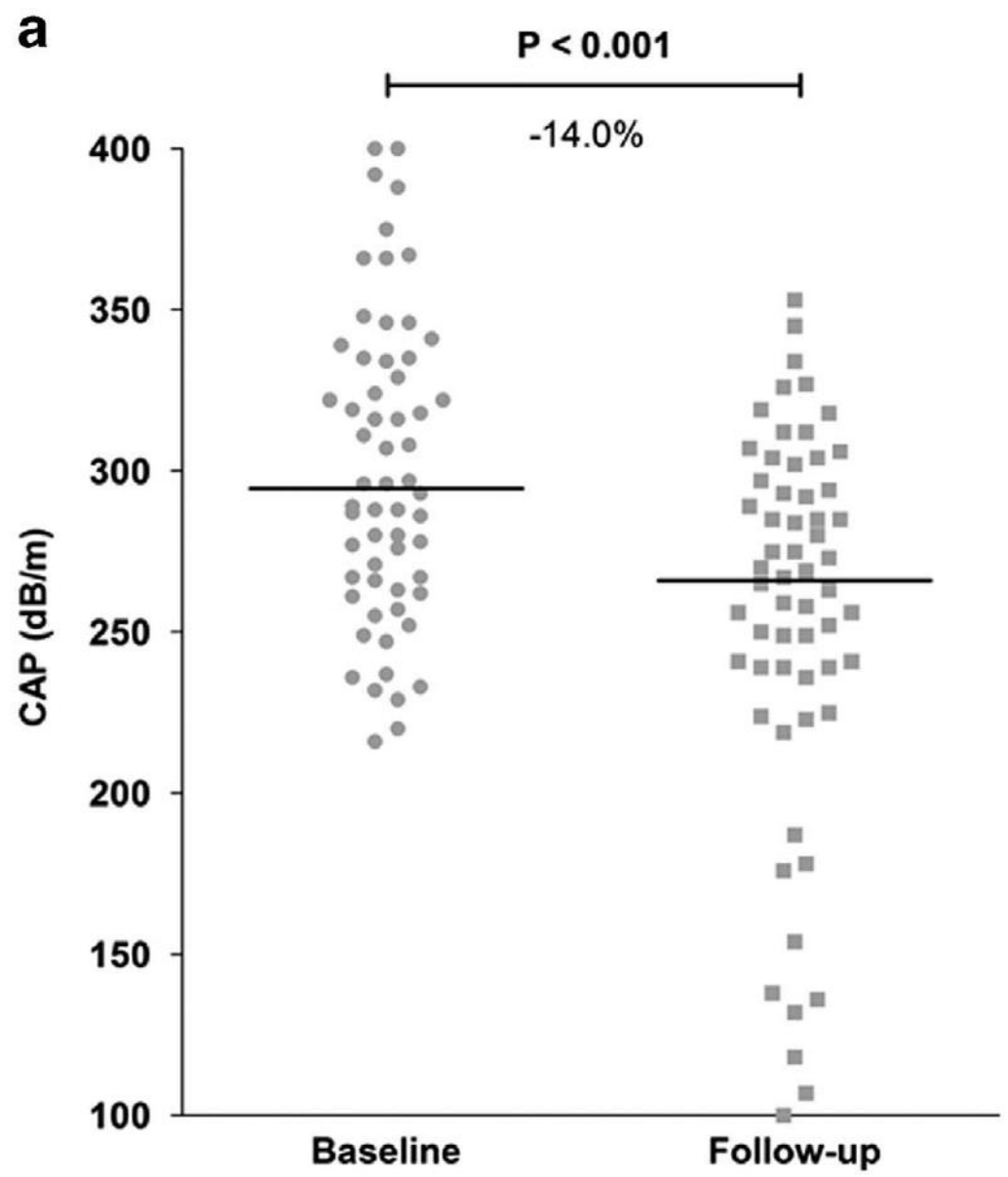
Arslanow A et al. Clin Translat Gastroenterol 2016;7:e176;

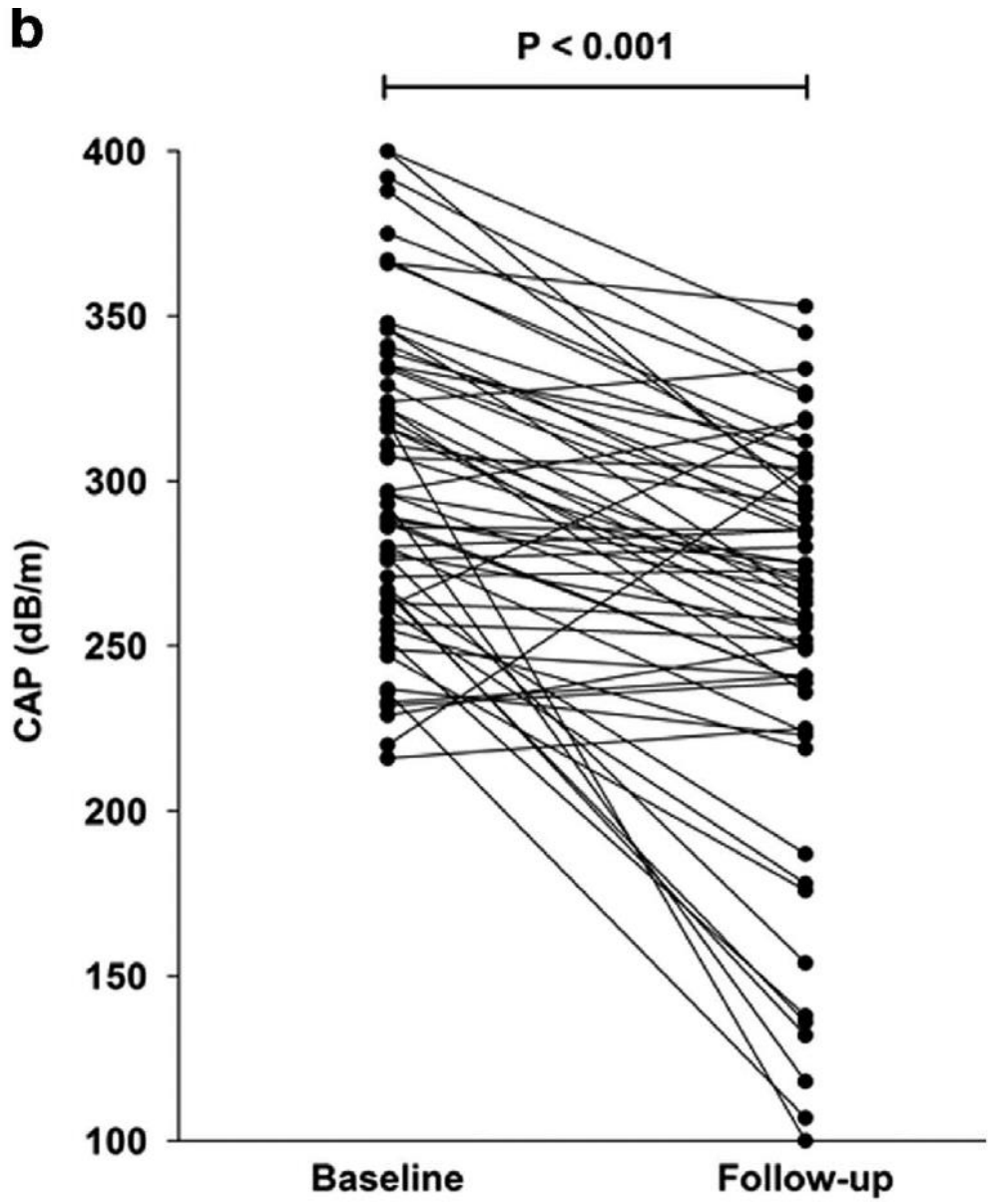
Liver-fastig – Study at the Universitäty Hospital Homburg with FibroScan® 522

	At baseline	At follow-up	Relative reduction (%)	*P*
Sociodemographic characteristics				
N (men/women)	60 (29/31)			
Age (years)	56 (25–78)			
Body composition				
Body weight (kg)	95.1 (60.7–125.6)	90.5 (58.2–120.1)	−4.6 (−8.0– −0.7)	<**0.001**
BMI (kg/m^2)	31.9 (22.4–44.8)	30.6 (21.3–43.5)	−4.7 (−8.1– −0.6)	<**0.001**
BFM (kg)	34.5 (16.8–63.4)	31.8 (13.4–59.5)	−6.9 (−27.0–4.6)	<**0.001**
BFFM (kg)	58.2 (39.5–84.9)	55.3 (39.3–81.9)	−3.3 (−9.1–4.2)	<**0.001**
TBW (kg)	42.6 (28.9–62.2)	40.5 (28.8–60.0)	−3.3 (−9.1–4.1)	<**0.001**
WC (cm)	107 (78–127)	103 (76–128)	−4.1 (−9.2–2.2)	<**0.001**
VFI	13 (5–24)	12 (4–21)	−7.1 (−20.0–11.1)	<**0.001**
Liver markers				
CAP (dB/m)	295 (216–400)	266 (100–353)	−14.0 (−68.6–38.2)	<**0.001**
FLI	83 (7–99)	63 (4–98)	−21.3 (−74.0–0.0)	<**0.001**
LSM (kPa)	6.2 (1.5–11.9)	5.3 (1.5–12.0)	−11.7 (−70.5–43.6)	**0.002**
ALT (U/l)	38 (12–118)	36 (14–150)	0 (−73.1–122.2)	>0.05
AST (U/l)	25 (10–121)	24 (8–141)	0 (−80.2–464.0)	>0.05
AP (U/l)	74 (37–159)	64 (32–144)	−11.5 (−43.0–24.1)	<**0.001**
γ-GT (U/l)	37 (7–335)	26 (7–113)	−26.7 (−77.3–50.0)	<**0.001**
PChE (kU/l)	10.7 (6.6–17.0)	10.4 (6.7–15.3)	−3.8 (−22.6–19.2)	**0.006**
Metabolic markers				
Glucose (mg/dl)	89 (63–232)	84 (60–126)	−7.1 (−50.4–52.4)	<**0.001**
TG (mg/dl)	128 (60–419)	83 (48–183)	−34.1 (−84.0–35.9)	<**0.001**
TC (mg/dl)	214 (147–303)	163 (95–249)	−23.5 (−45.6–10.9)	<**0.001**
LDL cholesterol (mg/dl)	142 (78–226)	96 (45–193)	−25.3 (−53.1–41.0)	<**0.001**
HDL cholesterol (mg/dl)	50 (29–110)	45 (28–77)	−13.0 (−66.4–28.9)	<**0.001**
Uric acid (mg/dl)	6.1 (2.9–8.6)	5.6 (3.1–10.0)	−7.6 (−40.9–43.5)	**0.024**
SBP (mm Hg)	138 (110–175)	130 (104–184)	−5.6 (−28.6–40.5)	<**0.001**
DBP (mm Hg)	92 (74–125)	87 (72–120)	−4.5 (−34.2–18.8)	**0.001**

Arslanow A et al. Clin Translat Gastroenterol 2016;7:e176;

Liver-fastig – Study at the Universitäty Hospital Homburg with FibroScan® 522





CAP = Controlled Attenuation Parameter

Arslanow A et al. Clin Translat Gastroenterol 2016;7:e176;

Type 2 Diabetes: The Pathologic Basis of Reversible β-Cell Dysfunction

Michael G. White, James A.M. Shaw, and Roy Taylor

The reversible nature of early type 2 diabetes has been demonstrated in in vivo human studies. Recent in vivo and in vitro studies of β-cell biology have established that the β-cell loses differentiated characteristics, including glucose-mediated insulin secretion, under metabolic stress. Critically, the β-cell dedifferentiation produced by long-term excess nutrient supply is reversible. Weight loss in humans permits restoration of first-phase insulin secretion associated with the return to normal of the elevated intrapancreatic triglyceride content. However, in type 2 diabetes of duration greater than 10 years, the cellular changes appear to pass a point of no return. This review summarizes the evidence that early type 2 diabetes can be regarded as a reversible β-cell response to chronic positive calorie balance.

