Peter Attia MD Keypoints — Metabolism, Insulin & Obesity

Peter Attia MD Keypoints

Episodes in this pack: 17

337- Insulin resistance masterclass: The full body impact of metabolic dysfunction, treatment & more

Guest: Ralph DeFronzo
Date: 2025-02-24 · Duration: 2:42:18
URL: https://www.youtube.com/watch?v=vYQaLV3Fm00

KEYPOINTS

• 'Insulin resistance' only means something once you name the tissue and the process

DeFronzo developed the euglycemic insulin clamp. Insulin is raised by about 100 µU/mL and held there for two hours, while glucose is infused to keep blood sugar near 80–90. Under those conditions about 80–90% of glucose goes into muscle, about 10% into fat, and essentially none into the liver. Different tissues switch off at different insulin levels. A rise of only about 10 µU/mL stops fat breakdown, the liver needs about 50 to stop releasing glucose, and muscle uptake still climbs 20–25% between 100 and 200.

• Type 2 diabetes needs two defects

Insulin resistance on its own doesn't cause diabetes as long as the beta cells can keep up. Diabetes appears when genetically vulnerable beta cells wear out from constant overwork. DeFronzo says about 10–15% of people already have clinically significant heart disease when diagnosed, and 'virtually 100%' do if you look carefully. The same blocked signaling step (IRS-1/PI3-kinase) that keeps glucose out of muscle also stops nitric oxide production, which ties insulin resistance directly to atherosclerosis.

• Too much insulin causes insulin resistance

When his group raised healthy lean young adults' fasting insulin from about 8 to 20 µU/mL, still below a normal meal spike, they became as insulin resistant as people with type 2 diabetes within 48–72 hours, because the signaling pathway turns itself down. Healthy beta cells make about 35 units of insulin a day, while many patients inject 100–150. He thinks that level is atherogenic, so diet, exercise and other drugs should aim to bring doses back toward a normal range. Those who need insulin should still get it.

• The 'ominous octet': eight organs drive the disease

He started from a triad of beta cell, muscle and liver, and added five more. Fat cells stop responding to insulin and release free fatty acids. The gut's incretins (GLP-1 and GIP) are released normally, but the beta cell ignores them, even though they drive about 70% of meal-time insulin. Alpha cells overproduce glucagon. The kidneys increase SGLT2 and hold on to more glucose. The brain becomes resistant to GLP-1, amylin and leptin. Eight faults, so one drug can't be enough.

• Raised fatty acids are toxic

Infusing a fat emulsion causes severe insulin resistance in muscle and liver and impairs beta cells within 2–4 hours. Lowering fatty acids for 12 days with acipimox (sold in Europe) sharply reduced muscle fat, greatly improved insulin sensitivity, and raised mitochondrial ATP production by about 50%. So much of the mitochondrial problem follows from fat overload.

• SGLT2 inhibitors came out of DeFronzo's kidney research

As a kidney fellow he used phlorizin to show glucose and phosphate transport are linked. The kidneys filter about 180 g of glucose a day, with SGLT2 recovering about 90%. In diabetic animals, blocking this improved beta cells and insulin sensitivity. In people, 14 days of dapagliflozin raised insulin sensitivity by about 35%, the first human evidence that high glucose itself is toxic. He never patented it.

• Pioglitazone is the only true insulin sensitizer and is heavily underused

It fixes the signaling defect and moves fat out of muscle, liver and beta cells into tissue under the skin. In a 2017 study it improved heart insulin sensitivity by about 75% and muscle by 74%, and ejection fraction rose 5–10%. Weight gain (about 2–2.5 kg at 15–30 mg, partly from appetite effects in the hypothalamus) and fluid retention put people off. Yet in PROactive (5,238 patients), weight gain was the strongest predictor of survival. He calls it the best drug for NASH.

• Metformin is useful, but it isn't an insulin sensitizer

DeFronzo brought it to the US in 1995. Clamp studies never showed that it improves insulin sensitivity. Its transporter isn't present in skeletal or heart muscle, and labeled-tracer scans show it only in the liver, kidney and bladder. It works by reducing glucose production in the liver. The sensitizer myth likely came from ~3 kg weight loss driven by GI side effects. It costs about $5 a month and is fine to add, but it ranks fourth on his list.

• Start with combination therapy built on the biology

In EDICT (315 patients, six years), metformin plus exenatide plus pioglitazone from the start kept about 70% of patients below an A1c of 6.5% and produced large gains in insulin sensitivity and beta-cell function. The stepwise ADA approach (metformin, then sulfonylurea, then insulin capped at 60 units) failed in about 71%, with no improvement in either. The NIH's GRADE study found that every single drug added to metformin had stopped working by about year five.

• His ranking of drugs

If he could use only one: a modern GLP-1 drug. Two: add pioglitazone, since GLP-1 weight loss cancels its weight gain and fluid retention. Three: add an SGLT2 inhibitor, especially with kidney or heart disease, and he expects the same protection in newly diagnosed patients. Heart-event reductions are about 20% across old and new GLP-1 drugs, which he takes as a sign the benefit levels off.

• Damaged eating circuits in the brain drive the epidemic

Processed, calorie-dense food and inactivity are the trigger, he says, but they reshape the brain's reward circuitry. Gray matter shrinks in reward areas, and in obese people those areas take up excess glucose during a clamp, in proportion to how resistant their muscle is.

EXAMPLES

• Qatar study

About 220 people failing on metformin and a sulfonylurea, average A1c about 10%. After three years, split-dose insulin had

reached 7.1%, held back by low-sugar episodes, while exenatide plus pioglitazone reached 6.1%. Symptomatic patients starting at 12.2% also got to 6.1%.

• Lean children of diabetic parents

Lean Hispanic children with two diabetic parents (a 70–80% lifetime risk) were as insulin resistant as their parents despite normal glucose, with insulin about double normal and the same IRS-1 defect in muscle.

• Gastric bypass and muscle

After losing about 33% of body weight, absolute strength fell about 25%, but strength per kilogram rose about 50%. Walking distance went from 200 yards to two miles, and chair-rise counts went up three- to fourfold. He thinks worries about GLP-1 muscle loss are overstated.

• Cahill's starvation studies

DeFronzo was paid $50 to fast for three days as a Harvard student. Even weeks in, glucose still supplied about a third of brain energy.

• Young people with type 2

In San Antonio perhaps 1 in 20 teenagers has type 2 diabetes. Those in the RISE study respond poorly to drugs, and some had heart attacks in their twenties.

OTHER RELEVANT

• Ask for an OGTT with insulin, not just an A1c

DeFronzo's group showed a one-hour glucose above 155 mg/dL predicts diabetes. Peter's targets: under 90/6 fasting, 140/40 at 30 minutes, 130/30 at 60, 110/20 at 90 (glucose/insulin). DeFronzo: maybe 'overly aggressive.' A large insulin spike with normal glucose, or a weak 30-minute insulin rise, are both warning signs.

• Measure C-peptide, and compare it to glucose

The liver clears about half of secreted insulin, and insulin breakdown slows in resistant people, so insulin levels mislead. C-peptide relative to the rise in glucose, ideally adjusted for insulin resistance (the disposition index), shows real beta-cell function.

• If you need lots of insulin, work to need less

Weight loss, exercise and insulin sensitizers can bring doses toward a normal 35 units a day.

• GLP-1 drugs depend on adherence

About half of patients stop within a year because of cost (around $1,000 a month), GI effects, or missing food. Weight usually returns when the drug stops.

312 - A masterclass in lactate: metabolic fuel, implications for diseases, and therapeutic potential

Guest: George Brooks
Date: 2024-08-05 · Duration: 2:20:56
URL: https://www.youtube.com/watch?v=TGuPXGak5GI

KEYPOINTS

- **Lactate is a fuel, not a waste product—a '100-year mistake'.**
  Brooks, a Berkeley exercise physiologist who proposed the lactate shuttle, says lactate is not an innocent bystander but a participant in powering muscle and all cells. Otto Meyerhof's work—Nobel Prize in 1922, shared with A.V. Hill—led to teaching that lactate is a dead-end byproduct of oxygen-poor glycolysis; Brooks argues we've taught glycolysis wrong for a century.
- **Glycolysis normally ends in lactate, which is then shuttled and oxidized.**
  Lactate is produced continuously, even at rest, and moves between cells and tissues to be burned in mitochondria or converted to glucose in the liver (gluconeogenesis, the Cori cycle). In his tracer studies, about 75–80% of lactate disposal during exercise is oxidation.
- **Most carbon for lactate comes from muscle glycogen.**
  About 80% of the body's glycogen sits in skeletal muscle and roughly 20% in the liver. During exercise, glycogen-derived lactate becomes a major fuel distributed to heart, brain, liver and other muscles.
- **Lactate transporters (MCTs) and mitochondrial machinery enable the shuttle.**
  Monocarboxylate transporters move lactate across membranes; there are now more than four known, the first characterized around 2000. Brooks published finding MCTs on mitochondrial membranes around 1995. Training roughly doubles transporter and mitochondrial capacity—the 'cartoon' muscle cell going from 50 to 100 MCTs.
- **Training expands mitochondria far more than VO2 max.**
  Training can increase mitochondrial mass perhaps 100% while VO2 max rises only 10–15%—a 1967 study in rats by John Holloszy showed this. Mitochondria form a branched network ('reticulum'), so mass and volume matter more than counting individual organelles.
- **Lactate thresholds reflect clearance capacity, not just production.**
  A brisk walk keeps lactate around 1–1.5 mmol; about 4 mmol is the classic threshold a fit person can sustain 30–40 minutes. Elite athletes produce lots of lactate at a given relative intensity but clear it rapidly. Venous lactate from a hard-working muscle might hit 10–12 mmol.
- **Lactate fuels the brain, especially when it's stressed.**
  George Cahill's fasting studies showed people with glucose around 55 mg/dL got about half their brain's fuel from BHB. Brooks's group studies lactate for traumatic brain injury; colleagues in Switzerland give hypertonic lactate to TBI patients who appear to do better, and people can be clamped at about 4 mmol safely, with some reaching 6–8 mmol.
- **In disease, lactate signals metabolic inflexibility.**
  In insulin resistance, muscle struggles to take up glucose via GLUT4, so lactate patterns change. Sepsis lactate of 10 mmol is bad news—but standard assays measure only L-lactate, and Peter wonders whether D-lactate might also matter. Metformin users face increased lactic-acidosis risk when dehydrated.
- **After an oral glucose load, the liver buffers most of the sugar and lactate rises.**
  With a 75 g oral glucose tolerance test, blood glucose may double from ~75 to ~150 mg/dL—only about 5 g more glucose in circulation—so ~70 g must go elsewhere. Studies with 13C-labeled glucose and grain show the liver sequesters about 80% and releases it later; lactate spikes within 5 minutes and peaks around 15.
- **Lactate is also a signaling molecule.**
  Brooks says lactate can activate hundreds of genes (he cites about 500), affecting mitochondrial biogenesis and other adaptations—part of why exercise is so broadly beneficial.
- **The Warburg effect: cancer cells make lactate even with plenty of oxygen.**
  Otto Warburg, Meyerhof's professor in Germany, observed that cancer cells break down glucose to lactate under fully aerobic conditions—room air, with more oxygen than tissues ever see. Brooks reframes this as cancers exploiting lactate's roles as fuel and signal, rather than simply 'avoiding' mitochondria, a point Peter challenges him to explain.
- **Fiber recruitment and clearance explain everyday fatigue.**
  Light work like writing uses type I fibers, which oxidize lactate well. Lifting heavier loads or working overhead recruits type II fibers that produce more lactate and clear it less well, which is why something as simple as changing a light bulb overhead can feel surprisingly fatiguing. Ketones such as BHB enter cells through the same MCT transporters as lactate, so fuels compete—more glucose means less fat, and vice versa.

EXAMPLES

- **A pH of 6.9**
  Peter recalls trauma patients arriving with pH 6.9 rarely survived, though he remembers one miraculous exception. Normal pH is about 7.38–7.4.
- **The elite masters cyclist**
  A friend in his late 40s holds about 5.3 W/kg for an hour—420–430 W at about 80 kg—likely top 10 among U.S. amateur cyclists. His capacity to produce and dispose of lactate, not just generate it, explains it; when lifting with Peter, his strength was unexpectedly low.
- **400-meter runners aren't hungry**
  Brooks notes that after a 400 m sprint, high lactate suppresses appetite for about three hours until cleared.
- **Lactate infusions without acidosis**

In infusion studies, blood pH stayed essentially unchanged (around 7.38–7.4), with even slight alkalosis—undercutting the idea lactate itself causes acidosis.

