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

### Risk Calculator „Fatty Liver Index“

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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</thead>
<tbody>
<tr>
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<tr>
<td>2</td>
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<td></td>
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<tr>
<td>3</td>
<td>Triglycerides (mg / dL)</td>
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<td>4</td>
<td>BMI (kg / m²)</td>
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<td>GGT (U / L)</td>
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<td>Waist circumference (cm)</td>
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<tr>
<td>7</td>
<td>Constant</td>
<td>************</td>
<td>-15,745</td>
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<tr>
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<td>************</td>
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<td>9</td>
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</tr>
<tr>
<td>10</td>
<td>The fatty liver index (FLI) is</td>
<td>88</td>
<td></td>
</tr>
</tbody>
</table>

Use this table to interpret the FLI

The FLI was developed at the Liver Research Center - Italy

- 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**: 30 – 40%
- **Overweight/Obese**: 60%
- **Type-2-Diabetics**: 70 – 90%
Prevalence of NAFLD in Overweight School Children in Germany

Overweight Children
30 %

Denzer C. Deutsches Gesundheitsblatt 2013;56:517-527
Traditionally a Disease for Hepatologists: Progression of Liver Steatosis

- Steatosis
  - NASH
    - Cirrhosis
      - Liver Cancer: 10-25%
      - Liver failure: 40%
Non-alcoholic fatty liver disease and cardiovascular risk: Pathophysiological mechanisms and implications

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

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome, the incidence of which is rising rapidly due to the increasing epidemic of obesity in adults and children. The initial accumulation of fat followed by subsequent inflammation results in the development of liver damage, and is critically influenced by a range of factors including age, gender, presence of diabetes, genetic polymorphisms and the gut microbiome. An increasing body of data suggest that NAFLD is an independent risk factor of cardiovascular disease, which remains the commonest cause of death in NAFLD patients. This review focusses on the pathogenesis of NAFLD, and the evolution of approaches 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 independent of metabolic syndrome, it might be better for predicting risk of type 2 diabetes and cardiovascular disease than is metabolic syndrome...“

Development of NAFLD

Lipolysis in Adipocytes

Dietary Fat

Triglycerides

Oxidation

De-novo Ligogenesis

Dietary Carbohydrates

Triglyceride

Secretion

Fat-Accumulation

VLDL

Triglyceride Uptake/Synthesis ↑

Triglyceride Oxidation/Secretion ↓

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
Dysfunctional Fat Storage, Ectopic Fat and NAFLD
Hypertrophy and Vascularisation of Adipose Tissue

Dysfunctional Adipocytes cause ectopic Lipid Deposition

Energy intake > Energy expenditure

↑Fatty acid flux
Defects in adipocyte fatty acid metabolism
↑Fatty acid flux

Skeletal muscle
Liver

Ectopic lipid deposition

Defects in mitochondrial metabolism, biogenesis, or both, leading to decreased fat oxidation

Dysfunctional adipocytes cause ectopic fat disposition.

Dysfunctional adipose tissue

Saturation of expansion capacity of AT OR Inability of subcutaneous AT to expand (e.g., lipodystrophies)

LIPID OVERFLOW

↑ Visceral adiposity
↑ Liver fat
↑ Epi/pericardial and myocardial fat
↑ Muscle fat
↑ Renal sinus fat
↑ Pancreatic fat
Adipose Tissue Function and Physical Exercise

Exercise training:

Muscle tissue:
- ↑ IL-6
- ↓ Pro-inflammatory cytokines
- ↑ Anti-inflammatory cytokines

Adipose tissue:
- ↑ Angiogenesis
- ↓ Vasoconstriction
- ↑ Blood supply
- ↓ Hypoxia
- ↓ Macrophage infiltration
- ↓ M1/M2 macrophage ratio

Endothelial cells:
- ↓ Adhesion molecules
- ↑ Cell regeneration
- ↓ Vascular wall inflammation

Immune cells:
- ↓ Toll-like receptors
- ↓ Inflammatory monocytes
- ↑ Regulatory T cells