White MG, et al. Diabetes Care 2016;39:2080–2088

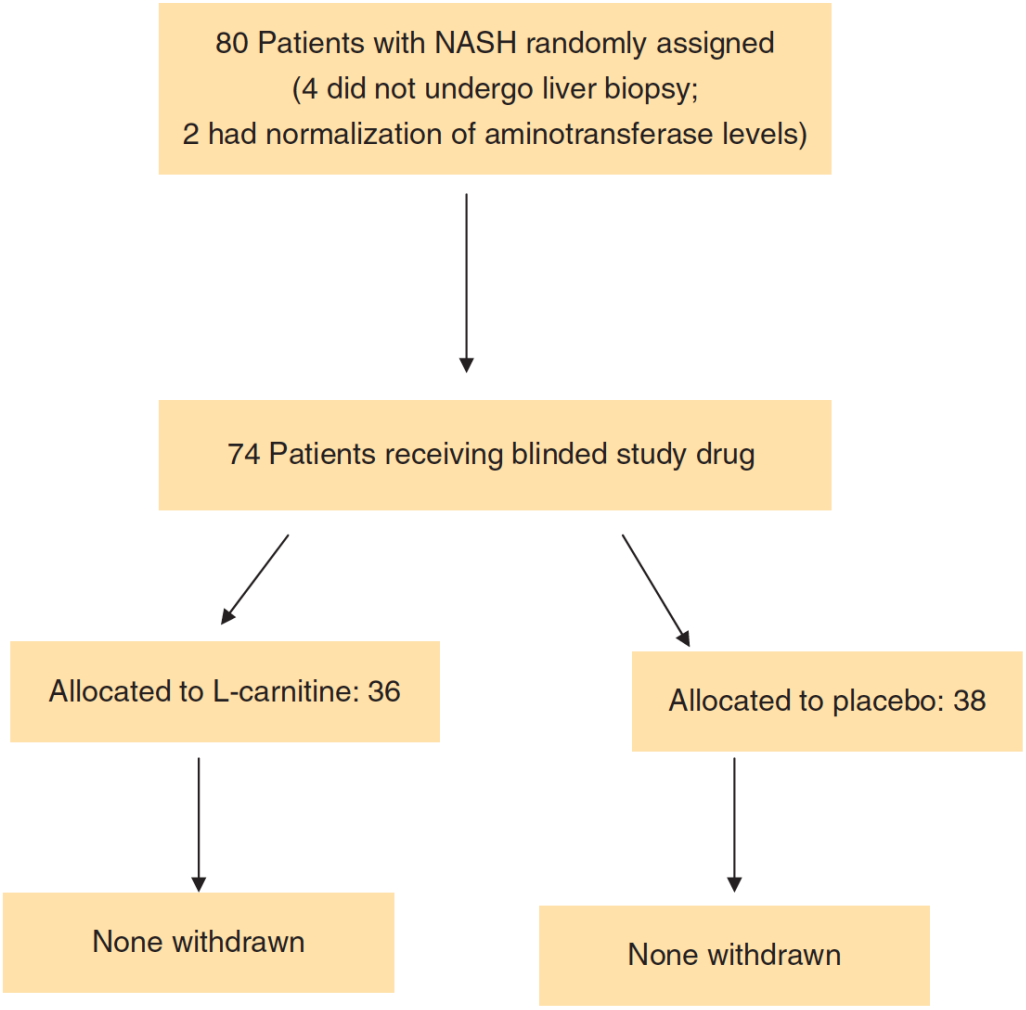
The effect of (L-)carnitine on weight loss in adults: a systematic review and meta-analysis of randomized controlled trials

Summary

This study provides a systematic review and meta-analysis of randomized controlled trials, which have examined the effect of the carnitine on adult weight loss. Relevant studies were identified by systematic search of PubMed, Embase, Cochrane Central Register of Controlled Trials and reference lists of relevant marker studies. Nine studies (total $n = 911$) of adequate methodological quality were included in the review. Trials with mean difference (MD) of 95% confidence interval (CI) were pooled using random effect model. Results from meta-analysis of eligible trials revealed that subjects who received carnitine lost significantly more weight (MD: −1.33 kg; 95% CI: −2.09 to −0.57) and showed a decrease in body mass index (MD: $-0.47\ \mathrm{kg\,m^{-2}}$; 95% CI: −0.88 to −0.05) compared with the control group. The results of meta-regression analysis of duration of consumption revealed that the magnitude of weight loss resulted by carnitine supplementation significantly decreased over time ($p = 0.002$). We conclude that receiving the carnitine resulted in weight loss. Using multiple-treatments meta-analysis of the drugs and non-pharmacotherapy options seem to be insightful areas for research.

Pooyandjoo M, et al. Obesity Reviews 2016;17:970–976

L-Carnitine Supplementation to Diet: A New Tool in Treatment of Nonalcoholic Steatohepatitis—A Randomized and Controlled Clinical Trial



Malaguarnera M, et al. Am J Gastroenterol 2010;105:1338–1345

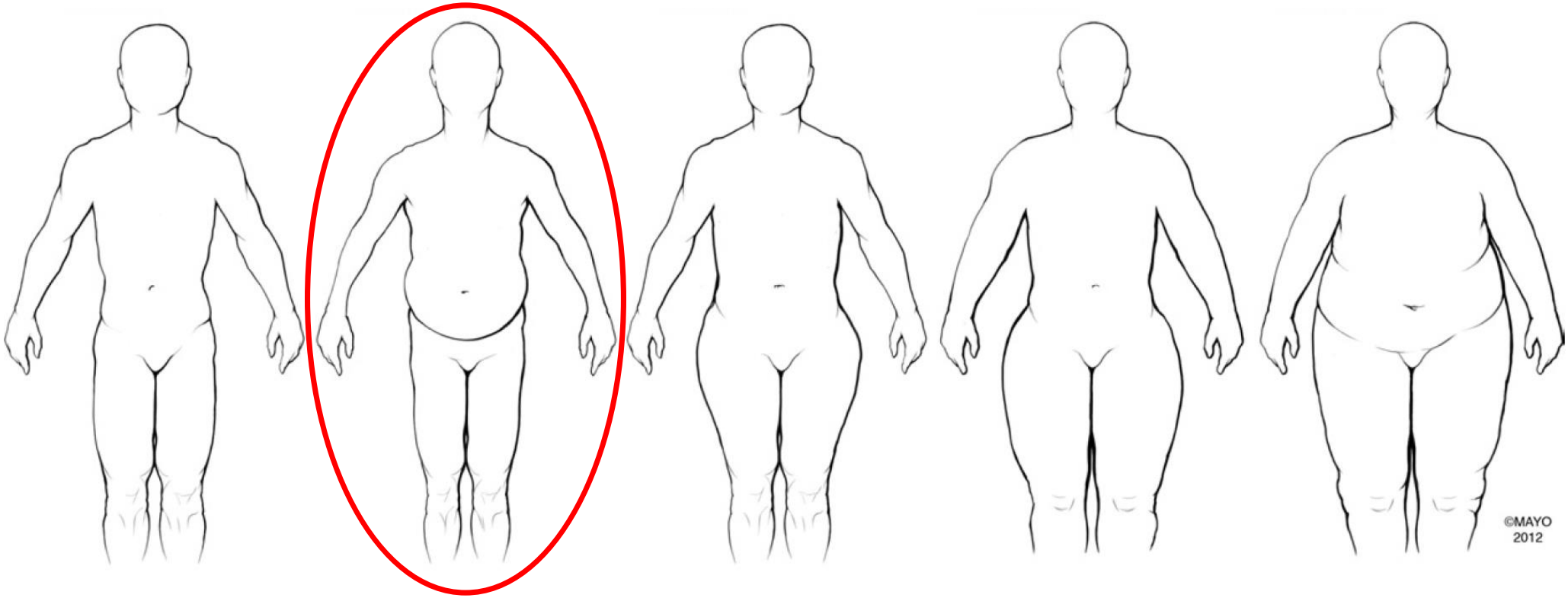
L-Carnitine Supplementation to Diet: A New Tool in Treatment of Nonalcoholic Steatohepatitis—A Randomized and Controlled Clinical Trial

- signifikante Senkung von AST, AL T und GGT
- signifikante Senkung von LDL- und Gesamt-Cholesterin
- signifikante Senkung der Serum-Glukose und HOMA-Index
- signifikante Senkung des CRP

Malaguarnera M, et al. Am J Gastroenterol 2010;105:1338–1345

Who has the Highest 5-Year-Mortality?

Meta-Analysis of 15,547 Participants with Coronary Artery Disease
5 Cohort Studies in 3 Continents, 4,699 Deaths in 4.7 Years of Follow-up

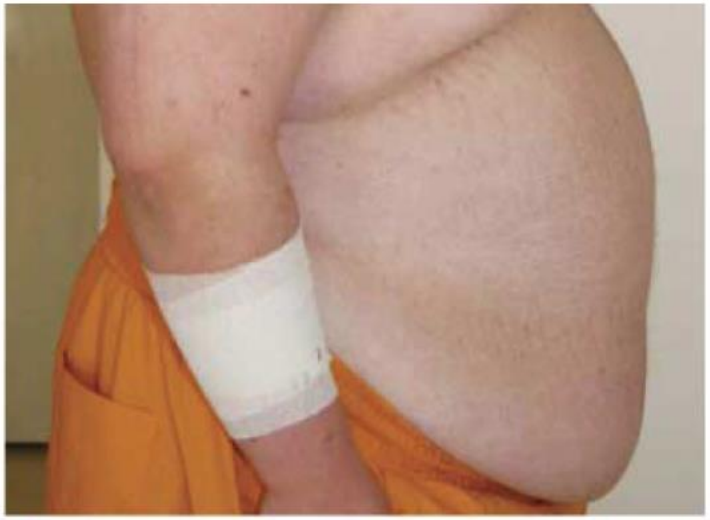


BMI 22 Waist 85 cm	BMI 22 Waist 101 cm	BMI 26 Waist 85 cm	BMI 30 Waist 85 cm	BMI 30 Waist 101 cm

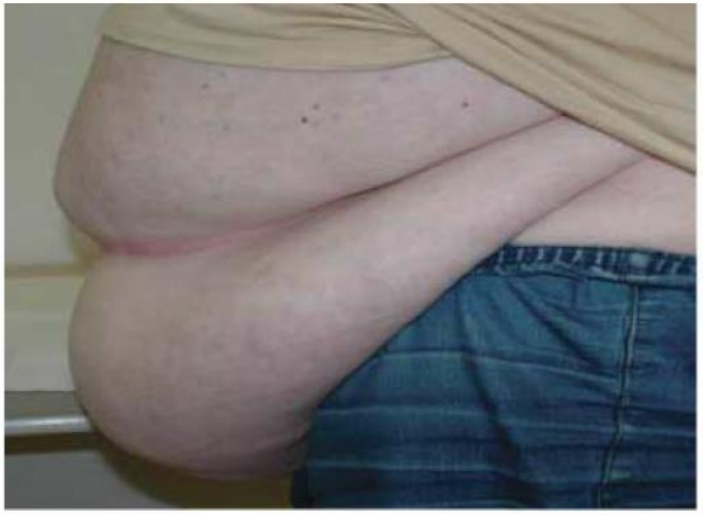
Coutinho Z, et al. J Am Coll Cardiol 2013;61:553–60

Dysfunction of Adipocytes and Systemic Inflammation

Klöting N, et al. Am J Physiol Endocrinol Metab 2010:299:E506-15.



BMI 45



Who has NAFLD?

Intraabdominal Fat and Metabolic Consequences

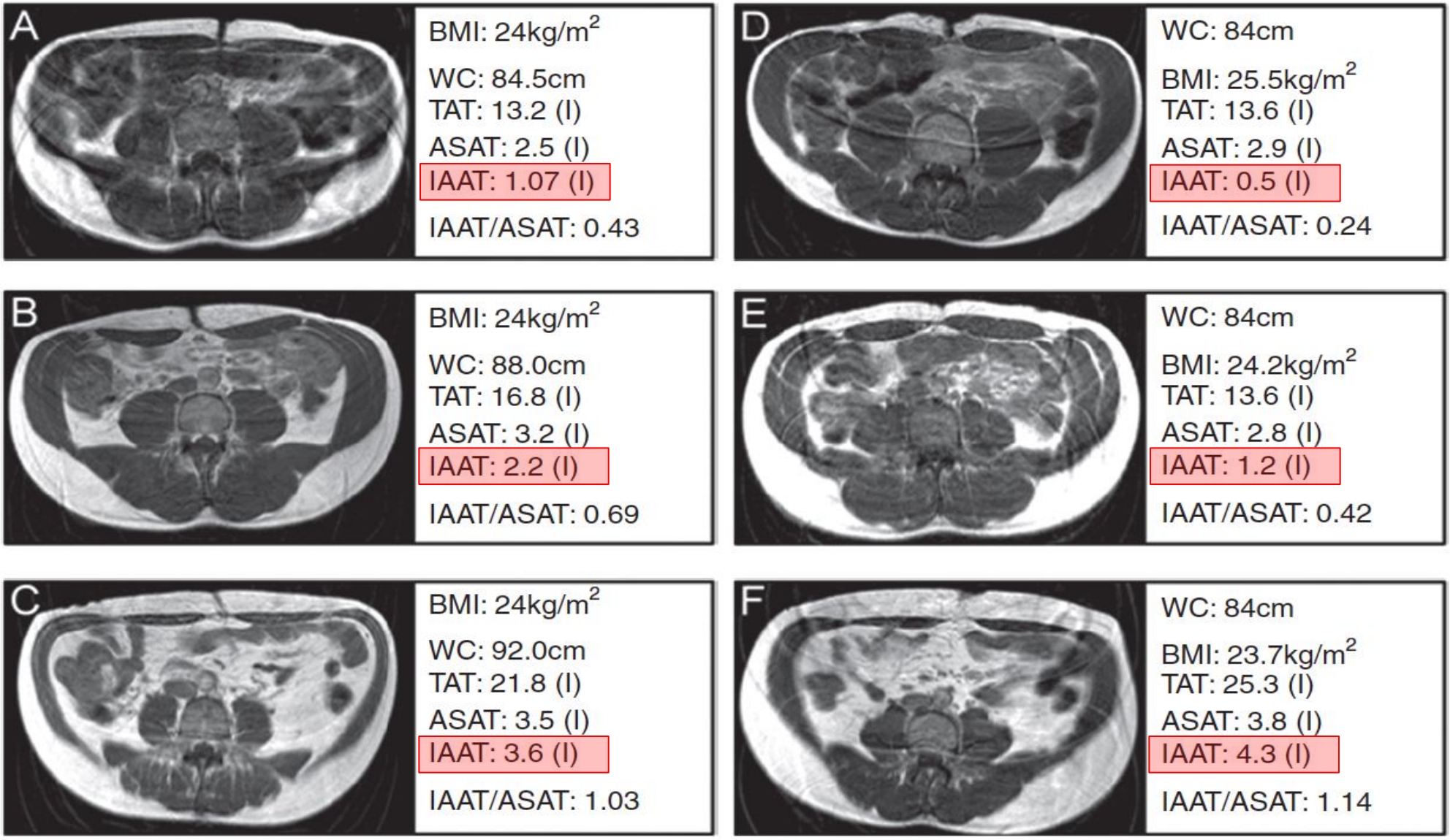
- fasting insulin ↑
- fasting glucose ↑
- blood pressure ↑
- VLDL / Triglycerides ↑
- HDL-Cholesterol ↓
- small dense LDL-Particles ↑
- Thrombogenesis ↑
- Uric Acid ↑
- Renal Function ↓
- NAFLD ↑