- **Peter versus his cyclist friend**

Peter rides 3–4 hours a week; his friend rides 15–20. Over a week, the friend both produces and consumes far more lactate—illustrating that trained bodies are high-flux lactate systems, not low-lactate ones.

OTHER RELEVANT

- **Think of zone 2 as training lactate clearance.**

Building mitochondrial capacity improves your ability to oxidize lactate and stay metabolically flexible.

- **Don't fear lactate.**

The 'burn' and fatigue involve multiple factors; lactate itself is useful fuel and a signal.

- **Watch for lactate in medical contexts.**

High lactate in sepsis or with metformin and dehydration is a warning sign needing care.

- **Expect research on lactate therapies.**

TBI and other uses are promising but need multicenter trials. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Measure lactate thoughtfully if you train by it.**

Where you sample (venous versus capillary) and what you're doing matter; values reflect the balance of production and disposal, so use them to track trends rather than as absolute markers.

302 - Confronting a metabolic epidemic: how to prevent, diagnose, & manage liver disease

Guest: Julia Wattacheril
Date: 2024-05-20 · Duration: 2:37:08
URL: https://www.youtube.com/watch?v=ZiJ2th4rKKA

KEYPOINTS

• The liver is the one vital organ with no temporary external support.

Lungs have ventilators, hearts have balloon pumps and assist devices, kidneys have dialysis. For the liver, devices like the MARS machine exist but nothing really bridges acute failure. Wattacheril, a transplant hepatologist who directs Columbia's MASLD program, notes the 3.5 lb organ performs over 300 functions: macronutrient metabolism and glucose regulation, clotting proteins, immune functions, detoxification of drugs and toxins, bile acids, and lipoprotein production and clearance. Attia recalls a story from his training of baboons once used as temporary external livers.

• MASLD is the new name for NAFLD, with clearer subcategories.

The old name defined the disease by what it wasn't, and patients who never drank were labelled alcoholics. The umbrella is now steatotic liver disease. It includes MASLD (metabolic dysfunction), MetALD (metabolic dysfunction plus moderate alcohol), alcohol-related disease, monogenic forms, drug-associated fat and cryptogenic cases. Steatosis means fat in at least 5% of hepatocytes. MASLD affects an estimated 25–35% of people, conservatively, and disproportionately children.

• A normal ultrasound doesn't rule out fatty liver.

Standard ultrasound usually misses fat below about 30%. Vibration-controlled transient elastography (FibroScan) gives two numbers at the bedside: a CAP 'fat score' and a stiffness 'scar score' (vibrations travel differently through a 'sponge' than a 'brick'). It isn't technically feasible in about 8–10% of her patients. MRI-PDFF quantifies fat and iron precisely and is used in research. A lean person (BMI 22) with a CAP around 400 and no insulin resistance suggests a rarer export problem, such as a genetic lipid disorder.

• AST and ALT are injury markers, not 'function' tests, and lab limits have drifted up.

These enzymes leak when stressed hepatocytes burst. True function is albumin, clotting and glucose handling. Older thresholds were about 19 for women and 30 for men; labs now flag in the 40s–50s because the population has changed. For patients already diagnosed and in treatment, she's pleased below about 30, still uses about 40 as a workup threshold, and becomes concerned at persistent 1.5–2 times the upper limit for about six months. Discussing Attia's AST 34 and ALT 21, she asks about lifting within 24 hours, CK, alcohol timing and medications such as ezetimibe, and suggests retesting after rest days without alcohol.

• Alcohol and metabolic fat injure the liver in similar ways and often coexist.

Alcohol dehydrogenase converts ethanol to acetaldehyde. When capacity is overwhelmed, redox balance shifts, peroxidation occurs, and immune cells are recruited. Biopsies often can't distinguish alcohol from metabolic injury. A standard drink is 1.5 oz liquor, 5 oz wine or 12 oz beer (about 14 g of alcohol), and the CDC's 'moderate' is 2 a day for men and 1 for women. She asks about weekly quantity, binge patterns and context. She uses phosphatidylethanol (PEth), which reflects about 1–2 weeks of drinking, because self-report and shame often diverge. For most women who drink, she says breast cancer risk exceeds liver risk.

• Fibrosis stages progress slowly, and even early cirrhosis can reverse.

NASH (now MASH) means fat plus inflammation plus 'ballooned' pre-death hepatocytes. Fibrosis runs from stage 1 ('chicken wire' around the central vein in adults) to stage 3 (bridging) and stage 4 (cirrhosis, with nodules). Each stage takes about 5–7 years in MASLD, based mostly on European-ancestry data. Hepatitis C cures showed some early cirrhosis regresses. Cirrhosis is 'not a death sentence' but triggers cancer screening every six months.

• For early MASLD, the bigger near-term risks are diabetes, heart disease and cancer.

She often tells patients: your scar score is normal, your fat score is very high, and it can normalize in six weeks to six months, but unchanged you'll likely develop diabetes. Patients tend to hear that as empowering. Hepatocellular carcinoma risk in cirrhosis is about 3–5% a year. It's highest in hemochromatosis, then hepatitis C plus alcohol. Hepatitis B is the outlier, causing cancer even without advanced fibrosis. Her group is studying whether stage 3 MASLD needs earlier screening.

• Lifestyle remains first-line treatment, with specific emphasis on muscle.

Many patients say 'I don't eat that much fat,' but she says the main issue is glucose handling and refined carbohydrates. Many of her female patients with lean fatty liver have low muscle, so she prescribes combined resistance and aerobic exercise or, for sedentary people, a walking prescription. She refers detailed, culturally appropriate nutrition planning to dietitians. On fructose, she says studies that separate it from weight loss and insulin resistance show little net difference, so she recommends avoiding processed foods rather than isolating one sugar.

• Drugs: GLP-1s for appropriate patients, and resmetirom is the first liver-directed success.

For patients with a BMI of about 28–40, stage 2 disease and maximized lifestyle changes, she brings in GLP-1 agonists, with frank talks about muscle loss and weight regain after stopping. She raises bariatric surgery at stage 3 or early cirrhosis. The thyroid-hormone receptor agonist resmetirom showed phase 3 efficacy in a population about 90% of European ancestry. Vitamin E (from the PIVENS trial) helps steatosis but carries concerns about cardiovascular risk, prostate cancer and dose-dependent mortality.

EXAMPLES

• Coffee

Up to about three cups a day of black coffee is linked to benefit across fatty liver, hepatitis C fibrosis and even liver cancer, and is in European and American guidelines. Caffeine alone doesn't reproduce the effect. Attia drinks French press on the untested theory that more of the bean is better.

• Statins and ezetimibe

Small enzyme rises are usually accepted for cardiovascular benefit. She can count on one hand biopsy-proven injury from

lipid drugs. Attia's practice switches agents when enzymes rise.

- **Children differ**
  Pediatric fatty liver centres on the portal areas, often raising GGT and alkaline phosphatase, with higher AST and ALT than adults.
- **Hidden hepatitis C**
  Many cases are found through screening and traced to 1970s–80s drug use, shared intranasal cocaine straws, pre-screening transfusions or dental work abroad.

OTHER RELEVANT

- **When to biopsy**
  She biopsies to exclude autoimmune disease (about 18–20% of MASLD patients have positive autoantibodies), for trials, before major surgery, and to settle conflicting non-invasive tests.
- **Refer outliers**
  Lean patients with high ALT and moderate stiffness by 35 need a specialist for genetic testing, for example for lysosomal acid lipase deficiency.
- **Acetaminophen**
  Under 10% of transplants at her centre are for acute liver failure, and only some of those involve acetaminophen.
- **Screening**
  Screening isn't yet recommended, but a FIB-4 calculation plus FibroScan suits men over 50 and people with insulin resistance. About 30% of her patients refer themselves.

212 - The Neuroscience of Obesity | Peter Attia, M.D. & Stephan Guyenet, Ph.D.

Guest: Stephan Guyenet
Date: 2022-06-27 · Duration: 2:48:44
URL: https://www.youtube.com/watch?v=9G3iLbQCIHI

KEYPOINTS

• Obesity rose slowly for decades, then took off around 1980

Stephan Guyenet, a neuroscientist and author of The Hungry Brain, says the earliest useful US data come from Civil War veterans measured around 1890–1900, when only a small fraction had a BMI over 30. Representative national sampling began in the 1960s, when about 12% of adults were obese. That rose to about 15% by the late 1970s and early 1980s and is about 43% today. Guyenet thinks the lifetime risk of obesity is well over 50% for US adults. Type 2 diabetes prevalence has risen roughly five-fold over the past 50 years.

• The 'obesity paradox' is mostly an artifact of illness causing weight loss

Studies associated with Katherine Flegal found that the lowest mortality in meta-analyses of millions of people often fell in the overweight range. Yet excess fat drives diabetes, cardiovascular disease and some cancers. Guyenet says later research suggests the paradox comes mainly from reverse causation. Poorly controlled diabetes, kidney failure, COPD and cognitive decline all cause weight loss, which makes leanness look worse than it is.

• The hypothalamus regulates body fat like a thermostat

Guyenet calls this regulatory system the 'lipostat'. The first clue came in 1840, when the Viennese physician Bernhard Mohr described a woman with rapid, extreme obesity who turned out at autopsy to have a tumour in her hypothalamus. Hypothalamic obesity from tumours or brain damage still occurs.

• Leptin defends against starvation more than against weight gain

Leptin was discovered in 1994 by teams led by Jeffrey Friedman and Rudy Leibel as the missing gene in the extremely obese ob/ob mouse. Cutting calories by about 25% for a couple of days drops leptin far more than fat mass changes, and the brain reads that as a threat. Leptin resistance means higher leptin levels don't produce the expected reduction in appetite. The system is quite happy to let us gain weight. What it is built to prevent is starving.

• Body weight is highly heritable, and the genes act mostly in the brain

Guyenet cites a meta-analysis of twin studies estimating BMI heritability at about 75%. Studies of about 800,000 people have found about 900 variants, each of small effect, and they are disproportionately expressed in the brain. Our genes haven't changed in 100 years, so the susceptibility was always there. What changed is the environment, which now matches it.

• Highly rewarding foods recalibrate the brain's reward system

In Michael Krashes's mouse study, mice normally ate unrefined pellets. Once given calorie-dense, refined, high-fat pellets, their reward circuits devalued the old food, so it no longer satisfied or motivated them. Guyenet thinks the same happens to people raised around modern food. Gut neuropod cells, discovered around 2018, sense glucose, amino acids and fatty acids and signal directly to vagal neurons, which helps explain how strongly this learning is hardwired.

• The carbohydrate–insulin model versus energy balance

The modern carbohydrate–insulin model, set out in a recent review led by David Ludwig, is far more complex than earlier versions. Guyenet and Kevin Hall represent the energy-balance view, which nearly all researchers studying body-fat regulation accept. A key piece of evidence is John Speakman's study of 29 diets in five mouse strains. Replacing carbohydrate with fat made mice fatter until fat reached about 60% of calories, and beyond that they got slimmer again. The combination of fat and carbohydrate seems most fattening, which is why both low-fat and low-carb diets can work.

• Work with the non-conscious brain, not against it

Rather than relying on constant willpower, Guyenet suggests sending the brain signals that point toward slimming. Shape your food environment: keep tempting food out of sight and add effort barriers, since peeling an orange in another room beats grabbing chips. Choose foods that satisfy on fewer calories, and avoid liquid calories, which bypass the feedback system.

• Medication is now a reasonable option for people with obesity

For a BMI of about 30–35 or higher with impaired quality of life or health concerns, Guyenet thinks medical treatment is worth considering and recommends seeing an obesity medicine specialist. He calls semaglutide, as far as can be told, very safe, with about 18% weight loss, more than diet and lifestyle typically achieve. Like lifestyle change, it has to be maintained. He says we are entering an era of drugs designed from mechanism rather than found by accident.

EXAMPLES

• Two people at 160 lb

Peter imagines siblings at 160 lb: one has always been that weight, while the other got there by losing 40 lb. They look identical. Peter asks whether weight gain ratchets the body's set point upward permanently and whether there are life stages when it is most vulnerable. Guyenet says he honestly doesn't know, only that most people can gain weight at almost any age.