↓ Systemic inflammation

Muscles, Myocines and Metabolic Regulation

**Fat cells**
- ↑ Lipolysis (visceral fat > subcutaneous fat)
- ↑ Adiponectin
- ↓ CRP
- ↓ TNF-α
- ↓ Macrophage infiltration
- ↓ IL-6
- ↓ IL-8
- ↓ MCP-1

**Liver**
- ↓ hepatic lipid

**Muscle**
- Muscle fiber type switching (glycolytic to oxidative)
- Muscle fiber hyperplasia
- ↑ Mitochondrial biogenesis
- ↑ FA oxidation
- ↑ GLUT4
- ↑ GLUT4 translocation
- ↑ IL-6 secretion
- ↑ Irisin secretion
- ↑ Microcirculation
- ↓ Intramuscular:
  - DAG
  - Ceramide
  - Dihydroceramide
  - Sphingosine

Ectopic Fat and Risk

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

- Visceral adiposity
- Liver fat
- Epi/pericardial and myocardial fat
- Muscle fat
- Renal sinus fat
- Pancreatic fat

Insulin resistance/inflammation

Increased cardiometabolic risk

Impaired insulin secretion

High risk of type 2 diabetes

INCREASED RISK OF CARDIOVASCULAR DISEASE
Liver Fat ↑

**Insulin Resistance**
+ CHO↑
Energy↑

Liver Fat ↑

VLDL-Cholesterol↑ + Lipolysis Fat Cells↑

ectopic Fat Lipotoxicity
Insulin Resistance of α- and β-Cells

Hyper-glycemia

Basal Insulin↑

IR Liver Glucose↑

Apoptose β-Cells

NAFLD predisposes to T2DM and CVD

Nonobese or obese individual with healthy functional adipose tissue

- ↓ VLDL₁
- ↓ VLDL₂
- ↑ Large LDL
- ↓ Small LDL
- ↑ Large HDL₂
- ↓ Small HDL₃
- Normal triglycerides
- Normal LDL cholesterol
- Normal HDL cholesterol

Visceral obese individual with ectopic fat and dysfunctional adipose tissue

- ↑ VLDL₁
- ↑ VLDL₂
- ↓ Large LDL
- ↑ Small LDL
- ↓ Large HDL₂
- ↑ Small HDL₃
- High triglycerides
- "Normal" LDL cholesterol
- Low HDL cholesterol

atherogenic Dyslipoproteinemia
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
NAFLD and Associated Cardiac Complications

NAFLD-related cardiac complications

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

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

Insulin Resistance
- Smoking
- Refined, Energy-Dense Food
- Lack of Sleep
- Inactivity
- Abdominal Adiposity
- Dysbiosis

Hyperinsulinemia

NAFLD and Other Non-Communicable Diseases

Pregnancy
- Lack of UVB/Sunlight
- Dysstress
- Age
- Genes
Insulin Resistance and Hyperinsulinemia

Patient with MetS and IGT postprandial insulin during OGTT (75 g Glucose)

- Healthy Male
- IR-Patient

Insulinspiegel uIU/ml

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
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 (\(\leq 85\) pmol/L) lean \((n = 9)\) and obese \((n = 6)\) and hyperinsulinemic (\(\geq 115\) pmol/L) obese \((n = 8)\) subjects. Mass isotopomer distribution analysis was used to measure the fraction of newly synthesized fatty acids in VLDL-triacylglycerol.

Hyperinsulinemia and de novo Lipogenesis

Isocaloric Diet
46 En% Carbohydrates

Fractional de novo lipogenesis (%)

Lean NI Obese NI Obese HI

Cave!