Lipodystrophy, Ectopic Fat Disposition and Risk

Cas index, 27 ans

- fasting insulin ↑
- fasting glucose ↑
- blood pressure ↑
- VLDL / Triglycerides ↑
- HDL-Cholesterol ↓
- small dense LDL-Particles ↑
- Thrombogenesis ↑
- Uric Acid ↑
- Renal Function ↓
- NAFLD ↑

Keine sichere Verfettungsvorhersage durch BMI und Taillenumfang bei Normalgewicht

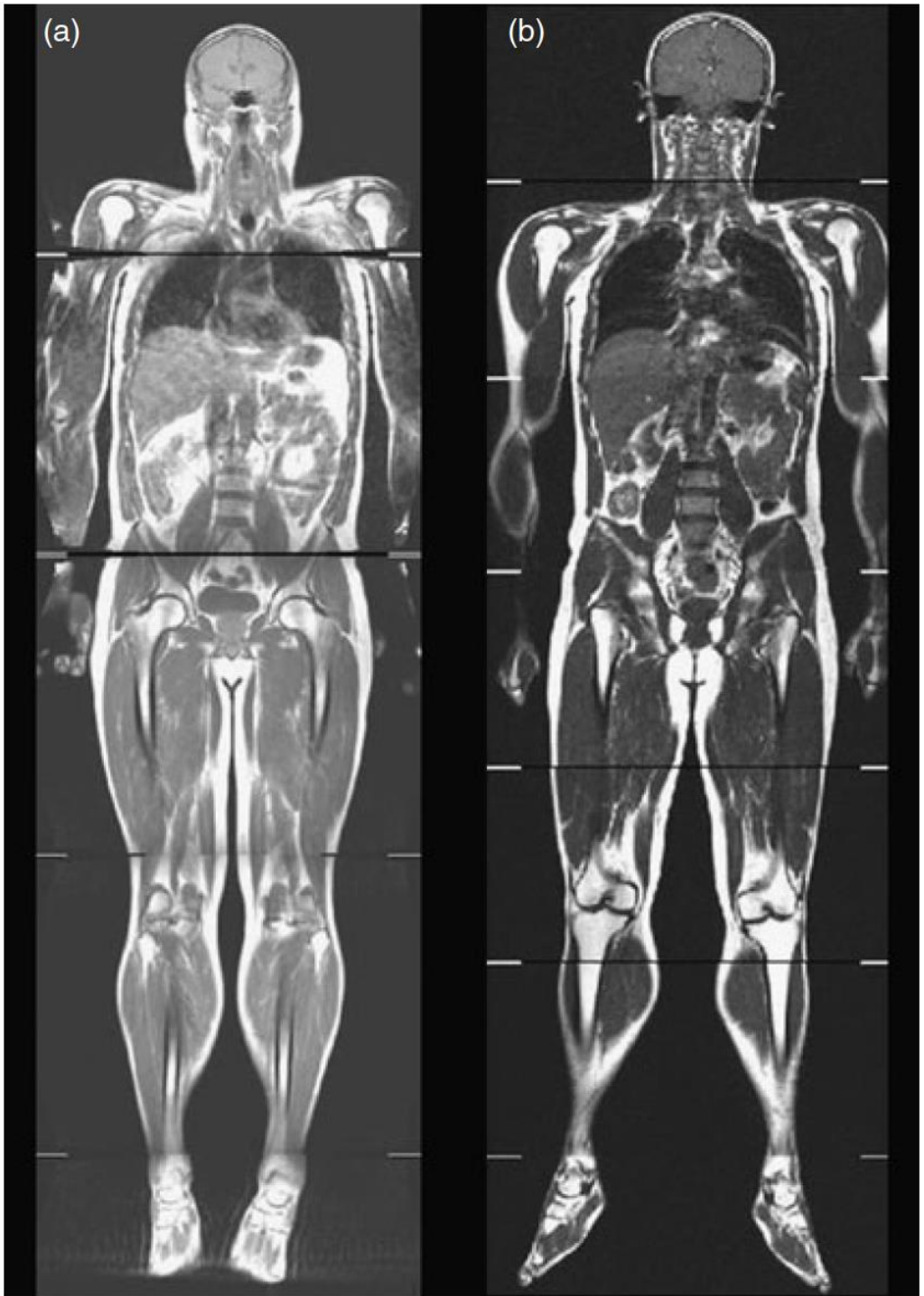


Thomas EL, et al. Obesity 2012;20:76–87

TOFI

BMI = 25.8 kg/m^2

3.3 l visceral fat



HEALTHY

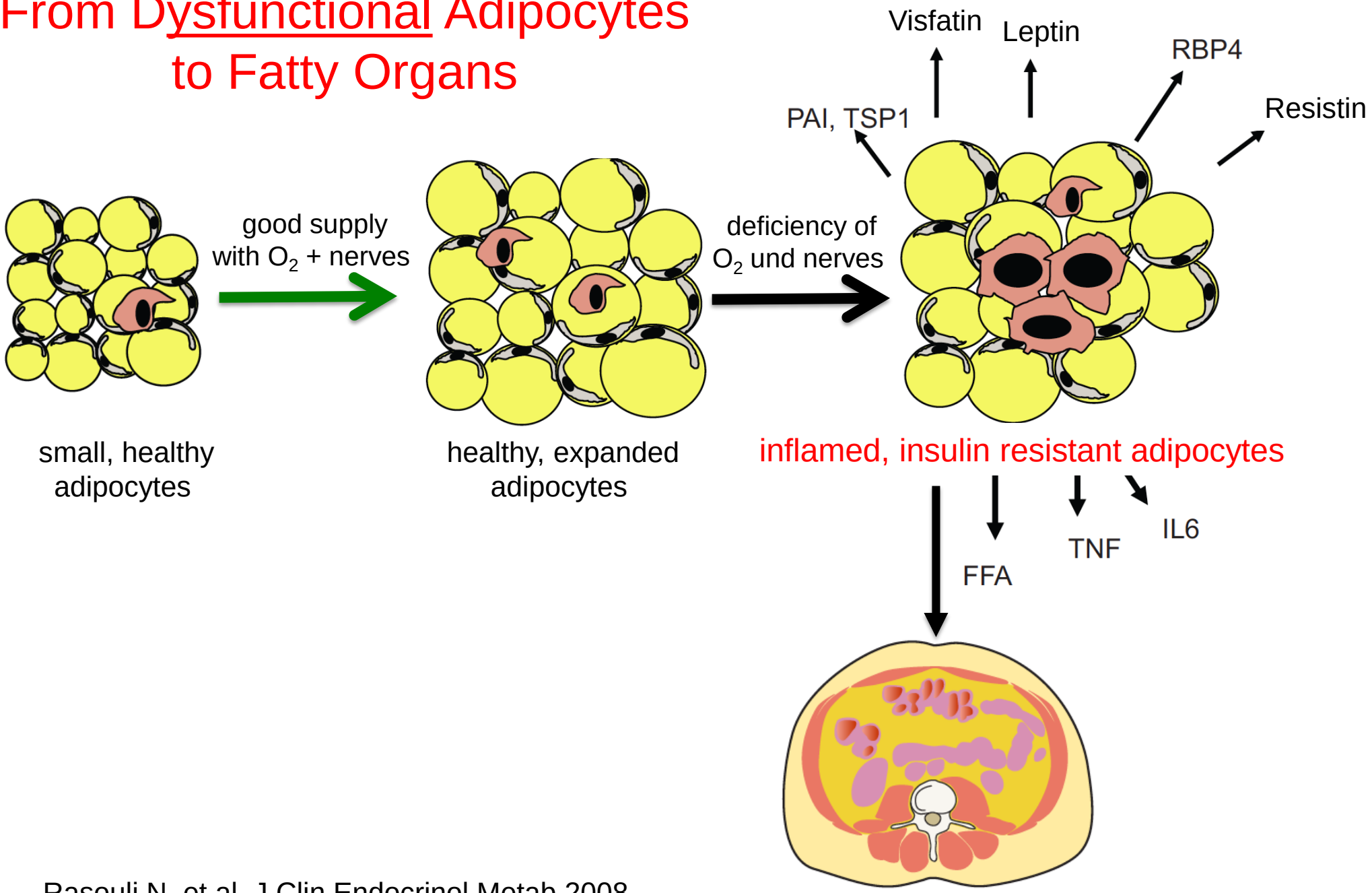
BMI = 26.5 kg/m^2

2.2 l visceral fat

Thomas EL, et al.
Nutr Res Rev 2012

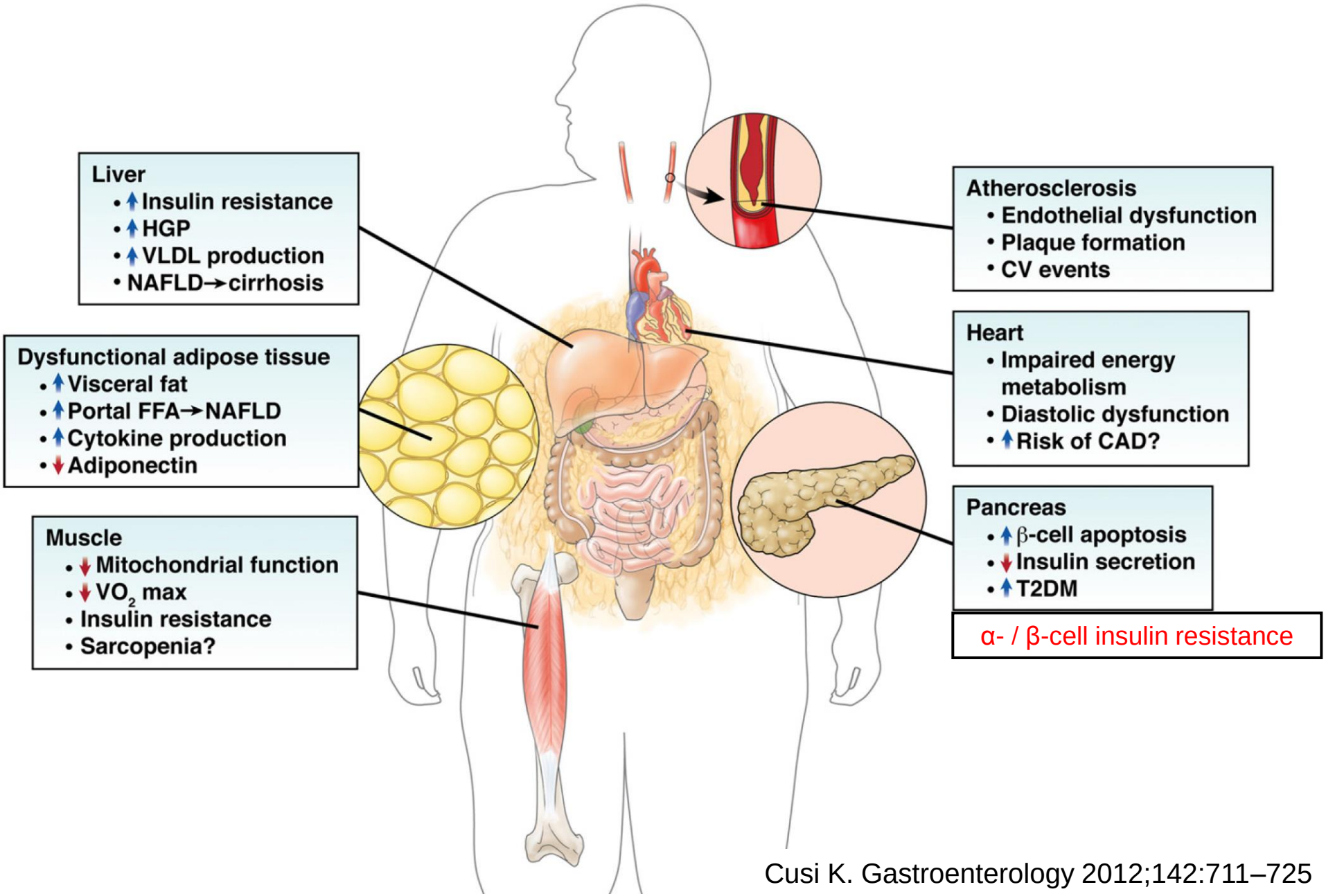
Muscle Activity, Adipose Function and NAFLD