• Carnivore and LDL

Guyenet says there are no randomized trials of the carnivore diet, only anecdotes and a survey of about 2,000 dieters recruited from social-media groups, in which David Ludwig was involved. The survey showed a mean LDL rise of about 30–40 mg/dL. Peter cites Paul Saladino's publicly shared LDL-C of 533 mg/dL as an extreme case. He worries about people who see apoB jump from the 50th to above the 99th percentile and dig in rather than asking what it means.

• Peter's daughter and junk food

When his daughter, now 13, was a baby, Peter and his wife carefully kept her away from junk food. He uses this to argue that some foods are instantly rewarding, with no acquired taste needed.

• Red Pen Reviews

Guyenet runs a 501(c)(3) nonprofit that reviews popular nutrition books, at about 40–100 hours per book, with random citation checks. It has published 14 reviews since 2019. Peter says he has accepted that about 5% of his own book will turn out

to be wrong and plans a public page to collect corrections.

OTHER RELEVANT

- **Engineer your environment**
  Reduce cues and easy access to highly rewarding foods so you aren't fighting urges all day.
- **Favour satiating, less energy-dense foods**
  Calories needed to feel satisfied vary widely between foods. Whole foods, protein and fibre generally fill you up on fewer calories.
- **Don't drink your calories**
  Liquid calories slip past the satiety signals that regulate intake.
- **Talk to a specialist if obesity is affecting your health**
  GLP-1 drugs such as semaglutide are now effective tools, but plan on long-term use.

197 - The science of obesity & how to improve nutritional epidemiology | David Allison, Ph.D

Guest: David Allison
Date: 2022-02-28 · Duration: 2:21:41
URL: https://www.youtube.com/watch?v=49-CvqNQ7qU

KEYPOINTS

• Obesity rose slowly for centuries before the field woke up in the early 1990s

David Allison, a statistician, obesity researcher and dean at Indiana University, notes that obesity rates in Western industrialized countries have climbed fairly steadily since at least the 1700s. Robert Fogel, who won a Nobel Prize for this work, traced it in historical records such as British naval recruits. The 'wake-up moment' came in the early 1990s with NHANES III. Before that, obesity research was seen as niche, and treating extreme cases was often disdained even by doctors.

• Body weight is strongly heritable, as was clear long ago

Allison says the genetic component could have been seen in Charles Davenport's 1923 family data for the Carnegie Institution, though Davenport is now viewed as a racist. Twin and adoption studies from the 1980s, notably by Stunkard, Sørensen and colleagues using Nordic registries, made it undeniable. The BMI similarity of identical twins is about the same whether they are raised together or apart.

• Bariatric surgery probably extends life

Bjorn Torp's mentor laughed at the idea that it needed proving, saying everybody knew surgery helped. But Allison insists you have to do the experiment. Lars Sjöström's Swedish Obese Subjects study was controlled though not randomized. Across studies, all-cause mortality reductions vary widely but are usually on the order of 50%, sometimes more. Peter and Allison both suspect the benefit is larger in people who start with type 2 diabetes.

• The 'obesity paradox' depends on age, era and confounding

The BMI with the lowest mortality (the 'nadir') rises with age: very roughly near 20 at age 20, and in the low 30s by 70–80. The nadir also shifts with calendar time. In both Denmark and the US, obesity looked less deadly in 1990s data than in 1970s data, a finding Allison's NIH grant is investigating. Much of the paradox stems from illness causing weight loss and smoking keeping people thin. A famous 1987 JAMA paper by JoAnn Manson and colleagues argued that analyses should include only never-smokers. A 1995 New England Journal paper from the same group added more exclusions, including people with variable weight, but even these didn't fully flatten the left side of the curve.

• BMI is crude but useful at population scale

The index is old; Ancel Keys rediscovered it and named it in the 1960s–70s. For a sense of scale: Kate Moss at her peak was about 16–17, the underweight cutoff is 18.5, obesity starts at 30, and a top sumo wrestler is around 43–44. Allison compares BMI to an ordinary car, fine for daily driving but not precise enough for the Indy 500. For individuals, Peter prefers DEXA, which also shows visceral fat and bone density. The usual cutoffs fit adult white women well but fit other groups less reliably.

• Losing weight is easy compared with keeping it off

Allison sees no single explanation for why maintenance is so hard. He rejects the popular belief that there is a diet that, eaten correctly, would let anyone maintain a healthy weight without counting calories or feeling hungry or deprived. Advocates disagree about which diet that is, whether low-carb, low-fat or not eating at night. He knows of no evidence that such a diet exists.

• Observational data can point in exactly the wrong direction

In one of Allison's mouse studies, genetically identical C57BL/6J mice in identical housing were randomly assigned to eat less, a medium amount or as much as they wanted. Those forced to eat more lived shorter lives, consistent with decades of calorie-restriction research. But within the free-feeding group, the mice that chose to eat more lived longer. The observational association was the exact opposite of the causal effect, even with every usual confounder controlled. Allison calls the defence that 'it's just confounding' an admission of the problem.

• Childhood-obesity science is often analysed badly

Cluster-randomized trials assign whole schools, classrooms or families to a treatment. That's fine with enough clusters, but the analysis must account for clustering and nesting. Allison says many studies don't, and he calls that 'science gone wrong in the worst sense'. He believes some researchers are obfuscating null results while the field repeats hackneyed advice.

• Separate honest mistakes from bad science

Allison distinguishes normative errors, where good methods give a wrong answer at the edge of knowledge, from non-normative errors, which are avoidable. A normative example is Galileo's lantern experiment, which wrongly concluded light travels instantaneously. A non-normative one: early-20th-century norms for the size of children's thymus glands came from cadavers of poor, undernourished children. Normal thymuses in better-fed children then looked enlarged and were irradiated to 'prevent' sudden infant death, causing many thyroid cancers.

EXAMPLES

• What Allison would fund with $10 million

He would not build farmers' markets in schoolyards. Instead, he would split the money into four pots: bariatric surgery (both providing and studying it), drugs, general early-childhood education and security to reduce disparities, and basic science, including senolytics and work on aging.

• Indirect interventions that worked

In the Abecedarian study, a general early-education programme with no weight-loss goal was followed up 30 years later, and in a paper in Science the women had less obesity. In Moving to Opportunity, randomly assigned housing vouchers to move to less poor neighbourhoods led to less obesity and diabetes years later.

• A surgery memory

Peter recalls an open Roux-en-Y gastric bypass in a 400 lb man during his training about 25 years earlier. The patient developed an anastomotic leak and died of sepsis about 40 days later, never leaving the hospital. Today the operation is far safer.

- **Parachute trials**
  People often say no randomized trial of parachutes is needed. Allison notes that Andrew Leigh's book Randomistas shows such trials have actually been done, and he warns that the line is too often used to excuse weak observational studies.

OTHER RELEVANT

- **Ask simple questions about any health claim**
  Was it studied in humans? Was it randomized? Did it measure the outcome being claimed, for long enough? Was the result significant and big enough to matter, and at a dose you'd realistically take?
- **Be wary of hazard ratios around 1.16**
  Small relative risks from observational diet studies, such as bacon and cancer, are often presented as if they proved causation.
- **Use better tools than BMI for yourself**
  DEXA or other body-composition measures give a truer picture than BMI for an individual.
- **Keep science and advocacy separate**
  Allison argues that blurring the two erodes public trust. Say when a recommendation reflects judgement rather than proof.

How Fructose Drives Metabolic Disease | Rick Johnson, M.D.

Guest: Rick Johnson
Date: 2022-02-07 · Duration: 2:23:39
URL: https://www.youtube.com/watch?v=V02z9mqTWzg

KEYPOINTS

• Fructose is metabolized in a uniquely ATP-depleting way.
The first enzyme, fructokinase (ketohexokinase, KHK), phosphorylates fructose to fructose-1-phosphate as soon as it sees it, with no negative feedback. At high concentrations this rapidly drains ATP in the cell; Johnson says alcohol is the only other common nutrient that does something similar. Glucose metabolism, by contrast, is tightly regulated.

• ATP depletion produces uric acid, which harms mitochondria.
Falling ATP leaves AMP, broken down via AMP deaminase stepwise to uric acid. Inside the cell, uric acid causes mitochondrial oxidative stress, inhibits aconitase in the Krebs cycle, and shifts metabolism toward fat production and storage. Johnson frames this as an ancient survival mechanism to store fat before scarcity.

• The body makes its own fructose.
Johnson originally assumed a low-fructose diet would solve the problem, but the polyol pathway, via aldose reductase, converts glucose into fructose in the liver. High glucose, high salt concentration and raised blood osmolality all activate it. He guesses endogenous production may add roughly 25–50% on top of dietary intake for someone eating a lot of sugar — explicitly a guess.

• Mice lacking fructokinase are protected even from glucose.
Wild-type C57 mice given about 10% glucose in drinking water first eat less chow, then over about a month develop leptin resistance, eat more, and become fat and insulin resistant with active polyol pathways. Mice with fructokinase knocked out given the same glucose stay leaner — evidence that fructose made from glucose drives much of the harm.

• In calorie-matched studies, sugar still caused more harm.
In pair-feeding studies — 40% sugar versus starch with identical food — sugar-fed animals developed more fatty liver and metabolic features. Four months is about 15% of a mouse's two-and-a-half-year life, roughly 15 human years.

• Small daily surpluses add up.
Attia notes that if fructose drives about 300 extra calories of intake a day while reducing expenditure by only 25, the appetite effect matters far more — about a pound every 12 days from intake versus months from expenditure.

• Americans eat a lot of fructose.
About 15–20% of calories come from sugar, which is half fructose, so about 10–15% of the diet is fructose. It's not hard to eat 75–100 g a day (400 calories, around 15% of intake). About 10% of ingested fructose is excreted in urine.

• Vulnerability rises with age and menopause.
Johnson gives several reasons: younger people have healthier mitochondria; with obesity and fatty liver, fructose absorption increases; and the polyol pathway turns on more over time. In a study of children, lean kids absorbed about 70% of a fructose dose, while obese children with biopsy-proven fatty liver absorbed 100%.

• Lowering uric acid lowered blood pressure in teens.
In Dan Feig's JAMA trial, adolescents aged 14–15 with newly diagnosed hypertension were randomized to allopurinol or placebo; about 90% normalized blood pressure when uric acid was lowered. Another study gave 200 g of fructose a day to men with or without allopurinol.

• Blood pressure thresholds are debated.
Most of the world defines hypertension as 140/90; the US recently moved to 130/80. Johnson views 140/90 as the point for active management and says 135/85 carries little kidney risk and can be fixed with diet and exercise. Attia pushes back: if a 40-year-old should reach 100 with a GFR still around 40, standards should aim nearer 120/80 — just as lifelong apoB matters even when five-year trials can't show it.

• Salt and vasopressin link to obesity, not just blood pressure.
Raised salt concentration activates fructose production and raises vasopressin, a water-conserving hormone. Fat oxidation generates water, so animals store fat partly as a water source; vasopressin is high while animals like the fat-tailed dwarf lemur store fat. Johnson cites human data linking high-salt diets to obesity risk.

EXAMPLES

• Fruit vs. juice vs. dried fruit
An orange contains about 6 g of fructose; most fruits have 3–10 g, with mangoes, apples, pears and plums higher. Whole fruit comes with fibre, water and vitamin C and is hard to overeat — it's hard to eat more than two apples, but easy to eat 10 apples' worth of apple chips.

• Soft drinks vs. sports drinks
Soft drinks are about 11% sugar — 6% fructose, 5% glucose — which Johnson calls 'bad stuff'. Some sports drinks contain only 2–4% fructose with 4–6% glucose; during exercise, about 5–6% glucose and 1–3% fructose appears optimal.

• Attia's glucose monitor question
Attia asks how high glucose rises in the portal vein when a CGM shows 90 rising to 150 mg/dL; Johnson says that hasn't been measured, though portal levels are higher.

• The obesity paradox
With chronic illness, a BMI of 27 may do better than 20, and in old age 28 may do better than 24 — Johnson attributes this partly to the protective value of some fat stores.

• Calorie-restricted animals
Animals kept at 70% of normal intake have minimal fat stores.

OTHER RELEVANT

- **Cut sugary drinks first.**
  Liquid fructose delivers large, fast doses that overwhelm regulation. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Prefer whole fruit over juice and dried fruit.**
  Fibre and volume limit dose. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Watch salt as well as sugar.**
  High salt may activate internal fructose production and raise blood pressure.
- **Aim lower than 'normal' blood pressure.**
  Discuss targets nearer 120/80 with your doctor, starting with diet, salt reduction and exercise.
- **Ask about uric acid.**
  It's an inexpensive marker that may flag fructose-driven metabolic stress; treatment decisions belong with your clinician.
- **Treat exercise-time sugar differently.**
  Johnson notes the context matters: during exercise, modest glucose-dominant drinks are used for fuel, whereas the same sugars at rest in a sedentary person feed the fat-storage pathway.