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

¹Center for Human Nutrition, Divisions of ²Endocrinology and ³Digestive 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 Basaranoglu¹, Gokcen Basaranoglu², Elisabetta Bugianesi³

¹Division of Gastroenterology and Hepatology, Department of Internal Medicine, ²Department of Anaesthesiology, Bezmialem Vakif University Faculty Hospital, Istanbul, Turkey; ³Division 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.
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

Together, it appears that a weight reduction in the magnitude range of \(\sim 5-7\%\) may clearly decrease steatosis but that more weight loss is needed (\(\sim 8-10\%\) reduction) to reverse steatohepatitis. Weight reductions of \(\geq 10\%\) may also cause a significant regression of fibrosis (65).
Very-Low-Calorie-Diets/Meal-Replacements: Superior Meta-Analysis: 20 randomized-controlled Studies; n = 3,017;

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)
### 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 %)

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<th>Variable</th>
<th>Controls</th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 4</th>
<th>Week 8</th>
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<tr>
<td>Weight (kg)</td>
<td>101.5±3.4</td>
<td>103.7±4.5</td>
<td>99.7±4.5*</td>
<td>94.1±4.3*</td>
<td>88.4±4.3*†</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>33.4±0.9</td>
<td>33.6±1.2</td>
<td>32.3±1.2*</td>
<td>30.5±1.2*</td>
<td>28.7±1.3*†</td>
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<tr>
<td>Fat mass (kg)</td>
<td>36.2±2.7</td>
<td>39.0±3.5</td>
<td>36.6±3.6*</td>
<td>31.7±3.7*</td>
<td>26.3±4.0*</td>
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<tr>
<td>ffm (kg)</td>
<td>64.7±3.8</td>
<td>64.7±3.0</td>
<td>63.2±3.1</td>
<td>62.4±3.0*</td>
<td>62.1±3.0*</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>105.0±1.5</td>
<td>107.4±2.2</td>
<td>104.4±2.2*</td>
<td>99.7±2.4*</td>
<td>94.2±2.5†</td>
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<td>Hip circumference (cm)</td>
<td>109.8±2.4</td>
<td>109.5±2.9</td>
<td>108.3±2.7*</td>
<td>105.0±2.6*</td>
<td>99.5±2.6*†</td>
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<tr>
<td>WHR</td>
<td>0.96±0.02</td>
<td>0.98±0.02</td>
<td>0.97±0.02</td>
<td>0.95±0.01</td>
<td>0.95±0.01</td>
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Liver-Fat
- 30 %  - 70 %

Fasting-Glucose

Hepatic Glucose Production

Formula-Diet, Fat Removal and Diabetes-Remission

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

Pancreas Fat Content
- 10 %
- 23 %

1st Week

Week

First-phase insulin response (nmol min$^{-1}$ m$^{-2}$)

0.0
0.2
0.4
0.6
0.8
1.0

0
2
4
6
8

Week

0
2
4
6
8

1st Week

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!
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.
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

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/m² 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.
Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction\textsuperscript{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

<table>
<thead>
<tr>
<th>Diet composition</th>
<th>Low-calorie diet (n = 9)</th>
<th>Low-carbohydrate diet (n = 9)</th>
<th>P value\textsuperscript{2}</th>
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<td>Energy intake (kcal/d)</td>
<td>1325 ± 180</td>
<td>1553 ± 517</td>
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<td>Diet composition</td>
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<tr>
<td>Protein (%)</td>
<td>16 ± 3</td>
<td>33 ± 4</td>
<td>&lt;0.001</td>
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<tr>
<td>Fat (%)</td>
<td>34 ± 6</td>
<td>59 ± 7</td>
<td>&lt;0.001</td>
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<tr>
<td>Carbohydrate (%)</td>
<td>50 ± 4</td>
<td>8 ± 5</td>
<td>&lt;0.001</td>
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<tr>
<td>Protein (g/d)</td>
<td>53 ± 12</td>
<td>121 ± 34</td>
<td>&lt;0.001</td>
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<tr>
<td>Fat (g/d)</td>
<td>49 ± 9</td>
<td>105 ± 44</td>
<td>0.002</td>
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<tr>
<td>Carbohydrate (g/d)</td>
<td>169 ± 33</td>
<td>26 ± 8</td>
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<td>Fat intake (%)</td>
<td>Saturated</td>
<td>42 ± 8</td>
<td>37 ± 4</td>
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<td></td>
<td>Monounsaturated</td>
<td>37 ± 2</td>
<td>38 ± 6</td>
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<tr>
<td></td>
<td>Polyunsaturated</td>
<td>18 ± 7</td>
<td>15 ± 4</td>
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</table>
Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction

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

22 Obese patients (BMI = 37), randomized to 2 groups with hypocaloric diet: ≈ 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;
High-Carb- vs Low-Carb-Low-Calorie Diet and Liver Fat


IHTG = intrahepatischer Fettgehalt
High-Carb- vs Low-Carb-Low-Calorie Diet and Liver Fat


Hepatic Insulin Sensitivity
High-Carb- vs Low-Carb-Low-Calorie Diet and Liver Fat


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,*

- 11 obese women with 60 g whey protein/day for 4 weeks in addition to their regular diet

- after 4 weeks of whey supplementation:
  - liver fat: - 21 %
  - serum triglycerides: - 15 %
  - serum cholesterol: - 7 %
  - fat-free body mass: + 4 %

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

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).

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.
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

- Liver Fat (%)
  - Mediterranean Low-Fat + Olive Oil: -7%
  - Mediterranean Low-Fat Olive Oil:...

- Fasting-Insulin (%)
  - Mediterranean Low-Fat + Olive Oil: ...
  - Mediterranean Low-Fat Olive Oil: ...

High-Fat Mediterranean Diet for Treatment of NAFLD

n = 45; randomized cross-over à 8 weeks;
isoaloric: CHO-rich + fibre-rich vs MUFA-rich mediterranean diet

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

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.
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 hydroxytyrosol (A), tyrosol (B), and oleuropein (C).

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. Parker¹, Nathan A. Johnson¹,³, Catriona A. Burdon¹, Jeffrey S. Cohn², Helen T. O'Connor¹,³, Jacob George⁴,*

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

<table>
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<th>Authors, year</th>
<th>Effect size</th>
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<th>Effect size and 95% CI</th>
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<td>Capanni et al., 2006</td>
<td>-0.938</td>
<td>-1.559, -0.316</td>
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<td>Sofi et al., 2010</td>
<td>-0.811</td>
<td>-1.948, 0.326</td>
<td>0.162</td>
</tr>
<tr>
<td>[53]</td>
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<tr>
<td>Spadaro et al., 2008</td>
<td>-1.709</td>
<td>-2.460, -0.958</td>
<td>0.000</td>
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<tr>
<td>[54]</td>
<td></td>
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<tr>
<td>Zhu et al., 2008</td>
<td>-0.626</td>
<td>-0.971, -0.281</td>
<td>0.000</td>
</tr>
<tr>
<td>[48]</td>
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<td></td>
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<tr>
<td>Cussons et al., 2009</td>
<td>-1.718</td>
<td>-2.326, -1.109</td>
<td>0.000</td>
</tr>
<tr>
<td>[56]</td>
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<td>Tanaka et al., 2008</td>
<td>-0.476</td>
<td>-0.894, -0.058</td>
<td>0.026</td>
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<td>[47]</td>
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<tr>
<td>Chen et al., 2008</td>
<td>-0.731</td>
<td>-1.441, -0.021</td>
<td>0.043</td>
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<td>[55]</td>
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<td></td>
<td>-0.965</td>
<td>-1.348, -0.582</td>
<td>0.000</td>
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</table>

-3.00  -1.50  0.00  1.50

Favors PUFA

Favors control
Nutrient-Specific Effects for the Reduction 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
Liver-Fasting
with/without Meal Replacement (Hepafast®)

Mediterranean Low-Carb Diet
Liver-Healthy Diet
with/without Meal Replacement (Hepafast®)

Mediterranean Low-Carb Diet

(+)

rarely
daily
Menschenstopfleber

Die verharmlost Volkskrankheit Fettleber
Das größte Risiko für Diabetes und Herzinfarkt

VolkSKrankheit Fettleber

VERKANNT VERHARMLOST HEILBAR
Leberfasten nach Dr. Worm

Dr. Nicolai Worm · Melanie Teutsch

Das innovative Low-Carb-Programm gegen die Fettleber
The *Flexi-CARB-PYRAMID*

**Rarely**

Your Earned Extra-Carbs

**Daily**

- **Fruit Juices, Soft Drinks**
- **Diet Sodas, Fruit Smoothies**
- **Wellness Water, Fruit Spritzers**
- **Vegetable Juice**
- **Black/Green Tea, Coffee**
- **Water, Fruit and Herbal Tea**

