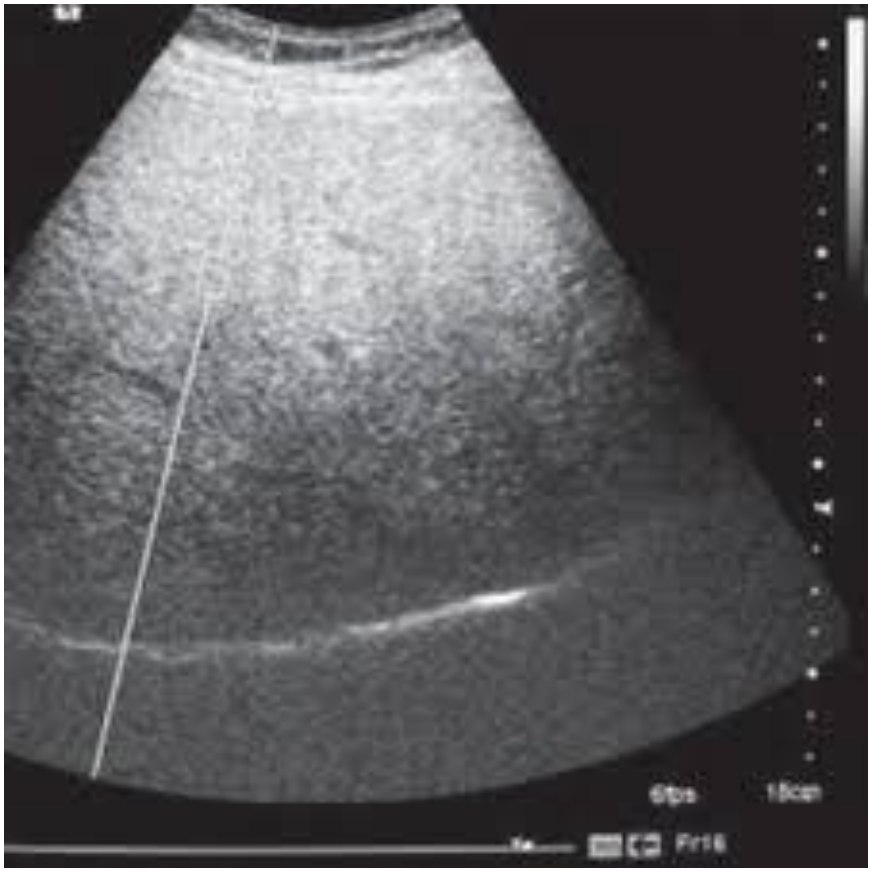
Dr Emma Greig

Consultant Gastroenterologist

NAFLD – THE BRIGHT LIVER EPIDEMIC

NAFLD

- What is it and why do we care about it?
- How to make the diagnosis?
- Treatment?

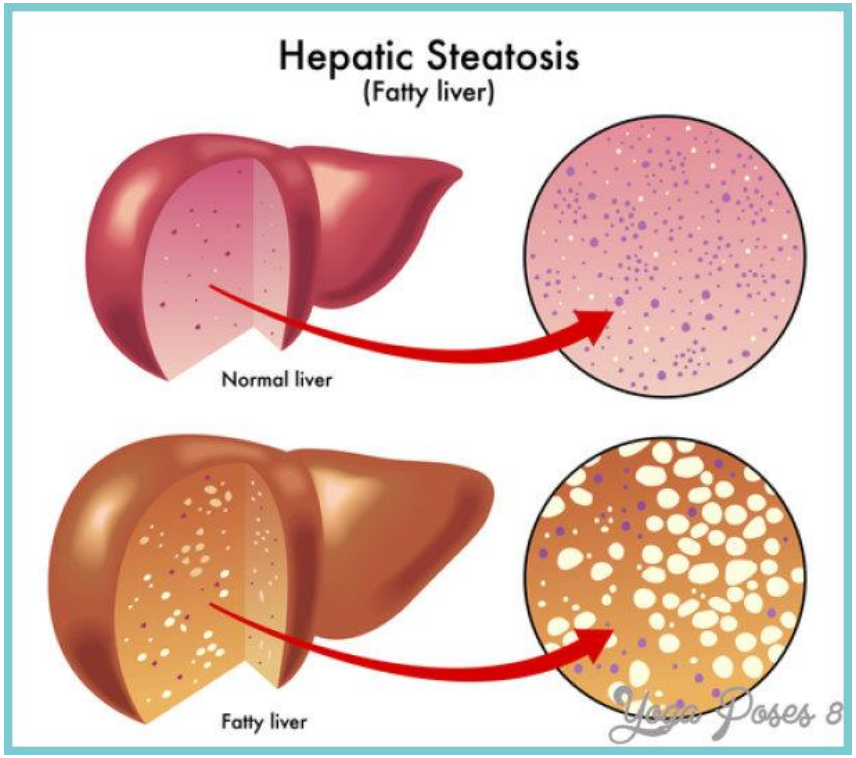


Fatty liver: what is it?