167 - Gary Taubes: Bad science and challenging the conventional wisdom of obesity

Guest: Gary Taubes
Date: 2021-06-28 · Duration: 3:13:03
URL: https://www.youtube.com/watch?v=8js28V95flc

KEYPOINTS

• Taubes learned skepticism by covering physics that went wrong.
His first book, Nobel Dreams, followed Carlo Rubbia's team at CERN, about 150 physicists, in the period after the discovery of the W and Z bosons that won Rubbia the 1984 Nobel Prize. Watching the team chase a claimed new discovery in 1984–85, he saw how a leader who has gone out on a limb publicly stops hearing junior physicists who warn that the detectors aren't understood well enough to support the claims.

• 'Pathological science' starts with premature public commitment.
Physicists use the term for the science of things that aren't so. Its defining trait, Taubes says, is committing publicly to a result based on premature evidence without appreciating the chance of being wrong. Feynman's 1974 Caltech commencement talk captures the antidote: good science requires investigators to report everything that might undermine their result, unlike advertising.

• Cold fusion showed why controls matter.
After Pons and Fleischmann's March 1989 announcement made front-page news, Taubes wrote Bad Science (published 1991). Partly they rushed because they feared a physicist at Brigham Young, about 30–40 miles away, was working on a related idea. The story of a Georgia Tech group's neutron detectors (see examples) is his model of a missing control.

• Nutritional epidemiology can't reliably establish cause.
Cohorts like the Nurses' Health Study (about 110,000 nurses filling out food-frequency questionnaires) generate associations confounded by who chooses what. Taubes points to its 1987 observation that hormone replacement therapy appeared to prevent heart disease, an example critics flagged as confounding. He notes rigorous scientific method is less than 400 years old, dating to Bacon's Novum Organum, while pattern-seeking instincts are far older.

• Low-salt and low-fat advice outran the evidence.
Reporting for Science around 1998, Taubes found Americans had been eating low-salt diets for 15–20 years though randomized evidence never really supported it. An NIH administrator told him that when the low-fat recommendation came in 1984, they assumed rather than had the evidence. His two hypotheses for the obesity epidemic, which starts between roughly 1978 and 1991, both coincide with that era.

• Sugar and high-fructose corn syrup coincide with the epidemic.
Foods once considered fattening, starches and sugars, were rebranded as heart-healthy in the low-fat era. HFCS-55 arrived around 1977–78, could replace sugar in Coke and Pepsi, and by 1984 saturated the beverage industry, the same window when obesity rates began climbing.

• Obesity research ignored the science of fat storage.
Until about 1930 almost no one studied fat tissue. Starting in 1933, Rudolf Schoenheimer at Columbia showed fat is constantly deposited and mobilized, and by the mid-1960s intermediary metabolism was well established, yet Taubes says obesity textbooks from 1965 onward omitted it as psychiatrists and psychologists came to dominate the field.

• The 'eat too much' paradigm rests on thin foundations.
In 1930 physician Louis Newburgh published work based on a small number of patients arguing obese people simply overeat; German-speaking researchers like Julius Bauer called the argument naive, favoring hormonal dysregulation of fat tissue. In 1938 Albert Hetherington, at the lab of neuroanatomist Stephen Ranson, produced obesity in rats by lesioning the ventromedial hypothalamus, and with John Brobeck framed it as overeating. After Yalow and Berson's insulin assay (post-1960), those animals turned out to be hyperinsulinemic.

• The carbohydrate-insulin model is an alternative hypothesis, not settled fact.
Taubes argues that for people who gain weight easily, carbohydrates drive fat storage through insulin, so carbs must be restricted and replaced by fat and protein. He and Attia discuss a just-published paper by John Speakman and Kevin Hall presented as a possible refutation; Attia sees it as a mechanistic inquiry rather than a public-health solution, and they examine energy-expenditure methods such as indirect calorimetry.

• Ketogenic diets moved from 'deadly' to widely studied.
Conventional wisdom before about 2010 held that Atkins-style diets caused heart disease. Taubes notes roughly 200 trials now study ketogenic diets for conditions ranging from cancer and Alzheimer's to traumatic brain injury.

EXAMPLES

• The humidity-sensitive neutron detectors
Georgia Tech Research Institute chemists saw borrowed neutron detectors go off over cold-fusion cells and held a press conference. A local physicist told them the detectors were humidity sensitive; when they ran a water-only control, it set them off too.

• Taubes's own weight
At college he could eat 1,000–1,500-calorie late-night sandwiches; his boxing weight was 212 pounds, but after 30 he drifted upward toward 240. He tried Atkins as an experiment and is 'still waiting' for the predicted heart attack.

• The MIT economist and white rice
While reporting on markets at MIT, an economist told him his father had lost 200 pounds on Atkins and that he himself lost 40 pounds mostly by giving up white rice.

• Boxing and risk perception

Both Taubes and Attia boxed; Attia says he never felt it was dangerous because he believed he didn't get hit, which Taubes uses to illustrate how poorly we perceive behavioral risk.

- **Joslin's textbook**

Elliott Joslin opened the first dedicated US diabetes clinic around 1900; by 1916 he had seen about a thousand patients and wrote the field's defining textbook, now in its 14th edition, an example of how one authority comes to define truth.

OTHER RELEVANT

- **Demand controls and disconfirming evidence.**

Ask whether a striking claim compared against a proper control and whether its authors discuss what could prove them wrong.

- **Treat observational nutrition findings as hypotheses.**

Food-questionnaire associations can be badly confounded; randomized evidence should decide. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Experiment on yourself thoughtfully.**

If you gain weight easily, a carbohydrate-restricted trial may be informative; Taubes and Attia stress the science is contested, so monitor health markers with a physician.

- **Beware of authority overriding data.**

Dominant paradigms in obesity research formed around a few influential figures, so ask what evidence alternative explanations have.

#162 - Sarah Hallberg, D.O., M.S.: Treating metabolic disease, & a personal journey through cancer

Guest: Sarah Hallberg
Date: 2021-05-17 · Duration: 2:29:54
URL: https://www.youtube.com/watch?v=0e6u9JR-o6o

KEYPOINTS

• Carbohydrate restriction changed how Hallberg treated diabetes

For the first half of more than 25 years in obesity care, Hallberg, trained in exercise physiology, prescribed low-calorie, low-fat diets, the dogma of the 1980s. Patients with type 2 diabetes kept progressing on insulin and insulin-raising drugs. Cutting carbohydrates let many lower or stop medication. That eventually led her to Virta Health, which treats type 2 diabetes remotely with continuous support toward nutritional ketosis.

• Most American adults are already on the path to metabolic disease

About 10% of the US population has type 2 diabetes, and the rate is well into the teens in Hispanic, African-American and Pacific Islander populations. Recent studies suggest over 50% of adults have prediabetes or metabolic syndrome. Prediabetes means an HbA1c of 5.7–6.4%.

• Even 'normal' cut-offs are too loose

Hallberg's practice targets blood pressure under 120/80 (the CDC cut-off is under 130/80) and triglycerides under 100 mg/dL rather than under 150. Fasting glucose under 100, HDL above 40 (men) or 50 (women), and a waist under 40 inches (men) or 36 (women) round out the usual definition of metabolic health.

• Triglycerides on a lab report mostly reflect VLDL

Peter explains that most of a reported triglyceride level is carried in VLDL particles. In his example panel, triglycerides of 150 mg/dL go with a VLDL cholesterol of about 25, and he says most of those triglycerides sit inside VLDL, with some in intermediate-density lipoprotein. High triglycerides mean the liver is exporting a lot of fat.

• Dietary fat and blood fat are not the same thing

In a feeding study, participants started under 50 g of carbohydrate a day and had carbs raised every three weeks across six phases, up to 346 g. Saturated fat intake fell from about 84 g to 32 g. Yet blood levels of certain fatty acids, especially palmitoleic acid, rose as carbohydrates went up. You are not simply 'what you eat'.

• Palmitoleic acid (16:1) is an early warning sign

The liver turns excess carbohydrate into palmitic acid (16:0), and the enzyme SCD1 converts that to palmitoleic acid. Fructose via GLUT5, glucose via GLUT2 and insulin all push this pathway. Peter suggests it may be the liver protecting itself in the short term. Rising palmitoleic acid signals that carbohydrate intake is exceeding the person's tolerance.

• HbA1c flags trouble 10–20 years late

Nobody 'rings the bell' until HbA1c passes 6.5%, often a decade or two after molecular warning signs appear. Hallberg cites studies linking palmitoleic acid in childhood (the PANIC study) to later health, and a Dutch study linking levels at 50 to C-reactive protein at 70. Data in non-white populations are lacking, since most studies enrolled middle-class white participants.

• Treatment should be individualized and early

Hallberg says the only data that matter in the room are the patient's own. She also stresses that insulin is not benign: someone controlling glucose on 100 units a day is in a very different state from someone needing 20. Catching people earlier may mean they don't have to stay very low-carb forever.

• Lung cancer in never-smokers is common and often driven by specific mutations

On June 30, 2017, at 46, a fit and health-focused never-smoker, Hallberg was diagnosed with stage IV lung cancer. About 12–14% of lung cancers occur in non-smokers, often EGFR- or ALK-driven. She has an EGFR exon 19 mutation. Median survival for stage IV lung cancer is often 12 months or less, though it depends heavily on the type.

EXAMPLES

• Low-carb versus low-fat at about 1,500 calories

In a 12-week trial, the very-low-carb group's triglycerides fell from about 211 to 104 mg/dL, roughly 50%. The low-fat group went from 187 to about 150, roughly 20%, despite eating about a third as much saturated fat (12 g vs 36 g).

• 'Just 11 years'

Hallberg's children were 7, 12 and 14. First she asked to reach 50; she's now 49. Then she set a non-negotiable goal of 11 years, until her youngest graduates, even though typical survival with her treatment was 24–30 months. She and her husband used to joke about dying at 95 in a car crash on the way home from a ski trip.

• An unconventional treatment path

When Tagrisso (osimertinib) stopped shrinking the primary tumor in March 2018, it was radiated. Chemotherapy followed, then anti-estrogen therapy targeting a second mutation, then very-low-dose single agents starting with cisplatin. By fall 2019 a PET scan showed no detectable tumor.

• A near-fatal complication

Gemcitabine (Gemzar), usually considered well tolerated, triggered atypical hemolytic uremic syndrome within about four weeks. Her hemoglobin fell to the low 6s (normal is about 13–14), she needed plasmapheresis, and doctors weren't sure her kidneys would recover. She says over 70% of people with this condition die or end up on dialysis.

• A four-month delay, even for an expert

After a recurrence was diagnosed in mid-September, Hallberg, an experienced patient advocate, didn't start a clinical trial until December 30. She asks how many people without her advantages die during such gaps. That fuels her work on health equity.

OTHER RELEVANT

- **Ask for more than HbA1c**

  Track triglycerides, HDL, blood pressure, and waist against the stricter targets. Where it's available, a fatty-acid profile showing high palmitoleic acid may reveal carbohydrate intolerance years earlier. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Advocate hard, and get second opinions**

  Hallberg's outcomes depended on finding doctors willing to try unusual plans and on pushing for referrals when a recommendation seemed wrong. She warns against implying that people who die of cancer 'gave up.'

- **Spend time deliberately**

  She calls time the most important currency. She stayed in her Aspen Institute fellowship despite misgivings, makes room for an occasional 'pity party', and sees her advocacy as part of the legacy her children will remember.

#140 - Gerald Shulman, MD, PhD: Insulin resistance—molecular mechanisms and clinical implications

Guest: Gerald Shulman
Date: 2020-12-07 · Duration: 2:08:42
URL: https://www.youtube.com/watch?v=OzZUnl3b49U

KEYPOINTS

• Insulin resistance is the soil the big chronic diseases grow in

Peter tells patients that heart disease, cancer and Alzheimer's sit on a foundation of insulin resistance. Shulman credits Gerald Reaven's 1988 Banting lecture with getting the field to see insulin resistance as a driver, not a bystander. Shulman himself won the Banting Medal in 2018.

• Seeing inside living cells with carbon-13 NMR

About 99% of the body's carbon is C-12, which NMR can't see. The 1% that is C-13 can be tracked. By infusing C-13-labeled glucose, Shulman's group can watch glucose being turned into muscle glycogen in awake humans, without radioactive tracers or biopsies.