From Dysfunctional Adipocytes to Fatty Organs



Rasouli N, et al. J Clin Endocrinol Metab 2008

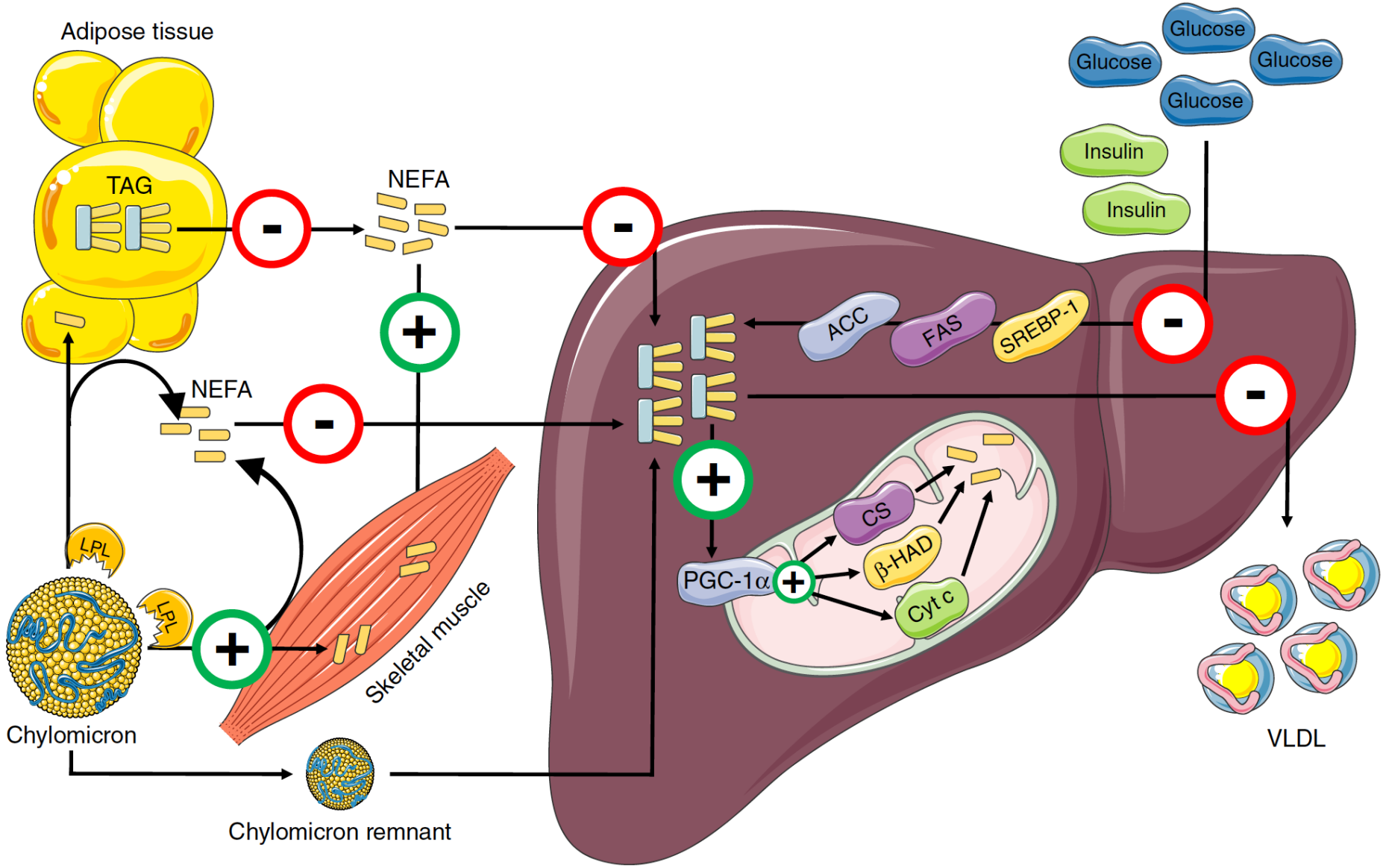
Ectopic Fat is the Real Risk – not „Overweight“!



Cusi K. Gastroenterology 2012;142:711–725

Change the Modern Lifestyle!

Exercise and Hepatic Lipid Metabolism



Brouwers B, et al. Diabetologia 2016;59:2068–2079

(Very-)Low-Energy-Diet with Meal Replacements (Formula) is the Most Successful Dietary Intervention Strategy with Obesity, NAFLD, MetS u. T2DM!

(600 – 1.000 kcal/Tag)

Citation: Clinical and Translational Gastroenterology (2016) 7, e176; doi:10.1038/ctg.2016.28

www.nature.com/ctg

Short-Term Hypocaloric High-Fiber and High-Protein Diet Improves Hepatic Steatosis Assessed by Controlled Attenuation Parameter

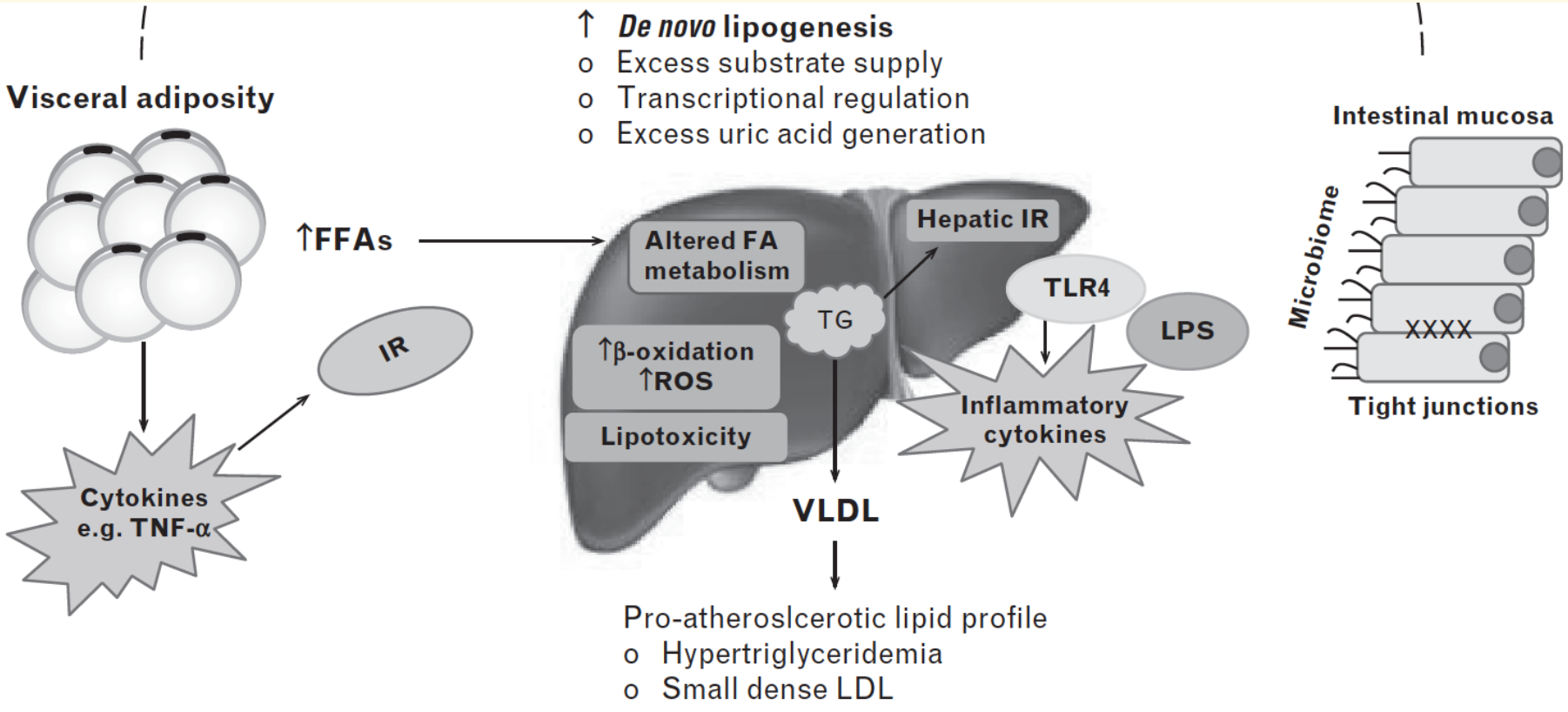
Anita Arslanow, MSc[1], Melanie Teutsch, MSc[2], Hardy Walle, MD[2], Frank Grünhage, MD, PhD[1], Frank Lammert, MD, PhD[1] and Caroline S. Stokes, PhD[1]

OBJECTIVES: Non-alcoholic fatty liver disease is one of the most prevalent liver diseases and increases the risk of fibrosis and cirrhosis. Current standard treatment focuses on lifestyle interventions. The primary aim of this study was to assess the effects of a short-term low-calorie diet on hepatic steatosis, using the controlled attenuation parameter (CAP) as quantitative tool.
METHODS: In this prospective observational study, 60 patients with hepatic steatosis were monitored during a hypocaloric high-fiber, high-protein diet containing 1,000 kcal/day. At baseline and after 14 days, we measured hepatic fat contents using CAP during transient elastography, body composition with bioelectrical impedance analysis, and serum liver function tests and lipid profiles using standard clinical–chemical assays.
RESULTS: The median age was 56 years (25–78 years); 51.7% were women and median body mass index was 31.9 kg/m^2 (22.4–44.8 kg/m^2). After 14 days, a significant CAP reduction (14.0%; $P<0.001$) was observed from 295 dB/m (216–400 dB/m) to 266 dB/m (100–353 dB/m). In parallel, body weight decreased by 4.6% ($P<0.001$), of which 61.9% was body fat. In addition, liver stiffness ($P=0.002$), γ-GT activities, and serum lipid concentrations decreased (all $P<0.001$).
CONCLUSIONS: This study shows for the first time that non-invasive elastography can be used to monitor rapid effects of dietary treatment for hepatic steatosis. CAP improvements occur after only 14 days on short-term low-calorie diet, together with reductions of body composition parameters, serum lipids, and liver enzymes, pointing to the dynamics of hepatic lipid turnover.
Clinical and Translational Gastroenterology (2016) **7**, e176; doi:10.1038/ctg.2016.28; published online 16 June 2016
Subject Category: Liver

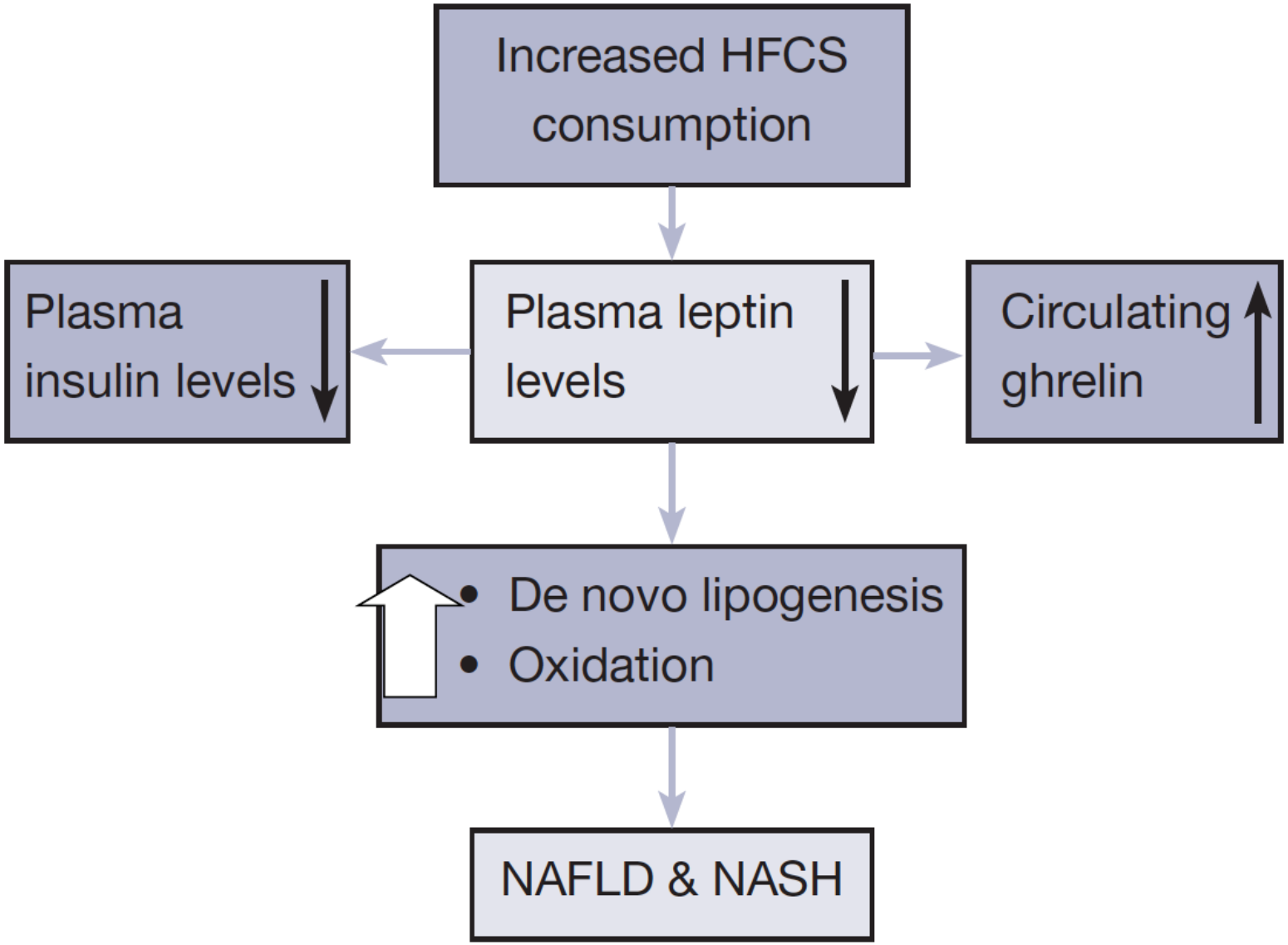
Fructose and liver function – is this behind nonalcoholic liver disease?