Fat accumulation in hepatocytes

Main causes:

Alcoholic (ALD)
Non-alcoholic (NAFLD)
Fatty liver of pregnancy (rare)



- ALD more common in:
  - Women
  - Obesity
  - Longstanding heavy alcohol
- NAFLD more common with:
  - Men (women higher risk of advanced fibrosis)
  - Diabetes/ obesity – increased waist circumference + IR
  - Increasing age
  - Racial groups: Hispanic higher
  - Dietary: high fructose
  - OSA
  - High blood pressure
  - Corticosteroids/ certain cancer drugs
  - Metabolic syndrome – independent predictor of fibrosis
  - Hepatitis C
- Both silent – few symptoms
- Tired
- RUQ discomfort

Why is the incidence rising?

1980

- Assassination of John Lennon
- Invention of post-it notes
- **Release of 'Nutrition and your health' Dietary Guidelines for America**

3

Avoid Too Much Fat, Saturated Fat, and Cholesterol

If you have a high blood cholesterol level, you have a greater chance of having a heart attack. Other factors can also increase your risk of heart attack — high blood pressure and cigarette smoking, for example — but high blood cholesterol is clearly a major dietary risk indicator.

Populations like ours with diets high in saturated fats and cholesterol tend to have high blood cholesterol levels. Individuals within these populations usually have greater risks of having heart attacks than people eating low-fat, low-cholesterol diets.

Eating extra saturated fat and cholesterol will increase blood cholesterol levels in most people. However, there are wide variations among people — related to heredity and the way each person's body uses cholesterol.

Some people can consume diets high in saturated fats and cholesterol and still keep normal blood cholesterol levels. Other people, unfortunately, have high blood cholesterol levels even if they eat low-fat, low-cholesterol diets.

4

Eat Foods with Adequate Starch and Fiber

The major sources of energy in the average U.S. diet are carbohydrates and fats. (Proteins and alcohol also supply energy, but to a lesser extent.) If you limit your fat intake, you should increase your calories from carbohydrates to supply your body's energy needs.

In trying to reduce your weight to "ideal" levels, carbohydrates have an advantage over fats: carbohydrates contain less than half the number of calories per ounce than fats.

Complex carbohydrate foods are better than *simple* carbohydrates in this regard. Simple carbohydrates — such as sugars — provide calories but little else in the way of nutrients. Complex carbohydrate foods — such as beans, peas, nuts, seeds, fruits and vegetables, and whole grain breads, cereals, and products — contain many essential nutrients in addition to calories.

Fructose

- Naturally:
  - 5-10% by weight in apples/ blueberries
  - Very little milk/ meat/ veg
  - 1900's average american ate 15 g/day, now 60-70 g
  - 50% by weight in dried fruits