The *Flexi-Carb-Pyramid* is weighted according to energy density, nutrient density, carbohydrate content, and degree of processing by Worm/Lemberger/Mangianelli e rive Verlag, 2015.
FlexiCARB
Mediterran genießen
Kohlenhydrate an Lebensstil anpassen
Schlank und gesund bleiben

Nicolai Worm

FlexiCARB
DAS KOCHBUCH

Vom Erfinder der LOGI-Methode

riva

Mit 60 Rezepten in verschiedenen Kohlenhydratstufen

Heike Lemberger
Franca Mangiameli
mit Nicolai Worm

www.flexi-carb.de
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.1148M 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 non-alcoholic fatty liver disease (NAFLD) is a global rapidly growing health problem. Non-invasive methods are increasingly being used to evaluate hepatic steatosis. 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.

<table>
<thead>
<tr>
<th></th>
<th>At baseline</th>
<th>At follow-up</th>
<th>Relative reduction (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic characteristics</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>N (men/women)</td>
<td>60 (29/31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 (25–78)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Body composition</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Body weight (kg)</td>
<td>95.1 (60.7–125.6)</td>
<td>90.5 (58.2–120.1)</td>
<td>-4.6 (-8.0-- 0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.9 (22.4–44.8)</td>
<td>30.6 (21.3–43.5)</td>
<td>-4.7 (-8.1-- 0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BFM (kg)</td>
<td>34.5 (16.8–63.4)</td>
<td>31.8 (13.4–59.5)</td>
<td>-6.9 (-27.0-- 4.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BFFM (kg)</td>
<td>58.2 (39.5–84.9)</td>
<td>55.3 (39.3–81.9)</td>
<td>-3.3 (-9.1-- 4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TBW (kg)</td>
<td>42.6 (28.9–62.2)</td>
<td>40.5 (28.8–60.0)</td>
<td>-3.3 (-9.1-- 4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>107 (78–127)</td>
<td>103 (76–128)</td>
<td>-4.1 (-9.2-- 2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VFI</td>
<td>13 (5–24)</td>
<td>12 (4–21)</td>
<td>-7.1 (-20.0-- 11.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Liver markers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAP (dB/m)</td>
<td>295 (216–400)</td>
<td>266 (100–353)</td>
<td>-14.0 (-68.6-- 38.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FLI</td>
<td>83 (7–99)</td>
<td>63 (4–98)</td>
<td>-21.3 (-74.0-- 0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LSM (kPa)</td>
<td>6.2 (1.5–11.9)</td>
<td>5.3 (1.5–12.0)</td>
<td>-11.7 (-70.5-- 43.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>38 (12–118)</td>
<td>36 (14–150)</td>
<td>0 (-73.1-- 122.2)</td>
<td>&gt;0.05</td>
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<tr>
<td>AST (U/l)</td>
<td>25 (10–121)</td>
<td>24 (8–141)</td>
<td>0 (-80.2-- 464.0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>AP (U/l)</td>
<td>74 (37–159)</td>
<td>64 (32–144)</td>
<td>-11.5 (-43.0-- 24.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>γ-GT (U/l)</td>
<td>37 (7–335)</td>
<td>26 (7–113)</td>
<td>-26.7 (-77.3-- 50.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PChE (kU/l)</td>
<td>10.7 (6.6–17.0)</td>
<td>10.4 (6.7–15.3)</td>
<td>-3.8 (-22.6-- 19.2)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Metabolic markers</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>89 (63–232)</td>
<td>84 (60–126)</td>
<td>-7.1 (-50.4-- 52.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>128 (60–419)</td>
<td>83 (48–183)</td>
<td>-34.1 (-84.0-- 35.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>214 (147–303)</td>
<td>163 (95–249)</td>
<td>-23.5 (-45.6-- 10.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>142 (78–226)</td>
<td>96 (45–193)</td>
<td>-25.3 (-53.1-- 41.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>50 (29–110)</td>
<td>45 (28–77)</td>
<td>-13.0 (-66.4-- 28.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>6.1 (2.9–8.6)</td>
<td>5.6 (3.1–10.0)</td>
<td>-7.6 (-40.9-- 43.5)</td>
<td>0.024</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>138 (110–175)</td>
<td>130 (104–184)</td>
<td>-5.6 (-28.6-- 40.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>92 (74–125)</td>
<td>87 (72–120)</td>
<td>-4.5 (-34.2-- 18.8)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Liver-fastig – Study at the Universitäty Hospital Homburg with FibroScan® 522