Summary

Fructose is a potentially modifiable environmental exposure that appears to exacerbate NAFLD through multiple mechanisms. Although larger, longer clinical studies are still needed, it appears that limitation of fructose sources in the diet is beneficial in NAFLD.



Jin R, et al. Curr Opin Clin Nutr Metab Care 2015;18:490–495



Basaranoglu M, et al. Hepato Biliary Surg Nutr 2015;4:109-116

Nutritional Therapy of NAFLD

4 Basic Principles:

- calorie-reduced
- low-carb
- protein-rich
- fat-modified

Nutrient Specific Effects:

- n-3-PUFA (EPA+DHA)
- β-Glucan
- Inulin
- Carnitine
- Vitamin E
- Choline
- Taurine
- Resveratrol
- Quercitine
- Coffeine

A double-blind, placebo-controlled randomized trial to evaluate the efficacy of docosahexaenoic acid supplementation on hepatic fat and associated cardiovascular risk factors in overweight children with nonalcoholic fatty liver disease

L. Pacifico [a], E. Bonci [b], M. Di Martino [c], P. Versacci [a], G. Andreoli [a], L.M. Silvestri [a], C. Chiesa [d,*]

Methods and Results: Of 58 randomized children, 51 (25 DHA, 26 placebo) completed the study. The main outcome was the change in hepatic fat fraction as estimated by magnetic resonance imaging. Secondary outcomes were changes in visceral adipose tissue (VAT), epicardial adipose tissue (EAT), and left ventricular (LV) function, as well as alanine aminotransferase (ALT), triglycerides, body mass index-standard deviation score (BMI-SDS), and insulin sensitivity. At 6 months, the liver fat was reduced by 53.4% (95% CI, 33.4–73.4) in the DHA group, as compared with 22.6% (6.2–39.0) in the placebo group ($P = 0.040$ for the comparison between the two groups). Likewise, in the DHA group VAT and EAT were reduced by 7.8% (0–18.3) and 14.2% (0–28.2%), as compared with 2.2% (0–8.1) and 1.7% (0–6.8%) in the placebo group, respectively ($P = 0.01$ for both comparisons). There were no significant between-group changes for LV function as well as BMI-SDS and ALT, while fasting insulin and triglycerides significantly decreased in the DHA-treated children ($P = 0.028$ and $P = 0.041$, respectively).

Conclusions: DHA supplementation decreases liver and visceral fat, and ameliorates metabolic abnormalities in children with NAFLD.

Pacifico L, et al. Nutr, Metab & Cardiovasc Dis 2015;25:734-741

Effects of Omega-3 Fatty Acid in Nonalcoholic Fatty Liver Disease: A Meta-Analysis

Wenxia Lu,[1,2] Sainan Li,[1] Jingjing Li,[1] Jianrong Wang,[1,2] Rong Zhang,[1,2] Yuqing Zhou,[1,3] Qin Yin,[1,3] Yuanyuan Zheng,[1] Fan Wang,[1] Yujing Xia,[1] Kan Chen,[1] Tong Liu,[1] Jie Lu,[1] Yingqun Zhou,[1] and Chuanyong Guo[1]

[1]*Department of Gastroenterology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China*
[2]*The First Clinical Medical College, Nanjing Medical University, Nanjing 210029, China*
[3]*The First Affiliated Hospital of Soochow University, Suzhou 215006, China*

A meta-analysis was conducted to assess the effect of omega-3 fatty acid supplementation (n-3 PUFAs) in lowering liver fat, liver enzyme (alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT) levels), and blood lipids (triglyceride (TG), total cholesterol (TC), high density lipoprotein (HDL), and low density lipoprotein (LDL)) in patients with nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). *Methods.* MEDLINE/PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, CINAHL, Science Citation Index (ISI Web of Science), Chinese Biomedical Literature Database (CBM), and Chinese National Knowledge Infrastructure (CNKI) were searched for relevant randomized controlled trials on the effects of n-3 polyunsaturated fatty acids (PUFAs) in patients with NAFLD from inception to May 2015. Ten studies were included in this meta-analysis. *Results.* 577 cases of NAFLD/NASH in ten randomized controlled trials (RCTs) were included. The results of the meta-analysis showed that benefit changes in liver fat favored PUFA treatment, and it was also beneficial for GGT, but it was not significant on ALT, AST, TC, and LDL. *Conclusions.* In this meta-analysis, omega-3 PUFAs improved liver fat, GGT, TG, and HDL in patients with NAFLD/NASH. Therefore, n-3 PUFAs may be a new treatment option for NAFLD.

Lu W, et al. Gastroenterol Res Pract 2016: Article ID 1459790

Nutrition&Metabolism

A randomized controlled trial: the effect of inulin on weight management and ectopic fat in subjects with prediabetes

Nicola D. Guess[1,4*], Anne Dornhorst[2], Nick Oliver[2], Jimmy D. Bell[3], E. Louise Thomas[3] and Gary S. Frost[1]

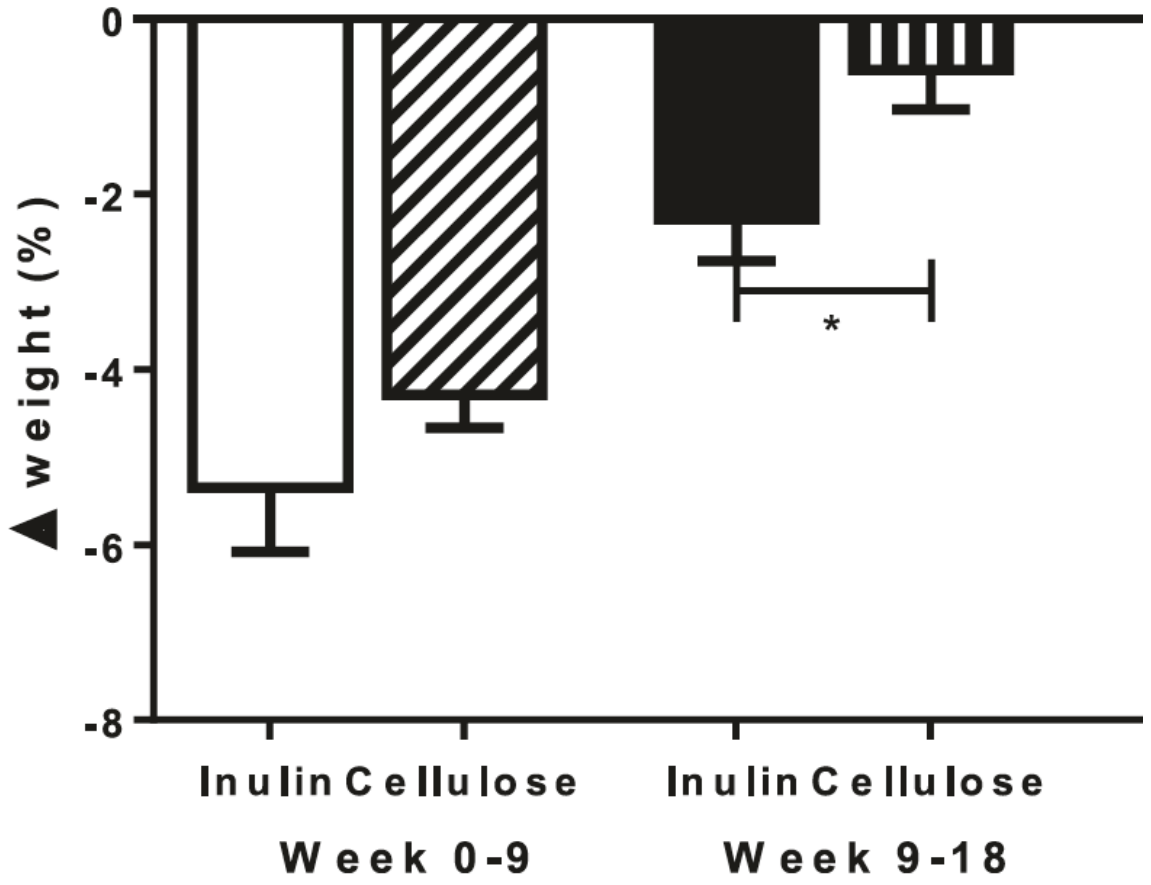
Double-blind, randomised-controlled intervention; 9 weeks identical hypocaloric diet/weight reduction + 9 weeks isocaloric/weight-stable + 30 g Inulin* vs 30 g Cellulose**; n = 44 Pre-Diabetics;

* fermentable
** non-fermentable

Guess ND, et al. Nutrition & Metabolism 2015;12:36

Inulin *vs* Cellulose and Body Weight

18 weeks with 30 g Inulin vs 30 g Cellulose; n = 44 Pre-Diabetics



Guess ND, et al. Nutrition & Metabolism 2015;12:36

Inulin vs Cellulose and Liver Fat

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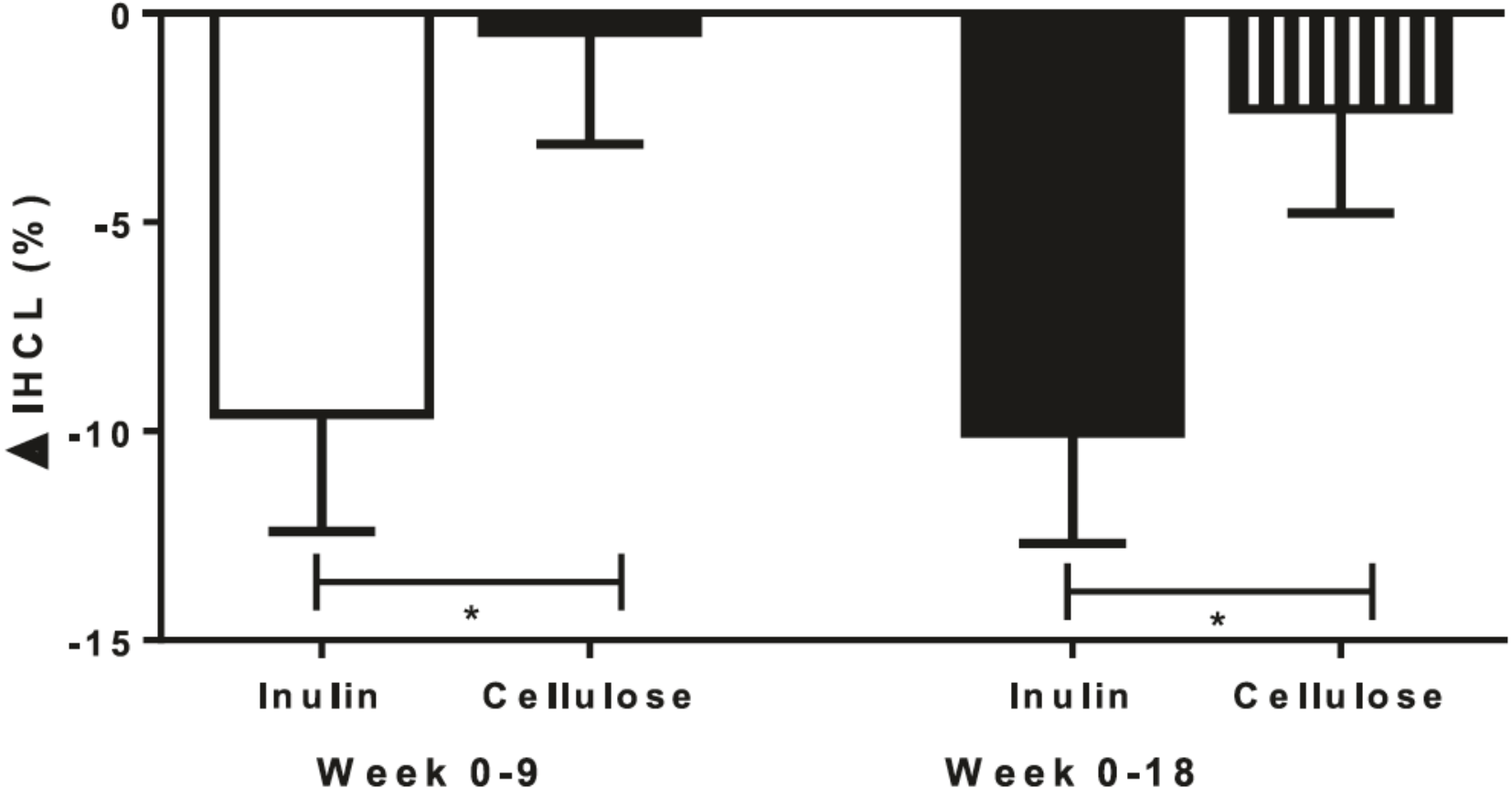