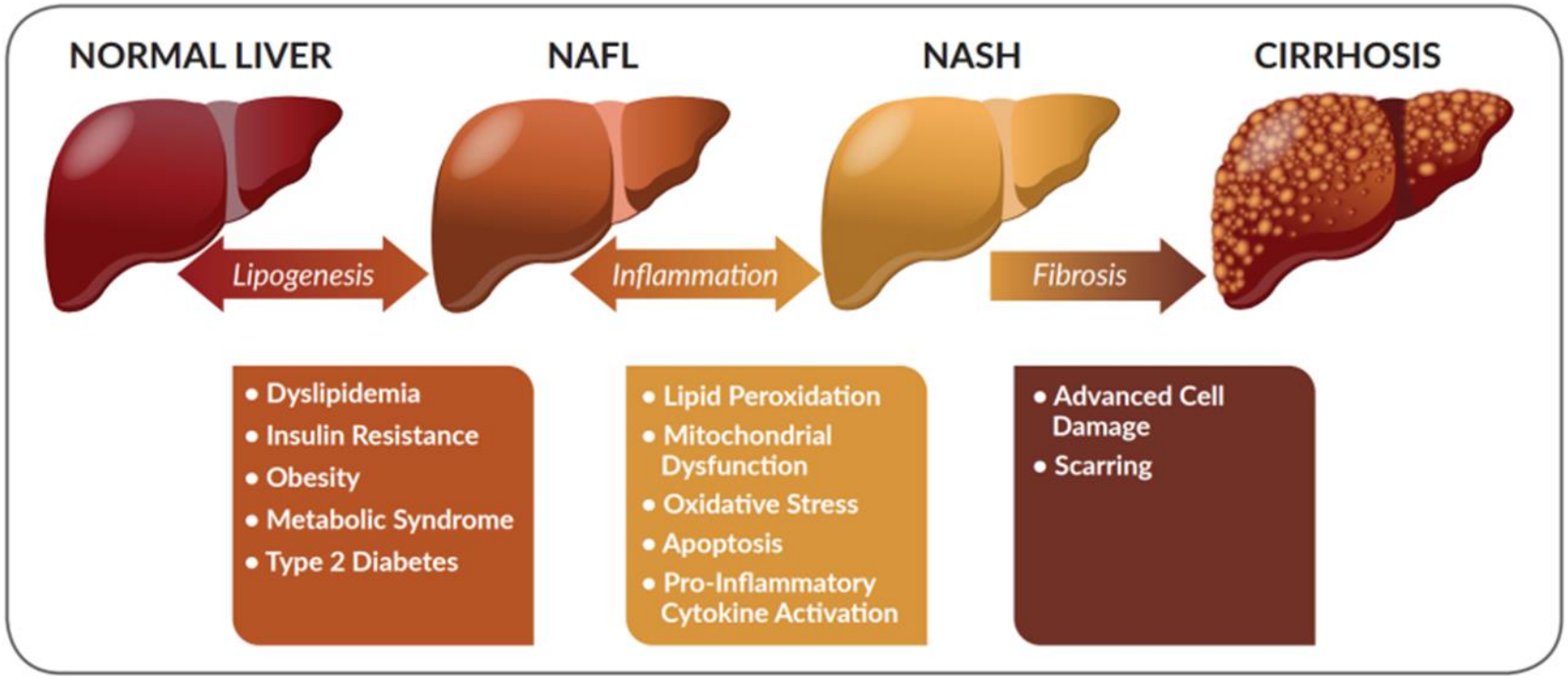
These days, where does it come from?

- Sucrose=glucose+fructose
- HFCS = 55% fructose and 45% glucose
  - Drinks
  - Highly processed foods

- Hepatic glucose regulated by phosphofructokinase, ATP and citrate so when energy levels high – limits hepatic uptake of dietary glucose
- Hepatic fructose is independent of energy status so excess leads to unregulated uptake with increased lipogenesis → NAFLD
  - Independently NAFLD - ↑TG;↑LDL; promotes visceral fat; ↑BP; ↑IR

NAFLD to cirrhosis: does it matter?