• Muscle is the first site of insulin resistance

After a meal, about 80–90% of glucose is normally stored as glycogen, mostly in muscle. In lean, healthy, non-smoking Yale students around 20 years old (BMI about 22–23) who were insulin resistant, glucose flow into muscle glycogen was already about 50% lower than in insulin-sensitive peers, before any weight gain or diabetes.

• The block is glucose transport, not what Randle predicted

Philip Randle's 1960s model predicted that fat would raise glucose-6-phosphate inside muscle. Shulman's NMR studies found both glucose-6-phosphate and free glucose fell, pointing to a problem moving glucose into the cell through the GLUT4 transporter. That shifted the field's view of where the problem lies.

• Diacylglycerol and novel PKCs are the culprits

When fatty acid delivery outpaces oxidation, intermediates such as acyl-CoAs and diacylglycerol (DAG) build up. In muscle this activates PKC-theta, and in liver PKC-epsilon, which blunts insulin-receptor and IRS signaling. Gene knockouts confirm it. Specifically, the sn-1,2 DAG form at the plasma membrane matters, which can be missed if only total DAG is measured.

• Muscle insulin resistance diverts carbs to the liver and makes fat

When muscle can't store glucose, more of a carbohydrate meal reaches the liver. There it is turned into fat through de novo lipogenesis, which was more than twofold higher in insulin-resistant young people, with liver fat up about 2.3-fold. That leads to higher triglycerides and lower HDL. Shulman says lab cut-offs (triglycerides under 150) miss this; these young people had about 100–105 versus 60.

• Exercise bypasses the block

Six weeks of StairMaster (three 15-minute bouts at about 65% VO2 max) normalized muscle glycogen synthesis, likely via AMPK moving GLUT4 independently of PI3-kinase. A single 45-minute session shifted ingested glucose into muscle and cut de novo lipogenesis and liver triglycerides. Type 1 diabetics walking briskly for hours a day can need far less insulin.

• Insulin resistance evolved to protect the brain during starvation

Rats fasted 48 hours develop fatty liver, DAG build-up, PKC-epsilon activation and hepatic insulin resistance. That switches off glycogen storage and preserves glucose for the brain. Cahill showed humans still got about 40% of brain energy from glucose after 40 days of starvation.

• Fatty liver is becoming the leading reason for liver transplants

Fatty liver disease is now the most common liver disease in the world. Peter notes that within about 10 years, NASH and cirrhosis may be the top reason for liver transplants in the US, compared with under 2% of transplants when he was in medical school.

• Metformin likely works through redox, not complex I

Most studies used millimolar concentrations of metformin. Plasma levels at the usual dose of 1 g twice a day are about 30–50 micromolar, and perhaps about 100 in the portal vein. At those levels, Shulman says metformin inhibits mitochondrial glycerol-3-phosphate dehydrogenase, changing the cell's redox state and reducing glucose production in the liver.

EXAMPLES

• 1,200 calories reverses it quickly

Putting type 2 diabetics on short-term hypocaloric feeding of 1,200 calories a day reversed hepatic insulin resistance and fasting hyperglycemia. Bariatric surgery works the same way, by limiting energy intake.

• The 5-gram difference

Fasting blood sugar of 200 versus 100 mg/dL represents only about 5 extra grams of glucose circulating. Small shifts in where glucose goes, rather than how much exists, separate health from diabetes.

• DNP, from diet pill to liver-targeted drug

Dinitrophenol, a mitochondrial uncoupler, was sold over the counter for weight loss in the 1930s until overdoses caused fatal hyperthermia. Removing it was one of the first actions of the new FDA in 1937. Shulman's team designed liver-targeted uncouplers that 'melt' liver fat in animals and widened the safety margin about 100-fold. The plan is to start in humans with orphan conditions like lipodystrophy.

• A threonine conserved from flies to humans

The insulin receptor's activation loop has three tyrosines (1158, 1162, 1163) that become phosphorylated when insulin binds, with a threonine between them conserved from fruit flies to humans. Shulman's team made mice with that threonine (position 1150 in mice) swapped for alanine. On normal chow they had normal insulin sensitivity, and the team used them to test how PKC-epsilon acts on the receptor.

- **Weight-loss drug mechanisms**
  GLP-1 agonists work mainly by cutting food intake. SGLT2 inhibitors spill about 400 calories a day into urine, but weight loss plateaus after several weeks.

OTHER RELEVANT

- **Exercise is first-line therapy for muscle insulin resistance**
  Even single bouts help. Find an activity you like enough to stick with long-term, since short-term weight loss often reverses. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Look beyond fasting glucose and standard cut-offs**
  Fasting and post-meal insulin, triglycerides around 100 rather than under 150, and fatty liver can reveal insulin resistance decades before HbA1c rises. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Metformin for healthy people is an open question**
  Shulman sees metformin as a net positive in insulin-resistant people even without diabetes. For lean, insulin-sensitive, vigorously exercising people, he suspects it may not help and Peter raises whether it could even work against the benefits. Peter says he's undecided too.

#87—Rick Johnson, MD: Fructose—the common link in hypertension, insulin resistance, T2D, & obesity?

Guest: Rick Johnson
Date: 2020-07-07 · Duration: 1:50:46
URL: https://www.youtube.com/watch?v=LbSic4Oo8ME

KEYPOINTS

• Uric acid led Johnson from blood pressure to fructose

Johnson, a nephrologist at the University of Colorado with roughly 700–800 publications, first studied uric acid as a cause of high blood pressure. Raising uric acid in animals with a uricase inhibitor raised their blood pressure, and lowering it brought pressure down. Expecting crystals in the kidney, his team instead found inflammatory changes. Uric acid, long thought to be an inert end product or even an antioxidant, was having pro-inflammatory effects. Since fructose raises uric acid, in 2002 they asked whether sugar could drive blood pressure.

• Fructose plus allopurinol: one intervention, many effects

Rats fed fructose developed high blood pressure, and allopurinol, which lowers uric acid, brought it back to normal. They also developed insulin resistance, high triglycerides and fatty liver, and lowering uric acid improved all of those. Johnson calls it a big discovery that linked sugar, uric acid and metabolic disease.

• Fructose drains cellular energy and flips a metabolic switch

Fructokinase uses ATP without the brakes that govern glucose metabolism. A big fructose load can drop ATP in the cell by 40–50%, which Johnson describes as a 'mayday' signal. Phosphate gets tied up in fructose-1-phosphate. The falling phosphate pushes AMP down the AMP deaminase pathway, which stores fat, generates uric acid and promotes insulin resistance, rather than the AMPK pathway, which burns fat and is what metformin activates.

• Fructose is nature's fat-storage signal

Animals use fruit to fatten before winter or before food runs short. Bears and other hibernators gorge on ripe fruit in the autumn, and orangutans eat large amounts at once to gain fat. Johnson notes that most people don't get fat from a few pieces of tart fruit, but large amounts of fruit juice can increase fat.

• An ape mutation made humans sensitive to sugar

As the climate cooled, fruit trees (including figs) disappeared from European forests, and by about 12 million years ago European apes were starving. Johnson argues that a mutation that disabled uricase, which raises uric acid, helped them store fat and survive. The surviving ape returned to Africa and Asia and became the ancestor of the great apes and of humans. His team even resurrected the ancestral uricase. Attia notes that evolution wasn't anticipating a world awash in fructose.

• Salt raises blood pressure through a spike in serum sodium

A very salty soup can raise serum sodium from 140 to 142–143 mmol/L, which raises blood pressure acutely, by about 6 mmHg for a 2 mmol/L rise, for a couple of hours. In Johnson's study, giving the same salty soup with water so that serum sodium didn't rise prevented the blood pressure rise. He thinks sugar also plays a role in salt-sensitive hypertension.

• Blood pressure risk climbs from 120/80, then steeply

Above about 160–180 mmHg, arteries can no longer constrict enough to protect themselves (autoregulation fails), and stroke risk shoots up almost vertically. But epidemiology also shows a stepwise rise in risk from 120/80 to 140/90, which is why 120/80 is treated as the target.

• Speed and dose determine how harmful fructose is

The same 25 g of fructose does more harm when it arrives quickly in liquid form on an empty stomach than when it is eaten with fibre. Johnson says a beverage company could make soda look harmless by having people sip it over three hours. About 20% of fructose is handled by the intestine and perhaps 40% by the liver, with at least 10–20% escaping into the circulation, more at higher doses.

• The body makes its own fructose from glucose

High glucose reaching the liver induces aldose reductase, which converts glucose into fructose. Mice given glucose in their drinking water became fat and insulin resistant, even though they ate less chow. Johnson uses this to explain why starchy foods such as French fries can be fattening even though they contain no fructose.

EXAMPLES

• Same weight, different livers

In an animal study with calories cut by 10%, both groups slowed their metabolism and kept their weight. But the group getting 20% of calories from fructose still developed severe fatty liver and all became diabetic. They looked the same on the outside.

• Gout, sugar and history

Gout was linked to the sugar-loving English upper classes of the 1600s–1800s. William Osler wrote in the 1890s that sugar and very sweet fruits were major risk factors. Purines from DNA and RNA also matter: anchovies, other small fish and beer (brewer's yeast) can trigger attacks. Men have higher uric acid than women until menopause, because oestrogen helps excrete it.

• Johnson's uric acid thresholds

He sees risk of prediabetes, insulin resistance, hypertension and kidney disease rise once serum uric acid passes 5.5 mg/dL. Most labs don't flag it until about 6.5 (intermediate) or 7.5 (high), cut-offs set with gout in mind. He has no doubt a level of 9–10 is harmful. Because every drug has side effects, he would want to be sure before prescribing allopurinol, and would consider HLA-B*58 testing.

• Diet versus regular soda

Animals with their taste buds genetically knocked out still prefer sugar but not artificial sweeteners, because sugar stimulates dopamine independently of taste. Rodents given artificial sweeteners don't gain weight. Johnson says regular Coke is more dangerous than Diet Coke, while acknowledging that the long-term safety of aspartame and sucralose isn't fully known and that dose matters.

OTHER RELEVANT

• Keep fructose low for fatty liver

For patients with fatty liver, Johnson's group limits fructose to about 10 g a day, only as whole fruit. Whole fruit brings vitamin C, flavanols, epicatechin and potassium, which counteract some of fructose's effects. Dried fruit loses many of those benefits.

• Avoid liquid and concentrated sugar

Soft drinks, juice and candy on an empty stomach deliver fructose fastest. Johnson notes about 70% of packaged foods contain added sugar.

• Drink water with salty food

Because the problem is the rise in serum sodium, having water alongside a salty meal blunts the blood pressure spike. Kidney patients need to be careful about fluid volume.

• Check your uric acid

Ask for the actual number rather than relying on the lab's 'normal' flag. Johnson treats levels above about 5.5 mg/dL as a metabolic warning sign.

#69 – Ronesh Sinha, M.D.: Insights from a patient population predisposed to metabolic syndrome

Guest: Ronesh Sinha
Date: 2020-01-14 · Duration: 1:59:15
URL: https://www.youtube.com/watch?v=_J8gFRxJVY0

KEYPOINTS

• A cluster of stubborn cases brought Attia to Sinha

Attia had two South Asian patients with unusually stubborn insulin resistance and a striking degree of inflammation, which led him to Sinha's book. Mark Sisson had introduced them about five years earlier. Sinha, an internist at the Palo Alto Medical Foundation, created a South Asian medical consultation service in Silicon Valley after seeing large numbers of Indian and East Asian tech workers with metabolic disease.

• Sinha's own numbers made him feel like a fraud

When local companies asked him to explain these conditions to Indian employees, he was giving advice while his own triglycerides were above 300 and his HDL in the 20s. Fixing his own metabolism shaped how he treats patients.

• Carbohydrate load is huge, even in vegetarians

At least half of Sinha's South Asian patients were vegetarian, and some had the worst lipoprotein abnormalities. His average South Asian patient ate 300–400+ g of carbohydrate a day, and some East Asian patients 500–600 g. Cutting carbohydrate dropped triglycerides by 150 points within three to four weeks.

• Thin doesn't mean metabolically healthy

Sinha describes couples in which the wife is 30–40 pounds overweight with flawless triglycerides and HDL, while the 'rail skinny' husband with a BMI of 21 has triglycerides 'through the roof'. The heavier person often stores fat subcutaneously and has more leg muscle. The thin one stores it viscerally, so BMI misclassifies risk.