Guess ND, et al. Nutrition & Metabolism 2015;12:36

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- Vitamin E
- Choline
- Taurine
- Resveratrol
- Quercitine
- Coffein

Excess fructose in kids linked to rise in liver disease

By Will Chu, 20-Feb-2017
Last updated on 20-Feb-2017 at 15:46 GMT

Post a comment

Fructose in a typical Western diet comes not from fresh fruit, but from glucose-fructose syrup or sucrose (sugar) that is found in soft drinks and sweets, which typically have few other nutrients. ©iStock

In 1979 I started a comprehensiv systematic review looking into the the „diet-heart“ hypothesis and to my great surprise realized it was a total scam conducted by the plant oil/margarine lobby...

Studies of dietary fat and heart disease.

Ravnskov U, Allen C, Atrens D, Enig MG, Groves B, Kauffman JM, Kroneld R, Rosch PJ, Rosenman R, Werkö L, Nielsen JV, Wilske J, **Worm N**.

Science. 2002 Feb 22;295(5559):1464-6. No abstract available.

Dietary fat and risk of coronary heart disease in men. Studies quoted showed opposite of what is claimed.

Worm N.

BMJ. 1996 Nov 16;313(7067):1258; author reply 1259. No abstract available.

PMID: 8939124 **Free PMC Article**

Similar articles

[Nutrition and coronary heart disease: how important is diet?].

Worm N.

Versicherungsmedizin. 1995 Aug 1;47(4):116-22. Review. German.

PMID: 7676547

Mechanisms Regulating Insulin Response to Intragastric Glucose in Lean and Non-Diabetic Obese Subjects: A Randomized, Double-Blind, Parallel-Group Trial

Anne Christin Meyer-Gerspach, Lucian Cajacob, Daniele Riva, Raphael Herzog, Juergen Drewe, Christoph Beglinger, Bettina K. Wölnerhanssen*

Department of Biomedicine, Division of Gastroenterology, University Hospital Basel, Basel, Switzerland

- 12 Normalgewichtige (BMI: 22,0±0,4 kg/m^2; BMI-Bereich 19,0-24,9 kg/m^2) 6 Frauen/6 Männer; mittleres Alter: 24,3±0,6 Jahre; Bereich 20-32 Jahre)
- 12 Adipöse (BMI: 38,8±0,9 kg/m^2, Bereich 30,5-48,4 kg/m^2); HOMA=3,5; 6 Frauen/6 Männer; mittleres Alter: 29,5±1,8 Jahre; Bereich 19-48 Jahre)
- an 4 Tagen: Glukose-Gaben (mit 10 g, 25 g oder 75 g in 300 ml Wasser oder als Kontrolle 300 ml Wasser – jeweils mit 3 Tagen Abstand;

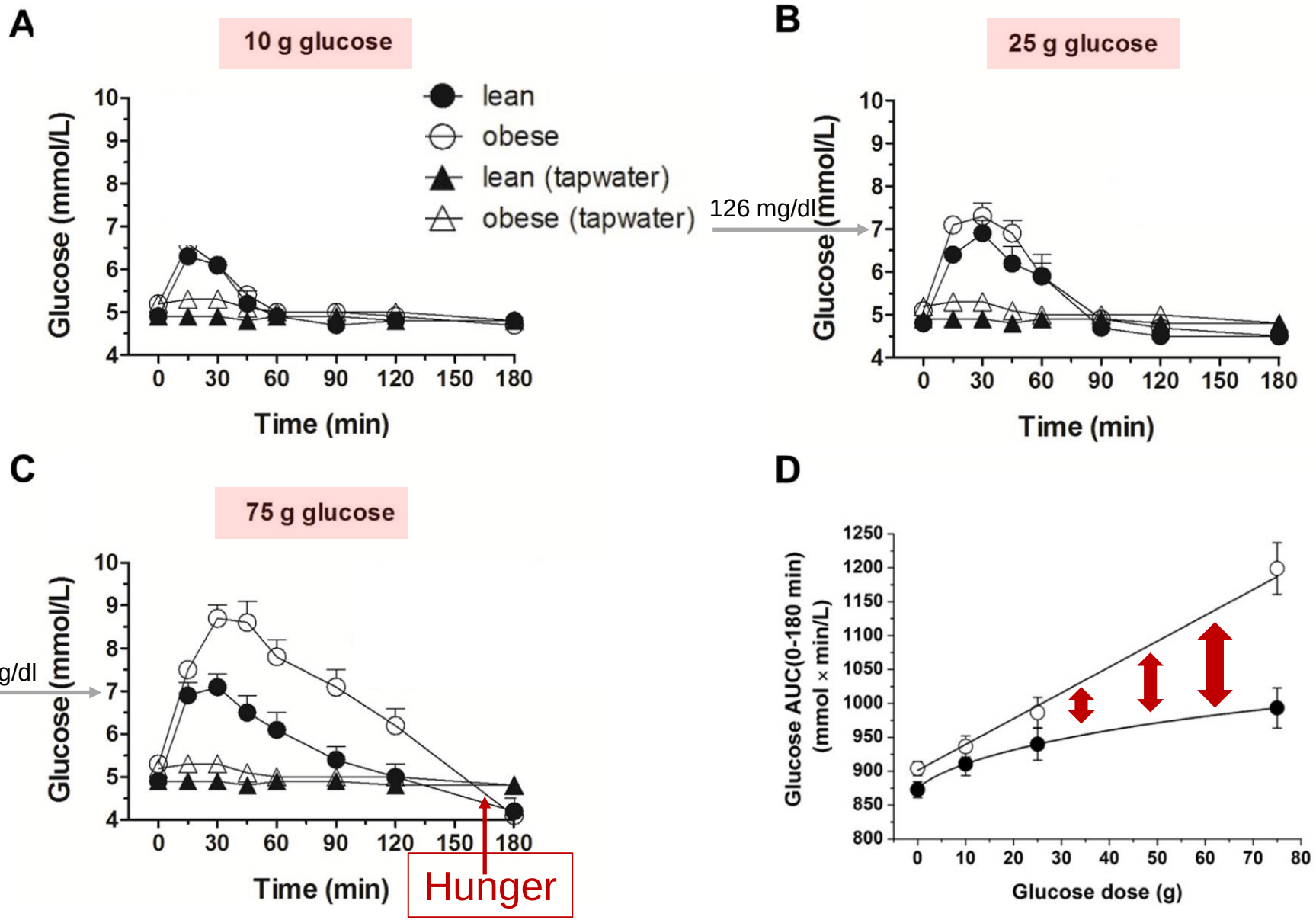
Meyer-Gerspach AC, et al. PLOS ONE 2016;

Zuckerstoffwechsel bei Gesunden mit Normalgewicht vs Adipösen (mit leichter Insulinresistenz)

Hormones and HOMA-IR		Lean controls (n=12)	Obese (n=12)	Significance
Plasma glucose	Fasting glucose (mmol/l)	4.9 ± 0.1	5.2 ± 0.1	*P = 0.005*
	Cmax (mmol/l)	6.6 ± 0.1	6.6 ± 0.2	*NS, P = 0.948*
		7.4 ± 0.3	7.7 ± 0.2	*NS, P = 0.340*
		7.8 ± 0.2	9.0 ± 0.3	*P = 0.006*
	iAUC (0–180 min, mmol x min/l)	21.9 ± 18.4	-3.3 ± 7.7	*NS, P = 0.224*
		75.0 ± 26.2	59.8 ± 13.2	*NS, P = 0.610*
		108.3 ± 36.9	251.6 ± 31.4	*P = 0.007*
Plasma insulin	Fasting insulin (µU/ml)	4.3 ± 0.5	15.2 ± 1.4	*P < 0.001*
	Cmax (µU/ml)	15.6 ± 2.5	45.6 ± 4.0	*P < 0.001*
		24.5 ± 3.3	82.3 ± 9.9	*P < 0.001*
		39.9 ± 5.9	101.5 ± 10.6	*P < 0.001*
	iAUC (0–180 min, µU x min/ml)	99.8 ± 64.3	280.7 ± 176.2	*NS, P = 0.351*
		656.5 ± 128.4	2959.7 ± 322.3	*P < 0.001*
		2791.8 ± 380.0	7747.2 ± 1246.3	*P = 0.002*
HOMA-IR		1.0 ± 0.1	3.5 ± 0.3	*P < 0.001*
Plasma glucagon	Fasting glucagon (pg/ml)	32.6 ± 3.4	66.7 ± 4.2	*P < 0.001*

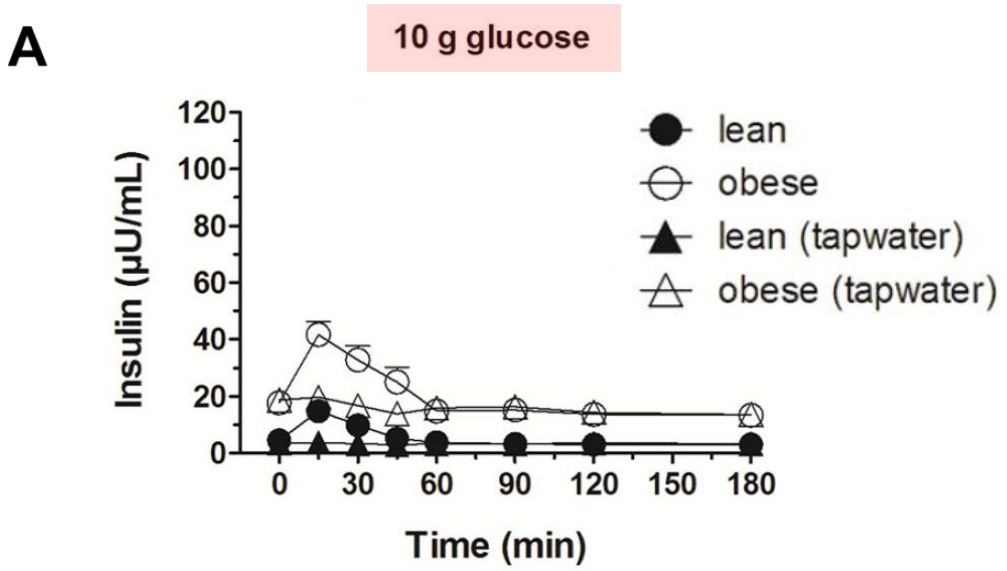
Meyer-Gerspach AC, et al. PLOS ONE 2016;

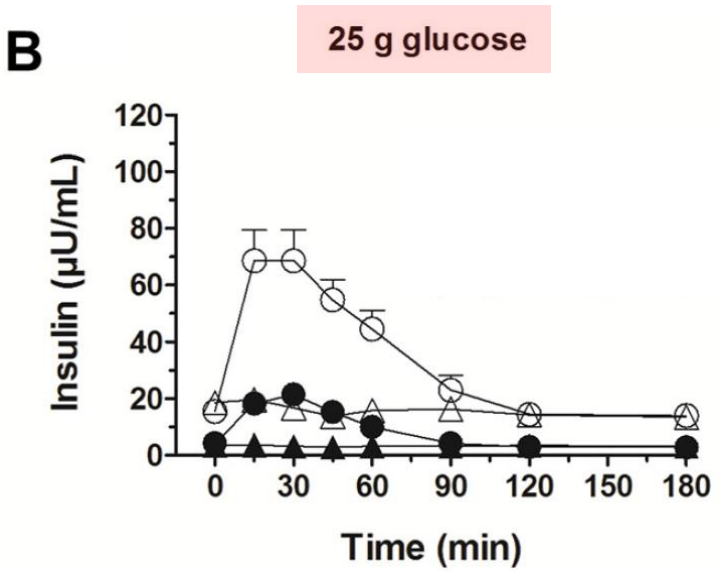
Postprandiale Glykämie: Schlanke vs Adipöse (mit IR)