1/3 population 5-10% 3-26%



Yes……

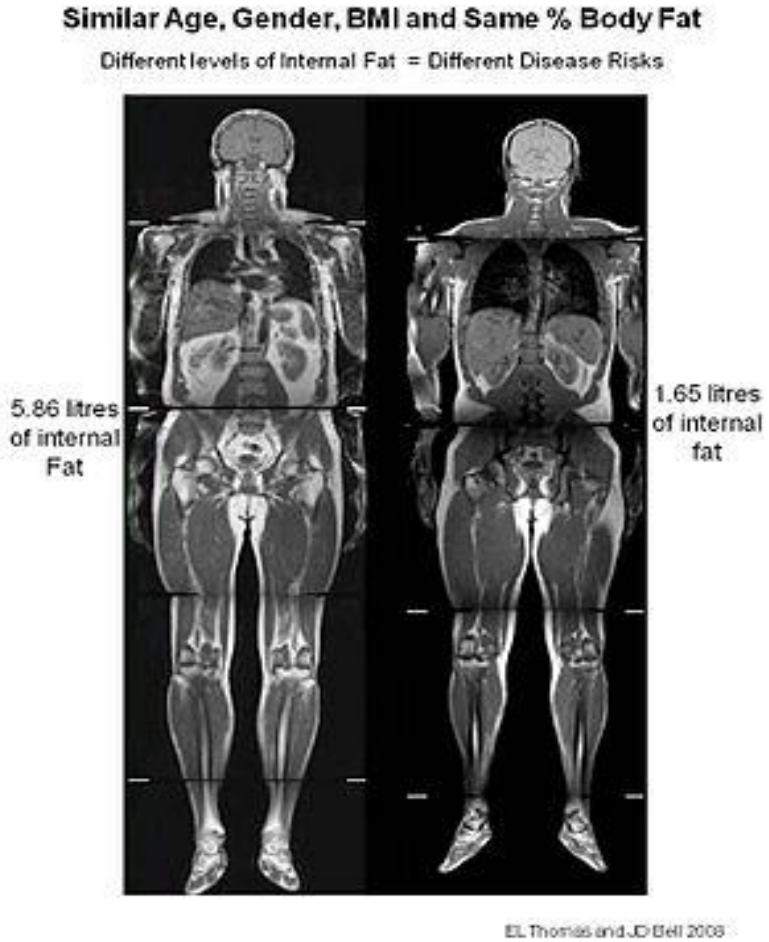
If NASH → cirrhosis

- 10-year mortality rate = 20%
- 45% will decompensate ≤ 10 years
- 2.6% per year risk of HCC
- Increased cardiovascular risk
- Second highest indication for liver transplant in USA

- BUT…

how to make the diagnosis and find those at highest risk?

Not all on appearances – TOFI v FOTI



How to diagnose?

- Steatosis on imaging/ histology
- Exclude other causes (NILS)
- ALT > AST but in 80% these are normal
- ALT ↓ as fibrosis progresses. Does not correlate with severity

- Clues:
  - 70-80% those with central obesity
  - 50-80% type II DM

- Definitive = liver biopsy (hepatocyte ballooning degeneration and steatosis)
- But risky/ uncomfortable so reserve if non-invasive indeterminate – rare in our practice

Non-invasive NAFLD grading

A

NAFLD fibrosis score

Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**
A noninvasive system that identifies liver fibrosis in patients with NAFLD
Hepatology 2007;45(4):846-854 doi:10.1002/hep.21496

Age (years)

BMI (kg/m²)

IGF/diabetes

AST

ALT

Platelets (x10⁹/l)

Albumin (g/l)

calculate score

BMI: body mass index
IGF: impaired fasting glucose

B

What is the ELF Blood Test?

ELF stands for Enhanced Liver Fibrosis. The ELF Blood Test combines three serum biomarkers, which have been shown to correlate to the level of liver fibrosis assessed by liver biopsy. These biomarkers include:

- Hyaluronic acid (HA)
- Procollagen III amino terminal peptide (PIIINP)
- Tissue inhibitor of metalloproteinase 1 (TIMP-1)

C

What is FibroScan® and transient elastography?

FibroScan® is a non-invasive device that assesses the 'hardness' (or stiffness) of the liver via the technique of transient elastography. Liver hardness is evaluated by measuring the velocity of a vibration wave (also called a 'shear wave') generated on the skin. Shear wave velocity is determined by measuring the time the vibration wave takes to travel to a particular depth inside the liver.[1] A graphical representation of this is provided on the screen (*Figure 1*). Because fibrous tissue is harder than normal liver, the degree of hepatic fibrosis can be inferred from the liver hardness. To improve test reliability a minimum of 10 valid readings, with at least a 60% success rate and an interquartile range of ≤30% of the median value, are taken with the results expressed in kilopascals (kPa).[1,2]

What to do with the results?

- Identify patients:
  - Metabolic risk factor profiling
  - LFT
  - Imaging (ultrasound)
- Risk stratify (NAFLD fibrosis score + ELF/Fibroscan)
- Low risk NAFLD

  V
- Intermediate/ high risk NASH/ fibrosis/ cirrhosis

- 1. Lifestyle modification
- 2. Target metabolic syndrome
- 3. Liver-directed pharmacotherapy
- 4. Screening for complications of cirrhosis

Management

1980

NHS Choices: 2018

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Home › Health A-Z › Non-alcoholic fatty liver disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD)

Page contents

- Stages of NAFLD
- Am I at risk of NAFLD?
- Symptoms of NAFLD
- How NAFLD is diagnosed
- Treatment for NAFLD

Non-alcoholic fatty liver disease (NAFLD) is the term for a range of conditions caused by a build-up of fat in the liver. It's usually seen in people who are overweight or obese.