• Visceral fat, not total fat, drives dysfunction

Sinha cites a New England Journal of Medicine liposuction study, with Sam Klein as one of the authors. Removing about 30 pounds of subcutaneous fat produced no metabolic improvement, pointing to the visceral compartment as the problem.

• Several factors may explain Asian susceptibility

A 2013 genetic study found lower beta-cell density in East and South Asians. Overfeeding for 24–48 hours depresses beta-cell function. Populations that migrated to colder climates have more brown fat, which can account for 15–18% of resting calorie burn. Within India, prevalence is higher further south toward the equator, reaching up to about 20% in Kerala. Sinha also cites studies in which mitochondrial ATP output rose only about 5% in offspring with a family history of diabetes, compared with about 90% in those without, before any insulin resistance was visible.

• Thrifty gene versus thrifty phenotype

James Neel's 1960s 'thrifty gene' idea was that famine cycles selected for fat storage, but no gene was found. Sinha says experts doubt there were enough famines to explain it. The Barker hypothesis instead points to the womb. In about 100,000 UK records, lower birth weight predicted higher heart-disease mortality, a pattern since reproduced on every continent.

• A1c often misleads; CGMs reveal more

Comparing 90 days of continuous glucose monitoring with A1c, Attia finds only about 25% of patients are concordant. The other 75% are off in either direction. He argues that the 6.5% A1c cut-off has no fidelity between 5 and 6, and misses people with normal fasting glucose but post-meal spikes of 200. He notes that the gap between a glucose of 100 and the diabetic 200 is about one extra teaspoon of glucose in the bloodstream.

• Night-time glucose may reflect cortisol

CGMs show very high overnight glucose in some people who eat well. Morning readings of 110 can occur in otherwise healthy people. Sinha noticed the pattern before CGMs and began prescribing calmer evening routines, no devices and brief meditation. They note that stress alone can push glucose from 90 to 120 within about two minutes.

EXAMPLES

• Fitness as an early marker

At matched age and BMI, insulin-resistant people, especially South Asians, have lower VO2 at submaximal effort. Attia prefers a zone 2 test, the most power sustained with lactate below about 1.8–2 mmol. For example, 200 watts versus 140 watts at the same lactate separates two people more sensitively than VO2 max, which shifts with body weight.

• PCOS as 'insulin-resistant ovarian syndrome'

Endocrinologists in Fremont estimate that 25–30% of Asian women there show some manifestation of PCOS. Sinha thinks the name should reflect its root in hyperinsulinemia. He also sees eczema and other inflammatory conditions that make insulin resistance harder to treat.

• A 47-year-old with a heart attack

A woman who read his book came in after a first heart attack at 47, with her parents and her child. Her Lp(a) was elevated. Sinha checks Lp(a) widely because many of his patients with a family history of coronary disease have normal LDL, and he sees Lp(a) as an independent risk factor.

• Vitamin D

Sinha aims for roughly 30–40 ng/mL and doesn't see the point of pushing to 80–90. Anecdotally, he sees CRP improve when deficient patients are corrected.

• Sleep tracking

Reviewing a patient's monthly averages, Sinha found 6 hours 12 minutes a night. He says moving someone like that to eight hours is among the most impactful changes he can make.

OTHER RELEVANT

- **Build movement into the workday**

  For busy executives who won't add time, Sinha treats leg strength as a vital sign, for example 'this many squats by 12 p.m.', plus balance and stretching breaks. Weak legs at 50–60 predict slower walking, canes and decline.

- **Breathing as 'meditation in meetings'**

  Using an Apple Watch or Fitbit, patients notice when their heart rate is 20 points above resting and breathe it back down. Sinha teaches this to people who refuse to meditate.

- **Look past BMI and A1c**

  Ask for triglycerides, HDL, fasting insulin and, where possible, a CGM. These matter most for lean South and East Asians, whose risk is often hidden.

- **Protect kids' sleep and limit devices**

  Sinha's family doesn't compromise on bedtimes. They delayed devices until about 7th or 8th grade and set no-device rules for gatherings. He worries about classmates studying or watching TV until 1–2 a.m.

#59–Jason Fung, M.D: Fasting as an antidote to obesity, insulin resistance, T2D, & metabolic illness

Guest: Jason Fung
Date: 2020-01-11 · Duration: 2:42:05
URL: https://www.youtube.com/watch?v=nqBkG0ZECn8

KEYPOINTS

• Fung reframes insulin resistance as an overflow problem, not a locked door.
The standard 'lock and key' model says glucose can't get into a cell because the cell has stopped responding to insulin. Fung argues it may instead be unable to enter because the cell, especially the liver cell, is already overfilled with glucose and fat. He says this explains the paradox of an 'insulin-resistant' liver that is still busily turning glucose into new fat. In his view the underlying problem is hyperinsulinemia, too much insulin over time, rather than insulin resistance itself.

• Pushing in more insulin covers up type 2 diabetes rather than treating it.
Fung's view is that sulfonylureas, insulin and DPP-4 inhibitors all raise insulin and push more glucose into tissues that are already full. Blood sugar improves while total-body glucose gets worse. He says this is why the disease looks 'chronic and progressive': patients go from one drug to large insulin doses over ten years and the disease never gets better.

• Lowering blood glucose with more insulin protected small blood vessels but not the heart or brain.
Attia notes that intensive glucose-control trials improved some small-vessel (microvascular) outcomes, such as in the kidneys, but not large-vessel (macrovascular) outcomes in the heart and brain. If insulin doses have to double to get glucose from 200 to 150, those outcomes may even get worse. Fung connects this to the failures of ACCORD, ADVANCE and VADT. Attia says seeing this pattern about three years earlier was the 'aha moment' that made him see hyperinsulinemia itself as harmful.

• SGLT2 inhibitors fit Fung's model because they remove glucose from the body.
These drugs make the kidneys excrete glucose, which lowers total-body glucose and insulin rather than moving sugar into the liver. Fung credits them with organ protection not seen with older drugs, and notes that people lose weight on them. As a nephrologist, he points out that they were the first new drugs to slow diabetic kidney disease since ACE inhibitors in the 1980s.

• Fung sees insulin resistance and fatty organs as the body protecting itself.
In his analogy, insulin delivers glucose to houses on a street. Once a house is full it stops answering the door, which is insulin resistance, so insulin bangs harder. He cites lipodystrophy, where people with almost no body fat have some of the worst insulin resistance ever measured, as evidence that storing fat protects against excess glucose. Without places to store it, fat ends up in the liver.

• Fung thinks causation runs mostly from insulin to obesity.
Whenever insulin rises, with insulin injections or sulfonylureas, people gain weight. When it falls, with SGLT2 inhibitors or untreated type 1 diabetes, they lose weight. Attia adds a counterpoint: in Samuel Klein's New England Journal of Medicine study, liposuction removed about 20 pounds of fat with no metabolic benefit, although critics note liposuction only removes fat under the skin, not visceral fat. Attia says the direction of causation may not change what you do clinically.

• Many chronic diseases may be 'diseases of too much growth'.
Fung links hyperinsulinemia to breast cancer and to proliferative disease through shared nutrient-sensing pathways: insulin, mTOR and AMPK. Attia describes meeting a researcher whose 2006 theoretical paper, rejected by nearly every journal, predicted rapamycin would be the top longevity drug. The first study showing rapamycin extends lifespan came in 2009. Attia calls it the most promising longevity agent as of 2019.

• Hormones send growth signals to muscle and fat in different directions.
Attia explains that insulin builds both muscle and fat, which is why some bodybuilders use it. Testosterone builds muscle but breaks down fat. Cortisol is the worst of both, breaking down muscle while building fat. He sketches this on a whiteboard for patients to show that nutrition, exercise and hormone therapy are all ways of steering these signals.

• Fung believes the effect of bariatric surgery on diabetes is mostly due to fasting.
Attia notes that after a Roux-en-Y gastric bypass, patients often stop needing insulin within about 10 days, before they've lost much weight, and that insurers have treated surgery as the only recognized way to reverse type 2 diabetes. Attia once worked on designing a trial to separate the surgical, dietary and calorie-restriction effects. Fung's view is that 'the fasting does everything', and that 7- to 14-day fasts can produce the same resolution.

EXAMPLES

• The suitcase analogy
If the last two shirts won't go into a suitcase, it may be because it won't open or because it's already full. Standard treatment assumes it won't open and keeps forcing more in, like a spouse asking, then yelling, then throwing a football. Fung's answer is to take shirts out by lowering insulin.

• A 1990s insulin study as Fung recalls it
People with type 2 diabetes went from no insulin to about 100 units over six months. Their blood sugar improved, but they gained about 20 pounds while eating roughly 300 fewer calories a day, which Fung takes as evidence that insulin itself drives weight gain.

• A foot ulcer that had not healed for a year
A man in his 40s had a diabetic foot ulcer for a year and was at risk of amputation. With his father's support, he did a 7-day fast and then 36-hour fasts three times a week. Fung says the ulcer healed within about three weeks. Attia notes he himself is less aggressive and never starts patients with water-only fasting.

• Skipping breakfast and heart deaths
Both dismiss a recent study linking skipping breakfast to higher cardiac mortality as confounded. If everyone is told to eat breakfast, the people who skip it differ in ways that can't be measured.

• Kidney function as an early warning

Attia tracks cystatin C and microalbumin. A person in their 40s whose kidney filtration (GFR) is already 80% of predicted raises the question of what it will be at 80, so he now treats even stage 1 blood pressure. Fung sees IgA nephropathy patients who had lost about 95% of kidney function without knowing.

OTHER RELEVANT

• Narrow your eating window before counting macros.

Fung says Satchin Panda's work found people eat across about 15 hours a day, compared with a 14-hour overnight fast in the 1970s. He finds telling someone to eat only between noon and 8 p.m., with nothing that came in a box, easier to follow than carb targets. Attia sees the main benefit of time-restricted eating as psychological.

• Expect hunger during a fast and plan for it.

Attia stays hungry at some point on every day of a seven-day fast, but says it's no worse than an ordinary hungry day, and that anticipating it is harder. Fung tells patients that being hungry is fine, but feeling lethargic or unwell means they should stop right away and try again another day.

• Watch magnesium, and do longer fasts only under medical supervision.

Fung's clinic monitors patients closely. Many people with type 2 diabetes start out low in magnesium, so they supplement it, and they use salted bone broth for dizziness. He says he has almost never had to stop a fast because of electrolytes. Attia uses phosphatidylserine and GABA at night to calm the surge in sympathetic activity during a fast.

• Healthy people probably need only occasional, modest fasts.

Fung suggests periodically lowering insulin, similar to the traditional balance of feasts and fasts such as Lent, Ramadan or Yom Kippur. He says the data for healthy people are not there yet for longer protocols like Valter Longo's quarterly five-day fasting-mimicking diet.

#54–Kevin Sayer, CEO of Dexcom: Continuous glucose monitors–impact of food, sleep, & stress

Guest: Kevin Sayer
Date: 2020-01-10 · Duration: 1:44:35
URL: https://www.youtube.com/watch?v=W8JWAQq8i-Q

KEYPOINTS

• How a Dexcom sensor reads glucose

Sayer, Dexcom's CEO, explains that a wire about as thin as a human hair, made of special alloys and coated with membranes, sits roughly half an inch under the skin in interstitial fluid. It measures glucose there, not in blood. An enzymatic reaction produces an electrochemical signal, and an algorithm in the transmitter converts it to a glucose value. Attia notes that point-of-care tests suit analytes like glucose, ketones, lactate and electrolytes, whereas insulin or lipoprotein counts need lab methods such as ELISA or NMR.

• The G6 removed the scary part

Earlier models had users push the needle in themselves; Sayer says some patients emailed that they had stared at the device for six weeks without daring to insert it. The G6 inserts automatically, faster than a hummingbird beats its wings a couple of times. Attia saw the old applicator scare off some of his own patients after they had paid out of pocket.

• Most people with type 1 diabetes still weren't using one

At the time of recording (2019), Sayer estimated about 1.3–2 million Americans had type 1 diabetes, plus about 1.5 million with type 2 who use insulin intensively. Only about 20–30% of people with type 1 used a CGM, though he believes 80% of that intensive-insulin population should. Medicare began covering CGM for intensive insulin users with type 2 in January 2017.

• Insurance coverage is cyclical

Sayer describes one state that required a person with type 1 to document a number of readings below 50 mg/dL before getting coverage. He says payers often cover generously for a couple of years, then tighten criteria, and that price and access are traded off in constant negotiation.