a

P < 0.001

-14.0%

b

P < 0.001

CAP = Controlled Attenuation Parameter

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.
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: $-0.47$ 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. © 2016 World Obesity
**L-Carnitine Supplementation to Diet: A New Tool in Treatment of Nonalcoholic Steatohepatitis—A Randomized and Controlled Clinical Trial**

80 Patients with NASH randomly assigned
(4 did not undergo liver biopsy; 2 had normalization of aminotransferase levels)

74 Patients receiving blinded study drug

- Allocated to L-carnitine: 36
  - None withdrawn

- Allocated to placebo: 38
  - None withdrawn

• 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
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

Dysfunction of Adipocytes and Systemic Inflammation


Who has NAFLD?
Intraabdominal Fat and Metabolic Consequences

- fasting insulin $\uparrow$
- fasting glucose $\uparrow$
- blood pressure $\uparrow$
- VLDL / Triglycerides $\uparrow$
- HDL-Cholesterol $\downarrow$
- small dense LDL-Particles $\uparrow$
- Thrombogenesis $\uparrow$
- Uric Acid $\uparrow$
- Renal Function $\downarrow$
- NAFLD $\uparrow$
Lipodystrophy, Ectopic Fat Disposition and Risk

- 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

TOFI

BMI = 25.8 kg/m²
3.3 l visceral fat

HEALTHY

BMI = 26.5 kg/m²
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

small, healthy adipocytes → good supply with $O_2$ + nerves → healthy, expanded adipocytes → deficiency of $O_2$ und nerves → inflamed, insulin resistant adipocytes

Visfatin, Leptin, RBP4, Resistin, PAI, TSP1, IL6, TNF, FFA

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

Liver
- ↑ Insulin resistance
- ↑ HGP
- ↑ VLDL production
- NAFLD → cirrhosis

Dysfunctional adipose tissue
- ↑ Visceral fat
- ↑ Portal FFA → NAFLD
- ↑ Cytokine production
- ↓ Adiponectin

Heart
- Impaired energy metabolism
- Diastolic dysfunction
- ↑ Risk of CAD?

Pancreas
- ↑ β-cell apoptosis
- ↓ Insulin secretion
- ↑ T2DM

Muscle
- ↓ Mitochondrial function
- ↓ VO₂ max
- Insulin resistance
- Sarcopenia?

Atherosclerosis
- Endothelial dysfunction
- Plaque formation
- CV events

α- / β-cell insulin resistance
Change the Modern Lifestyle!
Exercise and Hepatic Lipid Metabolism

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

Anita Arslanow, MSc¹, Melanie Teutsch, MSc², Hardy Walle, MD², Frank Grünhage, MD, PhD¹, Frank Lammert, MD, PhD¹ and Caroline S. Stokes, PhD¹

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/m² (22.4–44.8 kg/m²). 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 (\( P = 0.002 \)), \( \gamma \)-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.
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.
Increased HFCS consumption

Plasma insulin levels

Plasma leptin levels

Circulating ghrelin

- De novo lipogenesis
- Oxidation

NAFLD & NASH

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.
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 Yingjun Zhou,1 and Chuanyong Guo1

1Department of Gastroenterology, Shanghai Tenth People’s Hospital, Tongji University School of Medicine, Shanghai 200072, China
2The First Clinical Medical College, Nanjing Medical University, Nanjing 210029, China
3The 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.
A randomized controlled trial: the effect of inulin on weight management and ectopic fat in subjects with prediabetes

Nicola D. Guess¹, Anne Dornhorst², Nick Oliver², Jimmy D. Bell³, E. Louise Thomas³ and Gary S. Frost¹

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
Inulin vs Cellulose and Body Weight

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

Inulin vs Cellulose and Liver Fat

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

Nutritional Therapy of NAFLD

4 Basic Principles:
- calorie-reduced
- low-carbohydrate
- protein-rich
- fat-modified

Nutrient Specific Effects:
- n-3-PUFA (EPA+DHA)
- β-Glucan
- Inulin
- Carnitine
- Vitamin E
- Choline
- Taurine
- Resveratrol
- Quercetine
- 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

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 comprehensive systematic review looking into 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.