A healthy liver should contain little or no fat. It's estimated that up to 1 in every 3 people in the UK has early stages of NAFLD where there are small amounts of fat in their liver.

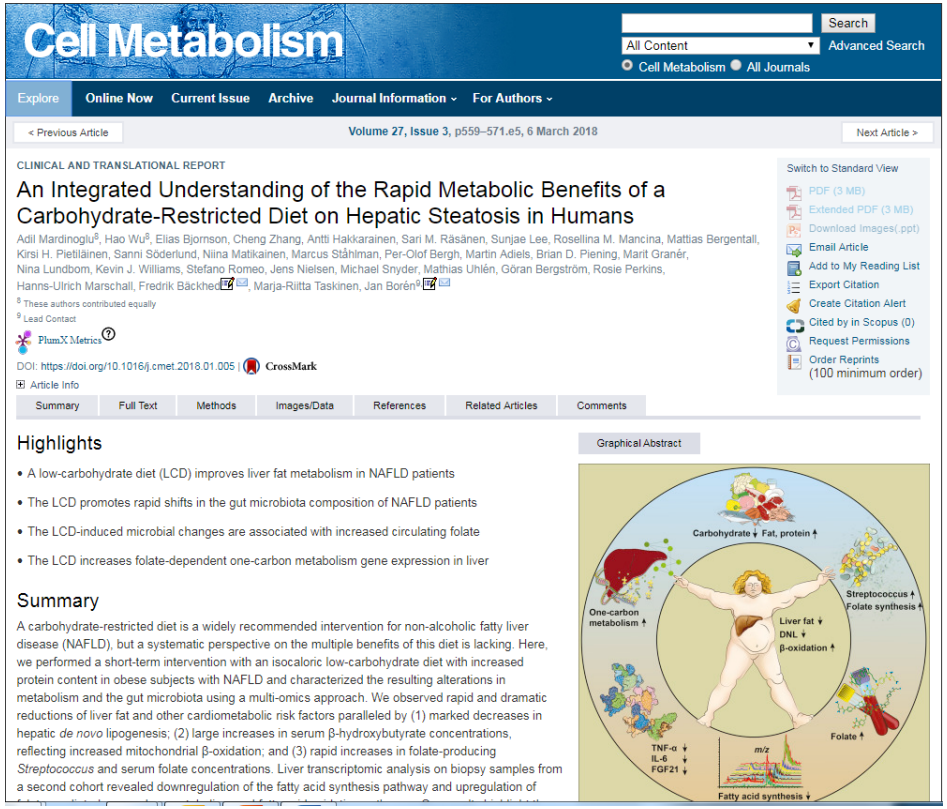
Early-stage NAFLD doesn't usually cause any harm, but it can lead to serious liver damage, including cirrhosis, if it gets worse.

Having high levels of fat in your liver is also associated with an increased risk of problems such as diabetes, heart attacks

Or……..the specifics

- Diet:
  - Mediterranean (high MUFAs, low carbohydrate, natural food)
  - Avoid sugars (esp. fructose), sweetened drinks
  - Lose >10% weight and maintain loss (reduces steatosis/ ballooning/ inflammation)
  - (Consider diet 600 kcal less than daily requirement)
  - Could supplement with ω-3 PUFA (fish oils) or eat more oily fish – needs more research
- Exercise:
  - Reduce sedentary time/ increase activity (↓steatosis)
  - Aerobic activity ↑insulin sensitivity in skeletal muscle
  - 30 min moderate exercise 5 x per week – improves LFT and reduces steatosis
  - Can be aerobic/ resistance/ HIIT – all reduce liver fat/ LFTs
  - Aim > 10,000 steps/day (pedometer)

Areas of research



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CLINICAL AND TRANSLATIONAL REPORT

An Integrated Understanding of the Rapid Metabolic Benefits of a Carbohydrate-Restricted Diet on Hepatic Steatosis in Humans

Adil Mardinoglu[8], Hao Wu[8], Elias Bjornson, Cheng Zhang, Antti Hakkarainen, Sari M. Räsänen, Sunjae Lee, Rosellina M. Mancina, Mattias Bergentall, Kirsi H. Pietiläinen, Sanni Söderlund, Niina Matikainen, Marcus Ståhlman, Per-Olof Bergh, Martin Adiels, Brian D. Piening, Marit Granér, Nina Lundbom, Kevin J. Williams, Stefano Romeo, Jens Nielsen, Michael Snyder, Mathias Uhlén, Göran Bergström, Rosie Perkins, Hanns-Ulrich Marschall, Fredrik Bäckhed, Marja-Riitta Taskinen, Jan Borén[9]