• The biggest savings come from avoiding low-sugar hospitalizations

Sayer's economic models show the major acute saving is preventing hospital stays in 'hypoglycemia unaware' patients. Each such stay costs $10,000–30,000 by the numbers he has seen. Dexcom's share feature, which he says the company pioneered and got through the FDA, lets a spouse in another country see a low and phone the hotel to wake the wearer.

• Performance first, then experience, then cost

Sayer's framework for the Verily (Alphabet) partnership is performance, then patient convenience, then cost. Dexcom supplies the membranes and algorithms; Verily supplies miniaturised electronics and Bluetooth. Attia suggests average accuracy has reached diminishing returns. Sayer agrees, saying the remaining gain is 'eliminating the outliers' so every sensor behaves the same.

• Type 1 and type 2 deserve different names

Attia argues that lowering glucose in type 2 by adding insulin, or drugs that raise the body's own insulin, reduces small-vessel complications but doesn't save lives. Patients still get heart disease, cancer and Alzheimer's at higher rates, because the problem is high glucose combined with high insulin. He points to drugs that remove glucose without adding insulin, such as metformin and SGLT2 inhibitors. Sayer says Dexcom's type 2 software focuses on daily feedback rather than nighttime alarms.

• Real-time feedback changes behaviour

Attia believes CGM improves outcomes even without a formal intervention, simply because it's hard to ignore how food, stress and sleep move the number. He finds the 7-day average and standard deviation, and the 90-day trailing average, more useful than single readings.

EXAMPLES

• Nighttime cortisol and morning glucose

Attia would go to bed at 93 mg/dL hours after dinner and wake at 105. Overnight urine cortisol tracked the rise. He now tells patients a fasting glucose of 100 versus 90 often reflects cortisol or liver glucose output rather than insulin resistance, though 130 is a different story.

• A1c can mislead

Attia has beta thalassemia minor, so his small red blood cells live longer. His lab A1c reads 5.6–6.0, in the prediabetic range, while his CGM-derived figure is 4.5–5.1. He says this has complicated his life-insurance applications.

• The airport trail mix he didn't eat

Stuck on a delayed flight, Attia bought a big bag of trail mix as a treat, looked at his glucose and put it away, certain he would have eaten it without the sensor. Sayer's worst spike, his only reading over 200, came 30 minutes after a cup of yogurt-covered raisins in Boston airport. He then dipped to about 60 before settling in the low 70s.

• Sixty finger sticks in a day

When a meter used in an FDA submission turned out to read high, Sayer bought three meters and pricked himself 20 times with each. Attia, who still calibrates his G6 daily and sees it match a finger stick to within a point or two, likes the OneTouch Ultra. Sayer's tip: wash your hands first, because a crumb of food can falsely raise the reading.

• What it costs without diabetes

Sensors last 10 days and come in boxes of three. Attia's office buys nine at a time, a roughly 90-day supply. They agree about $9 a day is right for paying out of pocket. Sayer says a prescription is required and most insured patients pay a 20% copay; he wouldn't guess at a future wellness price.

OTHER RELEVANT

- **Context changes the curve**
  Attia says the same pasta produces very different responses 30 minutes after a hard workout than without exercise, and that poor sleep and high-carb dinners track with higher glucose.
- **Older-sensor caveat on acetaminophen**
  Acetaminophen pushed G5 readings high; Sayer says Dexcom studied large doses and the G6 no longer carries that warning.
- **Let kids fail**
  Sayer, a father of five, once told a coach to cut his son so he would learn something. He says people often learn more from failure than success, a lesson he applies to leading Dexcom.

#41–Jake Kushner, M.D.: How to thrive with T1D and the valuable insights that can benefit anyone

Guest: Jake Kushner
Date: 2020-01-08 · Duration: 2:07:30
URL: https://www.youtube.com/watch?v=sz-zwJqlm88

KEYPOINTS

• Type 1 diabetes is common and often missed.

Kushner says about 1 in 300 people have type 1 diabetes, typically diagnosed around age nine. He calls it the most common life-threatening, medication-requiring illness of childhood, meaning one to three new diagnoses a year in a typical school. Its incidence has roughly doubled since 1960. At Boston Children's he was the first clinical fellow in 10 years to specialize in it, instead of the rare metabolic diseases academic medicine tends to prize.

• It is a slow autoimmune loss of the pancreas's insulin-making beta cells.

Beta cells make up only about 5% of the pancreas, in islets surrounded by digestive tissue. As they release their unique antigens, autoimmunity can spiral and destroy them over time. No single virus has been proven to cause it. Kushner says higher body weight raises risk at the population level but predicts poorly for individuals. It could either strain beta cells or expose autoimmunity that would otherwise have stayed hidden.

• Genetics raises risk but leaves most children unaffected.

HLA genes are a major factor. A tenfold family risk turns 1 in 300 into about 1 in 30, which still gives about a 97% chance a child won't develop it. Identical twins share it only about 50–60% of the time early on, rising toward 80% by adulthood, according to George Eisenbarth's cohort. Kushner once treated identical twins where only one had it, and knew a family in which all three sons had it.

• The DCCT showed that tighter glucose control prevents complications.

Beginning in the mid-1980s, roughly 1,400 patients at a cost of about $100 million, which Kushner says should be checked, went from an A1c of about 9% to 7%. Centers crowdsourced methods on conference calls. The trial was stopped at about seven years because the eye and kidney benefits were too large to withhold. The downside was more hypoglycemia and weight gain, as patients ate carbohydrates to treat lows.

• Seven years of tighter control still paid off decades later.

After the trial both groups drifted to an A1c of about 8%, yet over the next 23-plus years the former tight-control group had less major kidney disease, less cardiovascular disease and fewer deaths. Kushner recalls about a third fewer primary cardiovascular events. He notes that people with type 1 who gained the most weight since the DCCT era have had somewhat worse cardiovascular outcomes, a weak association.

• Volatility is the core problem, and blaming patients makes it worse.

Kushner says the same meal can need very different insulin depending on stress, sleep, exercise and the fat and protein in it, so fixed insulin-to-carb formulas fall short. He calls the label 'noncompliant' grotesque. Attia compares chasing glucose readings to a beginner pilot fixated on the instruments, which causes overcorrection back and forth, instead of watching the horizon.

• Diabetes distress is huge and often unspoken.

On a 1–10 distress scale, Kushner says teenagers with type 1 diabetes for five years or more on high-carb diets typically score 7–8. Some with an A1c near 14 break down in tears because no one had asked. Because the distress feels normal to them, they assume life just 'sucks'. He has seen patients go from an A1c over 14 to under 7 and be astonished at how differently they could think and feel.

• Bernstein's 'law of small numbers' reshaped Kushner's practice.

Richard Bernstein, who has type 1 diabetes, is still practicing in his 80s and was one of the first to test glucose at home. He argues that fewer carbohydrates mean less insulin and therefore smaller mistakes. His Diabetes Solution recommends low-carb, higher-protein eating, not a ketogenic diet, with longer-acting insulin to cover protein and fat. Kushner estimates about 10 grams of protein act like roughly 6 grams of carbohydrate, with a delay of hours.

• Strict keto and SGLT2 inhibitors carry particular risks in type 1 diabetes.

Without beta cells, nothing limits ketone production. Attia fasting for a week peaks around 6–7 mM BHB, while acidosis begins around 10–14 mM, so Kushner calls prolonged fasting probably a bad idea in type 1. Off-label SGLT2 inhibitors can cause diabetic ketoacidosis with normal glucose (euglycemic DKA), including deaths. Kushner discloses he has consulted on one of these drug programs.

EXAMPLES

• Insulin price: about $25 versus $300–400

Kushner says a 1,000-unit vial cost about $25 when he was a fellow and now costs $300–400 in the US, compared with about $25 in Spain. He blames a federal government that acts as a 'promiscuous customer', paying whatever sellers ask.

• Attia's box of Mini-Wheats

Attia ate a whole box, got a splitting headache and saw his glucose reach about 170 mg/dL, the highest he had seen in years. Kushner compares this to a child with type 1 diabetes eating two cupcakes unseen at a birthday party.

• Kushner's family went low-carb

About four years before the interview, his wife cleared refined carbohydrates out of the pantry. He now suspects he is in ketosis much of the time. Attia recalls Kushner's low-carb patients averaging an A1c of about 5.7% with fewer lows.

• Hour-long clinic visits

Kushner began seeing patients from 4:30 p.m. for as long as needed, mostly asking open-ended questions. Some teenagers with an A1c of 10–14, headed for heart attacks at 35, spent five visits just building trust before making changes.

OTHER RELEVANT

• Find peer support.

Kushner points to the TypeOneGrit Facebook group of Bernstein-method followers, who share CGM traces and meals, and to a Virta Health teleconference for low-carb type 1 clinicians.

• Know the warning signs of undiagnosed type 1 diabetes.

Apart from keeping a child closer to a normal BMI, which only helps at the margins, Kushner says parents can't do much to prevent it. Awareness among families and teachers matters because undiagnosed type 1 diabetes is dangerous.

• Use a CGM as a stand-in for insulin exposure.

Attia's dream measurement is total daily insulin output, which people with type 1 diabetes effectively get from what they inject. Without it, he works to minimize average glucose and glucose variability.

#33 – Rudy Leibel, M.D.: Finding the obesity gene and discovering leptin

Guest: Rudy Leibel
Date: 2020-01-07 · Duration: 2:20:41
URL: https://www.youtube.com/watch?v=EJHf-6vNLdk

KEYPOINTS

• Rudy Leibel was a chief architect of the leptin discovery story.
Peter spends the first hour-plus on how Leibel, with Jeff Friedman and others, moved from obese mouse genetics to the hormone that told the brain about fat stores. Douglas Coleman's Jackson Lab parabiosis and mutation work (ob/ob and db/db) set the biologic chessboard they then molecularized.

• ob/ob and db/db mice proved obesity could be single-gene and circulating-factor driven.
ob/ob lacked a circulating satiety signal; db/db failed to respond to it—classic ligand/receptor logic Coleman inferred before the molecules had names. That framed obesity as physiology, not merely moral failure. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Cloning the OB gene required teaching themselves molecular genetics.
Leibel and Friedman were not born CRISPR-native; they trained into the tools with their students because the physiologic question demanded DNA-level answers. The culture of Rockefeller/Columbia labs made that cross-training possible. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Leptin is a signal of fat mass to the hypothalamus and brainstem.
When fat stores fall, leptin falls, and the brain mounts hunger, energy conservation, and reproductive throttling. That explains why willpower alone fights a coordinated endocrine defense during weight loss. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Most common obesity is not simple leptin deficiency.
Rare congenital leptin deficiency is dramatic and treatable with replacement; garden-variety obesity often involves leptin resistance or overlapping pathways. Hype that 'leptin shots fix dieting' misreads the biology Leibel helped uncover. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Adipose tissue is an endocrine organ, not inert storage.
Rudy's career kept asking what fat communicates. Cytokines, leptin, and other adipokines change how medicine sees obesity-related diabetes and inflammation. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Zucker rats and lesion studies show many insults converge on overeating.
Peter's fascination with hypothalamic damage models meets Rudy's genetic ones: different injuries, similar hyperphagia phenotypes. The brain's weight-regulation circuitry is robustly defended and multiply vulnerable. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Set-point language is useful if held loosely.
Biology defends a range shaped by genes, environment, and history. Leptin's discovery gave that defense a molecular spokesperson without proving the range is destiny. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Discovery science needed both mouse husbandry and human curiosity.
Spontaneous Jackson Lab mutations plus careful phenotyping beat any amount of abstract theorizing. Rudy credits collaborators generously while Peter insists on his central coordinating role. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Clinical takeaway: respect physiology when counseling weight loss.
Expect hunger and metabolic adaptation; build environments and meds (when appropriate) that work with the leptin axis rather than shaming patients for biology. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

EXAMPLES

• Coleman ob/ob and db/db work
Parabiosis-era inference that a circulating factor and its receptor existed—roadmap for leptin and LEPR. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Friedman–Leibel cloning collaboration
Two PIs learning molecular genetics on the job to capture OB. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Congenital leptin deficiency contrast
Rare, dramatic, replaceable—versus common leptin-resistant obesity. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Hypothalamic convergence
Lesions and mutations funnel into similar hyperphagia, underscoring central regulation. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• First-hour deep dive
Peter structures the episode as a leptin detective story before broader obesity counseling. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

OTHER RELEVANT

- **Stop moralizing common obesity as simple gluttony.**
  Leptin biology shows a defended system; design treatment accordingly. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.
- **Do not buy DIY leptin therapy for typical weight loss.**
  Deficiency syndromes "` garden-variety resistance. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.
- **Anticipate adaptation during caloric deficit.**
  Hunger and energy conservation are features; plan protein, sleep, and activity to blunt them.
- **Support research literacy in patients.**
  Knowing the mouse history inoculates against fad hormone pitches.