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.**
PMID: 7676547
Mechanisms Regulating Insulin Response to Intragastric Glucose in Lean and Non-Diabetic Obese Subjects: A Randomized, Double-Blind, Parallel-Group Trial

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• 12 Normalgewichtige (BMI: 22,0±0,4 kg/m²; BMI-Bereich 19,0-24,9 kg/m²) 6 Frauen/6 Männer; mittleres Alter: 24,3±0,6 Jahre; Bereich 20-32 Jahre)

• 12 Adipöse (BMI: 38,8±0,9 kg/m², Bereich 30,5-48,4 kg/m²); 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;
Zuckerstoffwechsel bei Gesunden mit Normalgewicht vs Adipösen (mit leichter Insulinresistenz)

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

Meyer-Gerspach AC, et al. PLOS ONE 2016;
Postprandiale **Glykämie**: Schlanke vs Adipöse (mit IR)

**A**
10 g glucose

- lean
- obese
- lean (tapwater)
- obese (tapwater)

**B**
25 g glucose

**C**
75 g glucose

**D**
Glucose AUC (0-180 min) [mmol × min/L]

Meyer-Gerspach AC, et al. PLOS ONE 2016; DOI:10.1371/journal.pone.0150803
Postprandiale **Insulinämie**: Schlanke vs Adipöse (mit IR)

(A) 10 g glucose

- lean
- obese
- lean (tapwater)
- obese (tapwater)

(B) 25 g glucose

(C) 75 g glucose

(D) Insulin AUC(0-180min) (μU·g/mL) vs Glucose (g)

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
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.
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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AP (n = 18)</th>
<th>P&lt;sub&gt;AP&lt;/sub&gt; value</th>
<th>PP (n = 19)</th>
<th>P&lt;sub&gt;PP&lt;/sub&gt; value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index, kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>31.0 ± 0.8</td>
<td>.003</td>
<td>29.4 ± 1.0</td>
<td>.001</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>104.2 ± 2.6</td>
<td>NS</td>
<td>100.7 ± 3.0</td>
<td>NS</td>
</tr>
<tr>
<td>Hip, cm</td>
<td>107.8 ± 1.8</td>
<td>NS</td>
<td>105.3 ± 2.0</td>
<td>.034</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.967 ± 0.018</td>
<td>NS</td>
<td>0.957 ± 0.024</td>
<td>NS</td>
</tr>
<tr>
<td>Fat mass, %</td>
<td>35.26 ± 2.19</td>
<td>.023</td>
<td>34.95 ± 2.30</td>
<td>NS</td>
</tr>
<tr>
<td>Fat-free mass, %</td>
<td>64.74 ± 2.19</td>
<td>.023</td>
<td>65.05 ± 2.30</td>
<td>NS</td>
</tr>
<tr>
<td>AT&lt;sub&gt;femur&lt;/sub&gt;, mL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>394.25 ± 17.51</td>
<td>.016</td>
<td>372.73 ± 26.18</td>
<td>NS</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>26.64 ± 1.85</td>
<td>NS</td>
<td>23.88 ± 2.13</td>
<td>.020</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>30.44 ± 2.47</td>
<td>NS</td>
<td>29.59 ± 2.97</td>
<td>NS</td>
</tr>
<tr>
<td>AST/ALT ratio</td>
<td>0.88 ± 0.06</td>
<td>NS</td>
<td>0.80 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>γ-GT, U/L</td>
<td>44.31 ± 6.82</td>
<td>.017</td>
<td>41.76 ± 5.25</td>
<td>NS</td>
</tr>
<tr>
<td>Keratin 18, U/L</td>
<td>184.9 ± 28.9</td>
<td>NS</td>
<td>197.4 ± 26.2</td>
<td>.021</td>
</tr>
<tr>
<td>ELF score</td>
<td>9.19 ± 0.15</td>
<td>NS</td>
<td>9.02 ± 0.17</td>
<td>9.11 ± 0.15</td>
</tr>
<tr>
<td>PIIINP, ng/mL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.73 ± 0.53</td>
<td>NS</td>
<td>8.07 ± 0.49</td>
<td>NS</td>
</tr>
<tr>
<td>Adiponectin, ng/mL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4063.6 ± 836.1</td>
<td>NS</td>
<td>4239.1 ± 395.6</td>
<td>.003</td>
</tr>
<tr>
<td>Adipose tissue insulin resistance&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11.99 ± 2.32</td>
<td>.019</td>
<td>10.24 ± 1.71</td>
<td>.026</td>
</tr>
</tbody>
</table>