[8] These authors contributed equally
[9] Lead Contact

PlumX Metrics

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Highlights

- A low-carbohydrate diet (LCD) improves liver fat metabolism in NAFLD patients
- The LCD promotes rapid shifts in the gut microbiota composition of NAFLD patients
- The LCD-induced microbial changes are associated with increased circulating folate
- The LCD increases folate-dependent one-carbon metabolism gene expression in liver

Summary

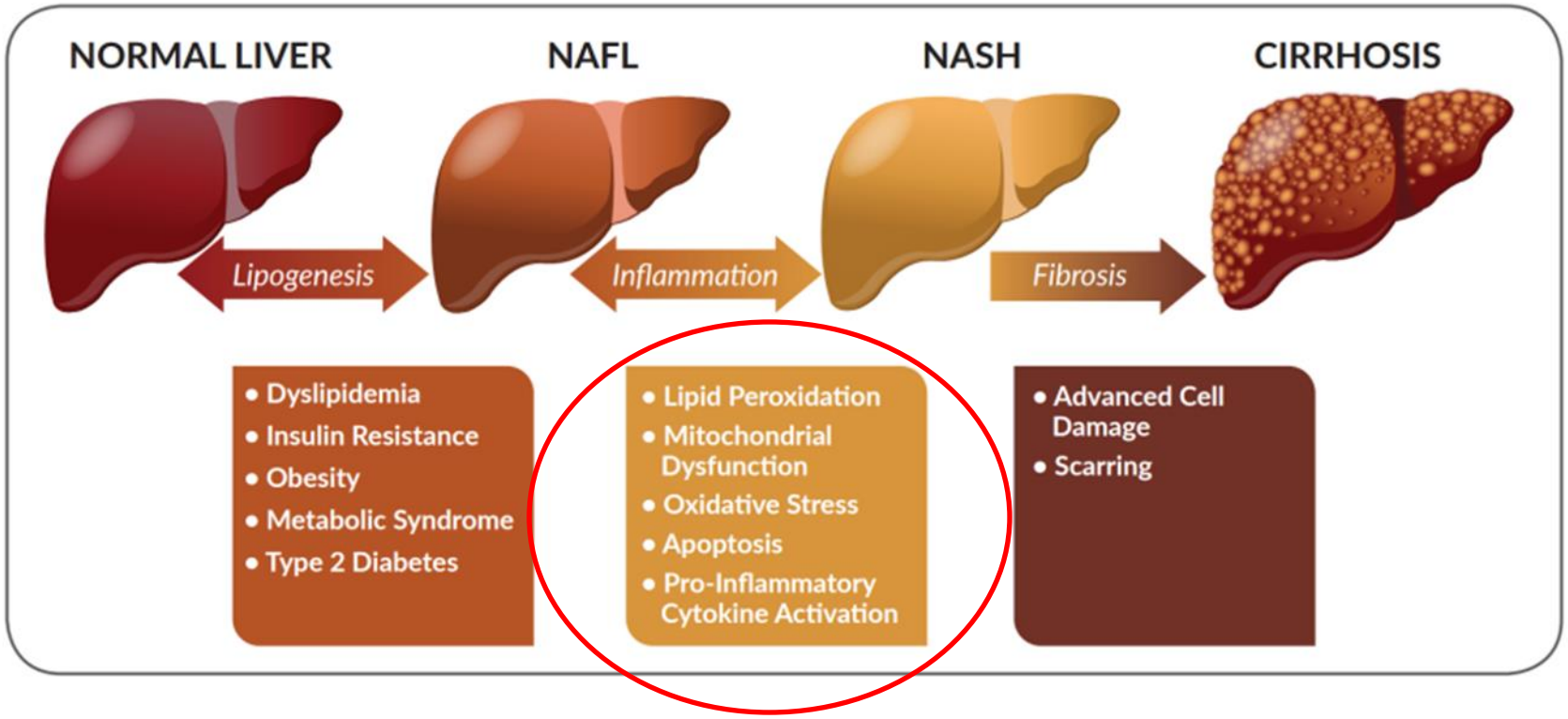
A carbohydrate-restricted diet is a widely recommended intervention for non-alcoholic fatty liver disease (NAFLD), but a systematic perspective on the multiple benefits of this diet is lacking. Here, we performed a short-term intervention with an isocaloric low-carbohydrate diet with increased protein content in obese subjects with NAFLD and characterized the resulting alterations in metabolism and the gut microbiota using a multi-omics approach. We observed rapid and dramatic reductions of liver fat and other cardiometabolic risk factors paralleled by (1) marked decreases in hepatic *de novo* lipogenesis; (2) large increases in serum β-hydroxybutyrate concentrations, reflecting increased mitochondrial β-oxidation; and (3) rapid increases in folate-producing *Streptococcus* and serum folate concentrations. Liver transcriptomic analysis on biopsy samples from a second cohort revealed downregulation of the fatty acid synthesis pathway and upregulation of