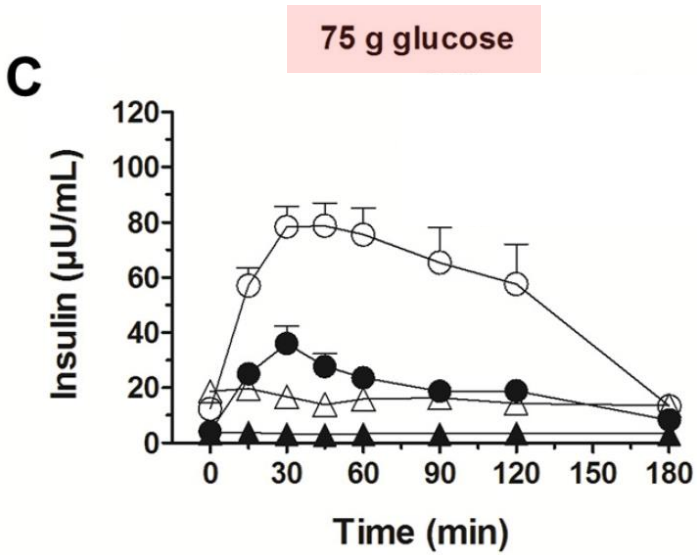


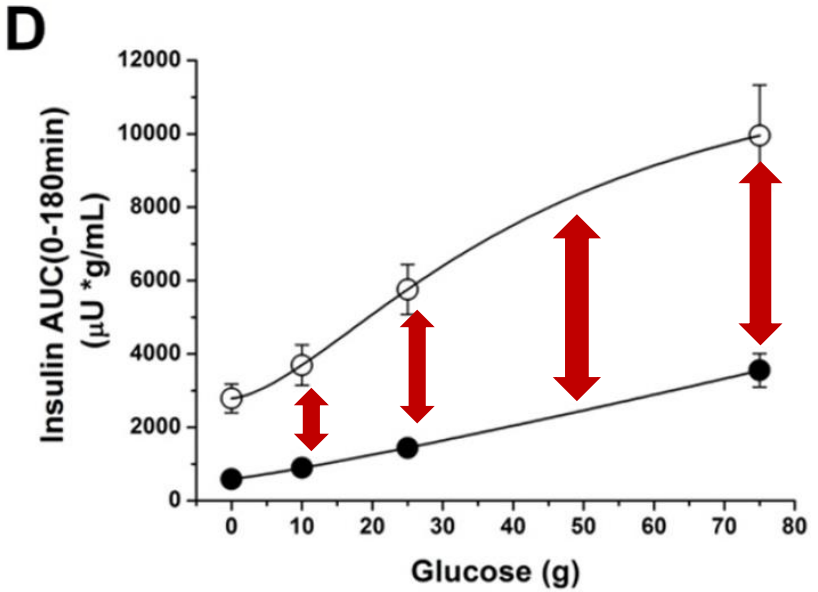
Meyer-Gerspach AC, et al. PLOS ONE 2016; DOI:10.1371/journal.pone.0150803

Postprandiale Insulinämie: Schlanke vs Adipöse (mit IR)





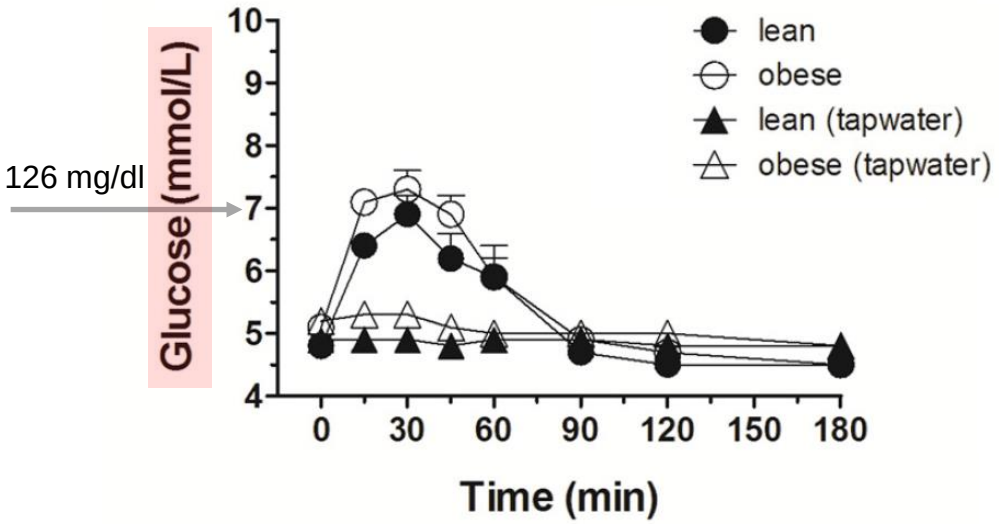


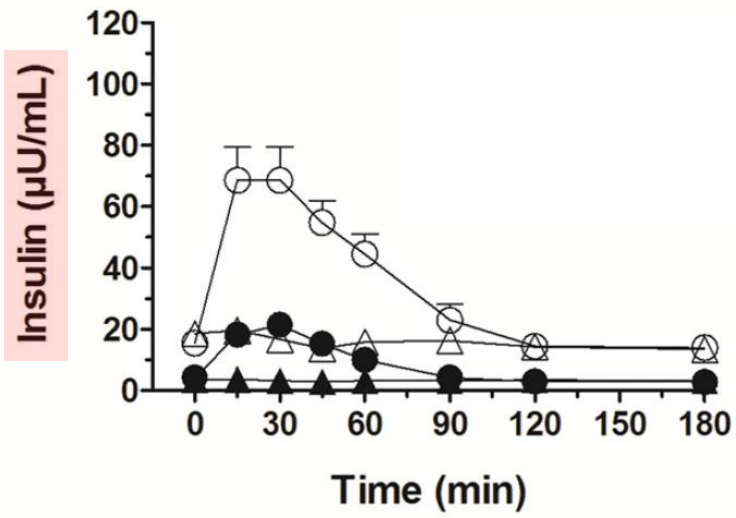


Meyer-Gerspach AC, et al. PLOS ONE 2016; DOI:10.1371/journal.pone.0150803

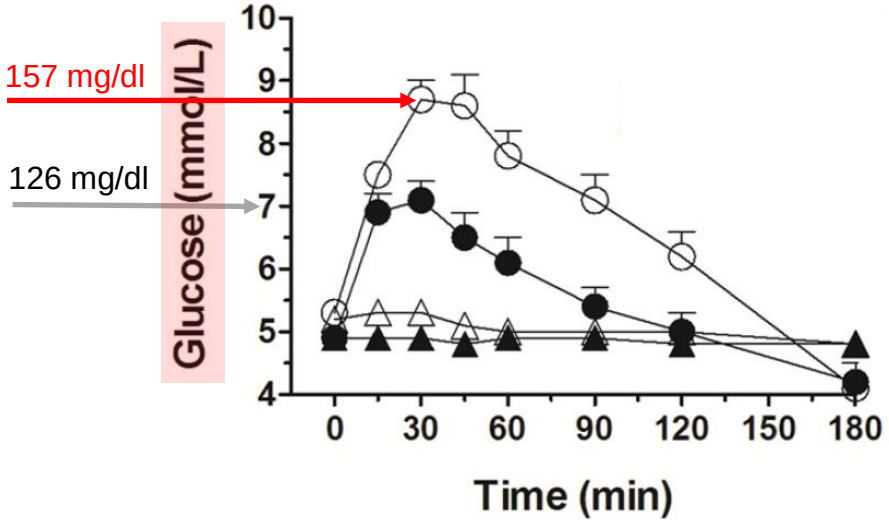
Kompensatorische Insulinämie: Schlanke vs Adipöse

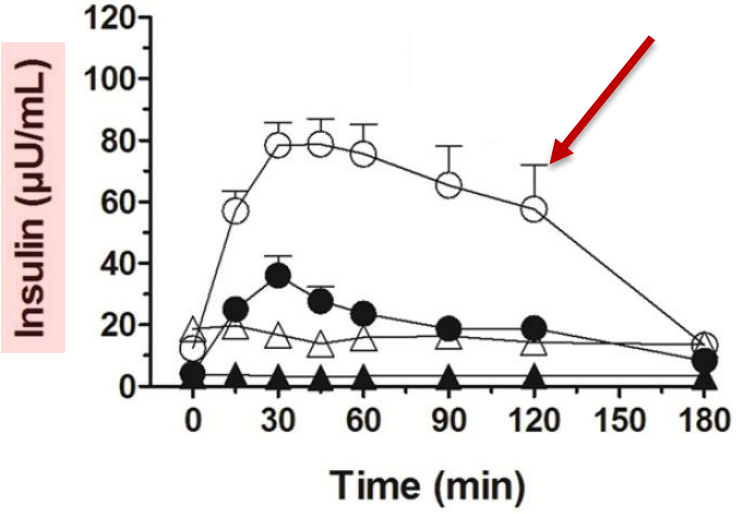
Gabe von 25 g Glukose in 300 ml Wasser





Gabe von 75 g Glukose in 300 ml Wasser





Meyer-Gerspach AC, et al. PLOS ONE 2016; DOI:10.1371/journal.pone.0150803

Isocaloric Diets High in Animal or Plant Protein Reduce Liver Fat and Inflammation in Individuals With Type 2 Diabetes

[1]German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany; [2]German Center for Diabetes Research, Germany; [3]Department of Endocrinology, Diabetes and Nutrition, Campus Benjamin Franklin, Charité University Medicine,

RCT: 37 subjects placed on a diet high in AP (rich in meat and dairy foods; n = 18) or PP (mainly legume protein; n = 19) without calorie restriction for 6 weeks. Diets were isocaloric with the same macronutrient composition (30 en% protein, 40 en% carbohydrates, and 30 en% fat). Macronutrient intake of individuals before enrollment was 17 en% protein, 42 en% carbohydrates, 41 en% fat.

Markova M, et al. Gastroenterology 2017;152:571–585

Isocaloric Diets High in Animal or Plant Protein Reduce Liver Fat and Inflammation in Individuals With Type 2 Diabetes

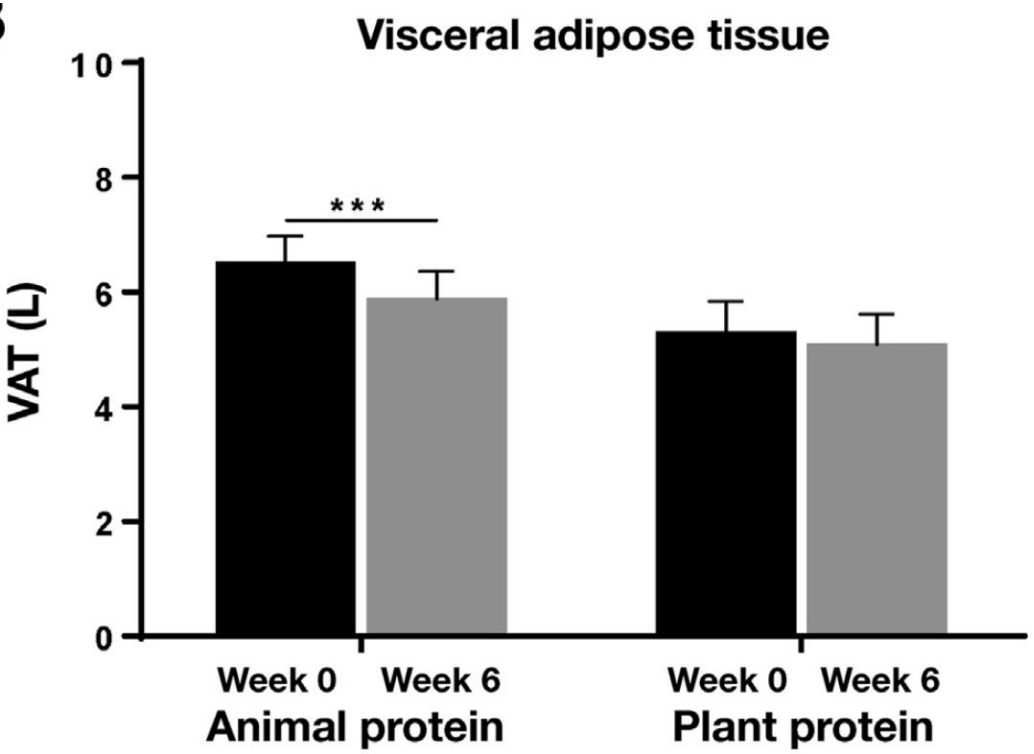
Parameter	AP (n = 18)			PP (n = 19)		
	wk 0	wk 6	P_{AP} value	wk 0	wk 6	P_{PP} value
Body mass index, *kg/m*^{2}	31.0 ± 0.8	30.2 ± 0.7	.003	29.4 ± 1.0	28.9 ± 1.0	.001
Waist, *cm*	104.2 ± 2.6	102.2 ± 2.0	NS	100.7 ± 3.0	99.4 ± 2.9	NS
Hip, *cm*	107.8 ± 1.8	106.3 ± 1.6	NS	105.3 ± 2.0	103.2 ± 1.9	.034
Waist-to-hip ratio	0.967 ± 0.018	0.962 ± 0.015	NS	0.957 ± 0.024	0.964 ± 0.025	NS
Fat mass, %	35.26 ± 2.19	33.36 ± 1.94	.023	34.95 ± 2.30	33.55 ± 2.20	NS
Fat-free mass, %	64.74 ± 2.19	66.64 ± 1.94	.023	65.05 ± 2.30	66.45 ± 2.20	NS
AT_{femur}, *mL*[a]	394.25 ± 17.51	372.15 ± 19.66	.016	372.73 ± 26.18	348.05 ± 17.56	NS
AST, *U/L*	26.64 ± 1.85	22.36 ± 1.44	NS	23.88 ± 2.13	20.37 ± 1.23	.020
ALT, *U/L*	30.44 ± 2.47	27.09 ± 1.93	NS	29.59 ± 2.97	26.52 ± 2.01	NS
AST/ALT ratio	0.88 ± 0.06	0.84 ± 0.05	NS	0.80 ± 0.04	0.80 ± 0.04	NS
γ-GT, *U/L*	44.31 ± 6.82	31.51 ± 4.23	.017	41.76 ± 5.25	31.94 ± 3.61	NS
Keratin 18, *U/L*	184.9 ± 28.9	159.7 ± 20.8	NS	197.4 ± 26.2	151.2 ± 13.9	.021
ELF score	9.19 ± 0.15	9.01 ± 0.16	NS	9.02 ± 0.17	9.11 ± 0.15	NS
PIIINP, *ng/mL*	7.73 ± 0.53	7.05 ± 0.26	NS	8.07 ± 0.49	7.98 ± 0.41	NS
Adiponectin, *ng/mL*[b]	4063.6 ± 836.1	3661.4 ± 727.0	NS	4239.1 ± 395.6	3653.5 ± 317.1	.003
Adipose tissue insulin resistance[c]	11.99 ± 2.32	8.61 ± 1.34	.019	10.24 ± 1.71	9.87 ± 2.20	.026