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).

![Graph showing visceral and non-visceral adipose tissue changes over 6 weeks for animal vs plant protein diets.](image-url)

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

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

High-Carb/Low-Fat

\[ r = -0.27, \ p = 0.930 \]

Low-Carb/High-Fat

\[ r = -0.642, \ p = 0.010 \]
# Lifestyle changes for the treatment of nonalcoholic fatty liver disease: a review of observational studies and intervention trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Study design</th>
<th>Patients, [% men]</th>
<th>Liver fat content evaluation</th>
<th>Intervention [type, time]</th>
<th>Effects on liver fat content</th>
<th>Effects on liver histological endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al. [2005]</td>
<td>USA</td>
<td>Intervention without control arm</td>
<td>16 obese, [50]</td>
<td>Liver biopsy</td>
<td>NC, 12 months</td>
<td>No effect</td>
<td>Decreased ballooning/inflammation</td>
</tr>
<tr>
<td>Kirk et al. [2009]</td>
<td>USA</td>
<td>RCT</td>
<td>22 obese, [18]</td>
<td>MRS</td>
<td>Low calorie HCD versus LCD, 11 weeks</td>
<td>Decreased in HCD and LCD</td>
<td>NP</td>
</tr>
<tr>
<td>Haufe et al. [2011]</td>
<td>Germany</td>
<td>RCT</td>
<td>102 obese, [18]</td>
<td>MRS</td>
<td>Low calorie LCD versus LFD, 6 months</td>
<td>Decreased in LCD and LFD</td>
<td>NP</td>
</tr>
<tr>
<td>Bozzetto et al. [2012]</td>
<td>Italy</td>
<td>RCT</td>
<td>36 diabetic, [81]</td>
<td>MRS</td>
<td>CHO/fiber versus MUFA, CHO/fiber + exercise, versus MUFA + exercise, 8 weeks</td>
<td>Decreased in MUFA and MUFA + exercise</td>
<td>NP</td>
</tr>
<tr>
<td>Ryan et al. [2013]</td>
<td>Australia</td>
<td>RCT</td>
<td>12 obese, [50]</td>
<td>MRS</td>
<td>MD versus LF/HCD</td>
<td>Decreased</td>
<td>NP</td>
</tr>
<tr>
<td>Trovato et al. [2015]</td>
<td>Italy</td>
<td>Intervention without control arm</td>
<td>90 obese, [49]</td>
<td>US</td>
<td>MD, 6 months</td>
<td>Decreased</td>
<td>NP</td>
</tr>
</tbody>
</table>
\[
\begin{align*}
\text{sn-1,2-diacylglycerol} & \quad \text{sn-2,3-diacylglycerol} & \quad \text{sn-1,3-diacylglycerol} \\
R'\text{COO} & - \overset{\text{C}}{\text{H}} & - \overset{\text{CH}_2\text{OOOCR}}{\text{H}} & - \overset{\text{CH}_2\text{OH}}{\text{H}} & - \overset{\text{HO}}{\text{C}} & - \overset{\text{H}}{\text{H}} & - \overset{\text{CH}_2\text{OOOCR}}{\text{H}} & - \overset{\text{CH}_2\text{OOOR'}}{\text{H}}
\end{align*}
\]