Graphical Abstract

- Low carbohydrate diet (<10% energy) and isocaloric)
  - Marked decrease in hepatic de novo lipogenesis with downregulation of fatty acid synthesis
  - Modulation of microbiota towards folate-producing streptococcus
    - High serum folate reduces oxidative stress
  - Reduction in IL-6 and TNFα cytokines at 14 days (known to be associated with progression to NASH)
  - Increases mitochondrial β-oxidation

NAFLD to cirrhosis: does it matter?

1/3 population 5-10% 3-26%



Complex/ experimental

Treatment	Intervention/ indication	Target/ outcome
Orlistat (enteric lipase inhibitor)	If BMI>30 kg/m^2 Need weight loss >5% in 3 months to continue for maximum of 12 months	Improves ALT/ steatosis Risk = fat soluble vitamin deficiency
Bariatric surgery	Not a primary treatment Only if BMI >40 or 35-40 with co-morbidities First line for obesity if BMI>50	Most benefits in first year Improves insulin sensitivity/ lipid profile Reduced steatosis/ steatohepatitis/ fibrosis (65% if loss 30% of BMI) May not be sustained after 5 years
Pioglitazone	Aggressive NASH failing lifestyle	Reduces hepatocellular injury and fibrosis BUT increased risk of weight gain (4.7%)/CCF/ bladder cancer/ ↓bone density
Vitamin E	Antioxidant Advanced pre-cirrhotic NASH failing lifestyle intervention	Improves steatohepatitis at 800 iU/day for 96 weeks Risk = small increase in overall mortality if >400 iU/day

Dyson, *et al*., 2017. Frontline Gastroenterology

20-30% of adult population

Reflux is expensive ($12.5 billion pa for PPI/ H2RA)

- **30-40% fail to respond to drugs**
- **60% incomplete resolution of symptoms**
- **Risks incomplete resolution = oesophagitis/ strictures/ Barretts/ adenocarcinoma**
- **Adenocarcinoma increased 3-4 fold over last 3 decades**

- Risk of reflux increases three-fold for every increase of >3.5 kg/m^2 in BMI
- Excess adiposity ↓oesophageal pH to <4 and ↑number of reflux episodes
- Reflux is three-fold greater in obese men and four-fold in obese women
- Greater insulin resistance in proportion to GORD symptoms

BONUS SLIDES: LOW CARBOHYDRATE DIETS AND REFLUX

Unexpected finding in our own study……

OPEN ACCESS

RESEARCH

Using best practice to create a pathway to improve management of irritable bowel syndrome: aiming for timely diagnosis, effective treatment and equitable care

Marianne Williams,[1] Yvonne Barclay,[1] Rosie Benneyworth,[2] Steve Gore,[3] Zoe Hamilton,[4] Rudi Matull,[4] Iain Phillips,[5] Leah Seamark,[1] Kate Staveley,[2] Steve Thole,[6] Emma Greig[4]

▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/flgastro-2016-100727).

[1]Department of Community Dietitian, Somerset Partnership NHS Trust, Bridgwater, UK
[2]Somerset Clinical Commissioning Group, Taunton, UK
[3]Yeovil District NHS Foundation Trust, Yeovil, UK
[4]Taunton and Somerset NHS Foundation Trust, Taunton, Somerset, UK
[5]Somerset Clinical Commissioning Group, Wincanton, UK
[6]NHS Somerset, Yeovil, UK

ABSTRACT

Background Irritable bowel syndrome (IBS) costs the National Health Service almost £12 million per annum. Despite national guidelines advising primary care management, these have failed to stem secondary care referrals of patients with likely IBS for unnecessary and costly assessment and investigation without necessarily achieving resolution of their symptoms.