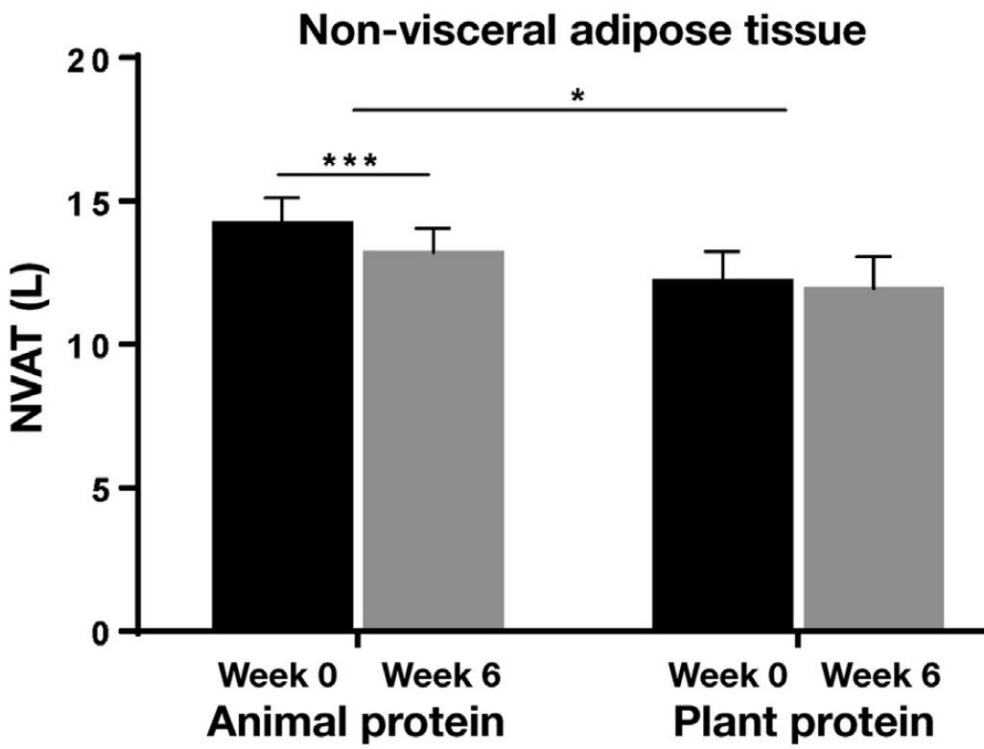
Markova M, et al. Gastroenterology 2017;152:571–585

High-Protein Diet and Body Fat

Animal vs Plant Protein

n = 18 on diet high in animal protein (AP rich in meat and dairy foods); n = 19 on diet high in plant protein (PP mainly legume protein); Diets without calorie restriction for 6 weeks. Isocaloric with the same composition (30% protein, 40% carbohydrates, and 30% fat).

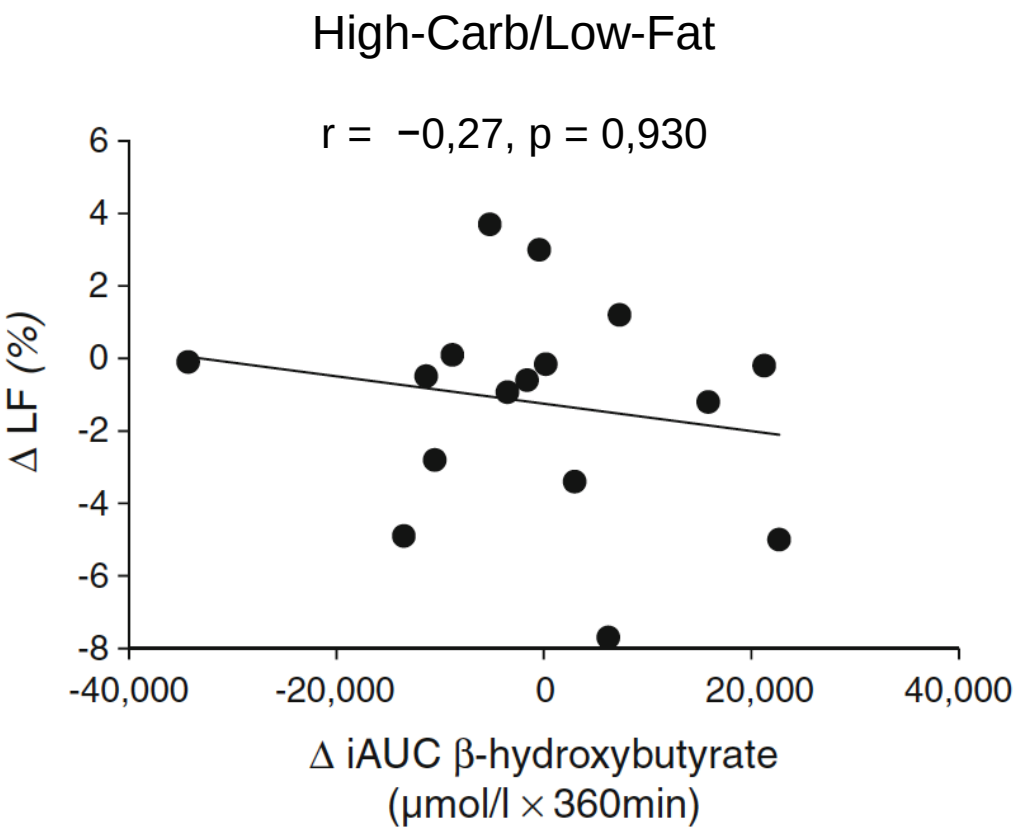


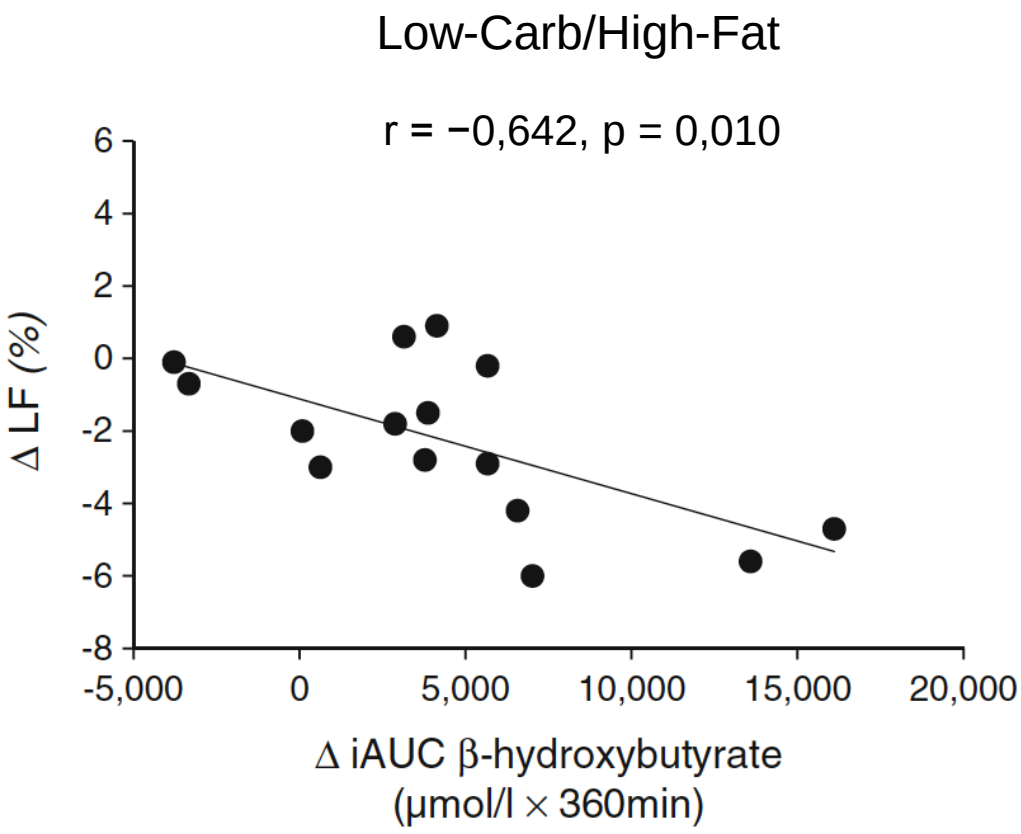


Markova M, et al. Gastroenterology 2017;152:571–585e8

Reduction in liver fat by dietary MUFA in type 2 diabetes is helped by enhanced hepatic fat oxidation

β-Hydroxybutyrat: isocaloric 30 en% vs 42 en% fat: virgine olive oil



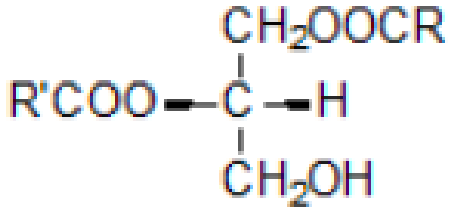


Bozzetto L, et al. Diabetologia 2016;59(12):2697-2701

Lifestyle changes for the treatment of nonalcoholic fatty liver disease: a review of observational studies and intervention trials

Reference	Country	Study design	Patients, (% men)	Liver fat content evaluation	Intervention (type, time)	Effects on liver fat content	Effects on liver histological endpoints
DIET INTERVENTIONS							
Huang *et al.* [2005]	USA	Intervention without control arm	16 obese, (50)	Liver biopsy	NC, 12 months	No effect	Decreased ballooning/ inflammation
Kirk *et al.* [2009]	USA	RCT	22 obese, (18)	MRS	Low calorie HCD *versus* LCD, 11 weeks	Decreased in HCD and LCD	NP
Haufe *et al.* [2011]	Germany	RCT	102 obese, (18)	MRS	Low calorie LCD *versus* LFD, 6 months	Decreased in LCD and LFD	NP
Bozzetto *et al.* [2012]	Italy	RCT	36 diabetic, (81)	MRS	CHO/fiber *versus* MUFA, CHO/fiber+ exercise, *versus* MUFA + exercise, 8 weeks	Decreased in MUFA and MUFA + exercise	NP
Ryan *et al.* [2013]	Australia	RCT	12 obese, (50)	MRS	MD *versus* LF/HCD	Decreased	NP
Trovato *et al.* [2015]	Italy	Intervention without control arm	90 obese, (49)	US	MD, 6 months	Decreased	NP

Zelber-Sagi S, et al. Ther Adv Gastroenterol 2016;9:392–407



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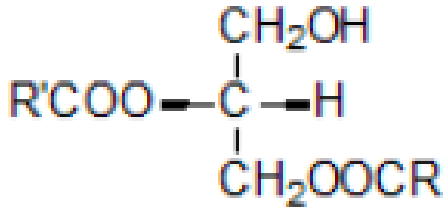
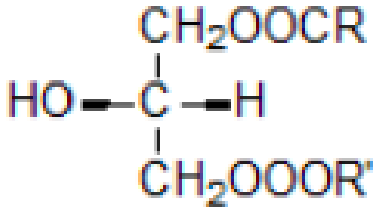


sn-2,3-diacylglycerol



sn-1,3-diacylglycerol