Methods In 2011, an integrated team from primary and secondary care developed a business case using baseline data to create a Somerset-wide IBS pathway using Clinical Commissioning Group funding. This provided face-to-face general practitioners (GP) education, developed a

Conclusions The combination of GP education, providing diagnosis and management pathways, using FC to exclude inflammatory pathology and providing an effective treatment for patients with likely IBS appeared successful in our pilot. This proved cost-effective, reduced secondary care involvement and improved patient care.

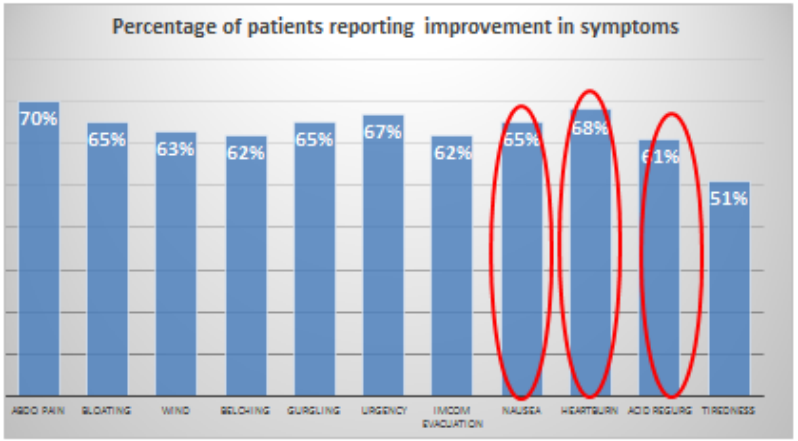
INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic and debilitating condition, which places a significant burden on the National Health Service (NHS), both in terms of financial cost and strain on primary and secondary care.[1–3] The total attributable cost of IBS in the UK was

Williams *et al.*, Frontline Gastroenterology. 2016

Patient outcomes

Percentage improvements in symptoms (n=335; all significant)



Confirmed with many others…..

HHS Public Access
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Dietary Carbohydrate Intake, Insulin Resistance, and Gastroesophageal Reflux Disease (GERD): A Pilot Study in European- and African-American Obese Women

Stephanie D. Pointer, MD[a], **Jace Rickstrew**[b], **Chris Slaughter, PhD**[c], **Michael F. Vaezi, MD, PhD**[a], and **Heidi J. Silver, PhD, RD**[a]

[a]Vanderbilt University Medical Center, Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, Nashville, TN, USA

[b]University of Kansas, School of Medicine, Kansas City, MO, USA

[c]Vanderbilt University Medical Center, Department of Biostatistics, Nashville, TN, USA

Abstract

Background—Although obesity rates are higher in African-American than European-American women, GERD and its comorbidities are more prevalent in European-American women. A common denominator for increased adiposity, and consequent insulin resistance, is excess dietary macronutrient intake – which may promote greater prevalence and severity of GERD in women.

Aim—We hypothesized that GERD would be more robustly associated with dietary carbohydrate intake, particularly dietary simple carbohydrate intake, and insulin resistance in European-American women.

Methods—144 obese women were assessed at baseline and 16 weeks after consuming a high-fat/low-carbohydrate diet. GERD diagnosis and medication usage was confirmed in medical records with symptoms and medications assessed weekly.

Results—33.3% (N=33) of European-American and 20.0% (N=9) of African-American women had GERD at baseline. Total carbohydrate (r=0.34, $P<0.001$), sugars (r=0.30, $P=0.005$), glycemic load (r=0.34, $P=0.001$) and HOMA-IR (r=0.30, $P=0.004$) were associated with GERD, but only in European-American women. In response to high-fat/low-carbohydrate diet, reduced intake of sugars was associated with reduced insulin resistance. By the end of diet week 10, all GERD symptoms and medication usage had resolved in all women.

Main points: dietary intervention study

- Women
- Simple carbohydrate intake (especially sucrose) predicts likelihood of reflux
- Thought to:
  - Reduce LO sphincter pressure/ increase transient relaxation
  - Increase gastrin production (thus acid secretion)
- Calorie restriction group = 10% weight loss but no medication discontinued
- 6 days after LCHF diet: 44% reduction in symptoms and 51% reduction in time pH <4
- All women discontinued medication at 10 weeks until end of LCHF diet intervention (16 weeks)