#31 – Navdeep Chandel, Ph.D.: metabolism, mitochondria, and metformin in health and disease

Guest: Navdeep Chandel
Date: 2020-01-07 · Duration: 2:22:36
URL: https://www.youtube.com/watch?v=JGB4gHYSZzo

KEYPOINTS

• Mitochondria are signaling organelles, not just powerhouses

Nav Chandel, a Northwestern professor of medicine and cell biology, says every talk he gives carries the same title: mitochondria as signaling organelles. Besides making ATP, they release molecules such as hydrogen peroxide and cytochrome c that tell the cell whether to live, die, proliferate or mount an immune response. In the mid-1990s most researchers assumed mitochondrial oxidants only leaked out when the organelle was damaged.

• Reactive oxygen species are mostly messengers, kept low by dozens of enzymes

Chandel argues that superoxide and hydrogen peroxide, at physiological levels, carry information during exercise or when the immune system meets a virus or bacterium, and those responses are healthy, not pathological. Nature keeps at least 30 enzymes constantly mopping these species up so they stay at signaling levels. Only when they get out of control, or convert into more reactive forms, do they become lethal.

• High-dose antioxidants can blunt the benefits of exercise

He cites exercise studies where muscle biopsies show the beneficial genes that vigorous exercise switches on. In those studies, high-dose antioxidants switched that response off. His caveat is that these were high doses, probably not what most people take. His reading is that the muscle may use hydrogen peroxide as the stress signal, so quenching it removes the message.

• Cytochrome c release is a key step in programmed cell death

Chandel's early work centred on how mitochondria help decide a cell's fate. Proteins called BAX and BAK make pores in the mitochondria, letting the 13-kilodalton protein cytochrome c escape and set off a caspase cascade that kills the cell. He notes that 22 years later the basic finding still stands, which is rare in biology. A drug targeting a protein that controls this release is used to make cancer cells more sensitive to treatment.

• The mitochondrial genome is small but holds the respiratory chain's critical parts

The nucleus holds about 20,000 genes, while mitochondrial DNA holds 37, including 13 that are essential for the respiratory chain to work. Complex I alone has 45 protein subunits, a few of them encoded in mitochondrial DNA.

• Mitochondrial decline with age may not be rate-limiting, and could even be adaptive

Data show less mitochondrial DNA, more deletions and lower maximal oxidative capacity with age. But Chandel says we use maybe 10–20% of maximal capacity at rest and 40–50% in hard efforts. When his lab knocks a mitochondrial protein down from 100% to 50%, they see no pathology even under stress. He admits he is 'way out in outer space' here, but he sees no evidence that healthy tissue is limited by its mitochondria. Supplements to 'boost' them rest on dogma.

• Metformin works in three main places: the liver, the gut and immune cells

Metformin is taken up selectively. It reaches the liver and kidney but not the heart very well, and it accumulates heavily in the gut, which is one reason some users get diarrhoea. The liver accounts for its glucose-lowering effect, and the colon for its effects on the microbiome. Chandel thinks the overlooked site is immune cells such as macrophages, where dampening inflammation may matter most.

• Metformin partially inhibits complex I and shifts the NAD+/NADH ratio

By partly blocking complex I, metformin slows the conversion of NADH to NAD+, slightly lowers the charge of the mitochondrial 'battery' and slows the TCA cycle. Chandel stresses the ratio of NAD+ to NADH, not the absolute amount of NAD, as the key readout. That separates metformin from NAD supplements, which he believes raise total NAD without much change to the ratio.

• Tumors need working mitochondria, despite the Warburg story

The classic view held that cancer cells rely on glycolysis, as seen in lactate production and glucose uptake on FDG-PET, so targeting glycolysis would spare normal tissue. Chandel argues that glycolysis is necessary but so is robust mitochondrial function. In most cancers, disabling the TCA cycle or respiratory chain prevents tumors from forming. A Science paper by Vander Heiden, Cantley and Thompson about a decade earlier reframed Warburg's observation as serving growth rather than energy.

• NAD precursors mostly end up in the liver

Attia describes a Cell Metabolism paper from Josh Rabinowitz's group: orally given NR or NMN were taken up heavily by the liver, which made plenty of NAD there, but little reached other cells. Chandel thinks NR's plausible effects are metabolic actions in the liver, somewhat like metformin's, plus possible uptake by immune cells. He labels both as hypotheses and notes NAD is not his core expertise.

EXAMPLES

• The yeast enzyme experiment that isolated metformin's anticancer mechanism

Yeast has a single protein that converts NADH to NAD+ like complex I but does not pump protons, and metformin cannot bind it. Chandel's lab put this yeast enzyme into human cancer cells grown in mice. Without it, metformin shrank tumors; with it, the mitochondria kept working and tumors did not shrink. The 2014 work suggests complex I inhibition is necessary for the anticancer effect, beyond lowering insulin and IGF-1.

• Metformin changed TCA-cycle metabolites in human ovarian tumors

Jason Locasale at Duke analysed tumor biopsies from University of Chicago ovarian cancer patients given metformin by Ernst Lengyel's team. He found metformin reached the tumor and altered TCA-cycle metabolites as the complex I model predicts. Chandel thinks both mechanisms, lower glucose and insulin and direct tumor effects, act together, noting about two-thirds of cancers seem sensitive to insulin and IGF.

- **An orange a day covers vitamin C's real job**
  Chandel says vitamin C matters not as an antioxidant but as a cofactor for enzymes that control DNA methylation and gene expression. One orange a day, or one or two, is enough. Megadoses add nothing, and he mentions a lung cancer trial, he believes of vitamin E, in which antioxidant users did worse.
- **L-2-hydroxyglutarate as a marker of failing mitochondria**
  When the respiratory chain fails, NAD+ drops, NADH rises and cells make L-2-hydroxyglutarate (L2HG). People with a genetic defect who can't clear it develop serious pathology. Chandel wants to test whether L2HG rises in Parkinson's and Alzheimer's. Attia suggests cardiac bypass patients, who are hypoxic. Metformin is too weak a complex I inhibitor to trigger this.
- **Attia's two-by-two for supplements and drugs**
  Attia plots harm against benefit: picking up a quarter or a Bitcoin, in front of a tricycle or a train. Chandel agrees most antioxidants, such as CoQ10 and MitoQ, are quarters in front of tricycles, and many have little measurable bioavailability. He sees metformin as having much more potential. Still, he doesn't take it, because he won't take any drug before a rigorous clinical trial.

OTHER RELEVANT

- **Don't megadose antioxidants around training**
  If exercise adaptations depend on an oxidant signal, high-dose antioxidants may cancel part of what you trained for. The caveat from this conversation is that the evidence involves high doses, not ordinary diets.
- **Be sceptical of 'mitochondrial booster' supplements**
  Chandel's view that normal aging rarely makes mitochondria the bottleneck, plus the poor bioavailability of many such products, suggests little upside for a healthy person.
- **Watch chronic stress and cortisol**
  Chandel now pays more attention to stress than anything else, citing travel, grant pressure and family. He wishes free cortisol were easier to measure; it is mostly bound to albumin and cortisol-binding protein, so it is measured in saliva or urine.
- **Weigh unproven longevity drugs with your own rule**
  Chandel requires rigorous trials before taking metformin. Others argue they can't wait for trials. The episode frames this as a personal risk–benefit choice, not a settled answer.

#14 – Robert Lustig, M.D., M.S.L.: fructose, processed food, NAFLD, and changing the food system

Guest: Robert Lustig
Date: 2019-12-23 · Duration: 1:23:24
URL: https://www.youtube.com/watch?v=6FiYyk0-PWk

KEYPOINTS

• Fructose browns proteins about seven times faster than glucose.
Lustig walks through non-enzymatic glycation (the same chemistry that turns newborn rib cartilage white and 88-year-old cartilage brown). Glucose drives that aging reaction slowly; fructose accelerates it roughly sevenfold, stiffening proteins wherever the reaction lands—not only on the lysine that hemoglobin A1c assays read.

• Hemoglobin A1c misses much of fructose's glycation footprint.
Classic A1c chemistry hits position 1 on hemoglobin. Fructose prefers other sites (he mentions positions 66 and 110), which need research-grade tandem mass spectrometry. So a 'normal' A1c can coexist with heavy fructose exposure. That measurement gap is why uric acid and ALT become his practical fructose 'bio-toxicity' proxies in clinic.

• 'Normal' ALT and uric acid ranges have drifted upward with the population.
When Lustig entered medical school in 1976, ALT's upper limit of normal was about 25; by the recording it had crept to the low 40s because labs set ranges from two standard deviations around a fatter, fattier-liver mean. Peter wants patient ALT below ~20–25; both want uric acid nearer 5–5.5 mg/dL even when the lab calls 7.0 normal.

• Fructose raises uric acid and blood pressure in a dose-linked way.
More sugar intake !' higher serum uric acid. Meta-patterns Lustig cites: every ~10% increase in fructose consumption associates with about +2 mmHg blood pressure and roughly +10% stroke risk. Endothelial inflammation, not only LDL folklore, is part of the cardiovascular story he wants restored. Benjamin Franklin already linked uric acid to gout; Lustig updates that folklore with stroke and endothelial risk.

• Kids' median added-sugar intake is still enormous.
About 18 teaspoons per day (~90–94 g), down from older estimates near 120 g as the obesity epidemic changed awareness. Roughly half of children's added sugar hides in foods people do not think of as dessert—bread, pasta sauce, pretzels—and about half of what children do see as sweets sits in candy, cake, ice cream and drinks.

• Infant sweet preference is plastic; savory acceptance takes far more exposures.
Lustig cites work suggesting savory foods may need on the order of a dozen introductions before acceptance, while sweet lands faster. His own daughter met Capri Sun at a birthday party after years of milk and water; the industry designs for taste-bud downregulation that keeps pulling intake upward.

• NAFLD exploded in pediatrics alongside sugar, not just calories.
He saw his first pediatric NAFLD case in 1996 (ALTs in the 300s) and his first pediatric type 2 diabetes in 1992; by the podcast era about a third of new childhood diabetes diagnoses were type 2. De novo lipogenesis, long dismissed as a ~3% pathway after Hellerstein 1998, was shown by Donnelly in 2005 to account for roughly 25% of liver fat. Rare export defects (~1 in 10,000) cannot explain a ~40% NAFLD prevalence—the pathway math points at sugar-driven DNL.

• PNPLA3 risk alleles concentrate NAFLD in Latino populations.
About 19% of Latinos carry the homozygous GG polymorphism that turns a little dietary sugar into a lot of liver fat. He recalls figures like half of obese Hispanic boys showing NAFLD at the time he last checked—likely an underestimate.

• Every diet that works is real food; every diet that fails is processed food.
His clinic heuristic: if it needs a Nutrition Facts label, it has been processed. Broccoli, carrots, and meat-case cuts do not. Targets like '20 g sugar/day' matter less than removing the packaged matrix that delivers sugar plus fiber-stripped starch.

• Ten CPG companies control most of the calories.
Lustig's tally: about ten consumer-packaged-goods firms control roughly 85–90% of the calories Americans eat. After high-fructose corn syrup and the late-1970s dietary guidelines era, industry profit margins reportedly jumped from ~1% to ~5% per year—sugar became the business model, not an accident. He wants Medicare/Medicaid costs yoked more tightly to farm-bill incentives so the metabolic bill shows up where food policy is written.

EXAMPLES

• ALT range creep: 25 !' ~42
Lab 'normal' tracked the population mean as hepatic steatosis became common (Dallas Heart Study–era estimates that ~40% of 'normal' people have liver fat). Clinical targets stayed near the 1976 line.

• Capri Sun birthday party
Daughter raised on milk and water meets pouches at age five; Lustig uses it to show how quickly the sweet environment recruits kids parents thought they had protected.

• Donnelly 2005 vs Hellerstein 1998
De novo lipogenesis reframed from a minor ~3% curiosity to ~25% of liver triglyceride—central to why fructose uniquely feeds NAFLD. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• PNPLA3 GG in ~19% of Latinos
Same sugar load !' disproportionate hepatic fat; ethnicity-aware counseling, not one-size nutrition advice. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Almond calorie absorption
Of ~160 labeled almond calories, roughly three-quarters may be absorbed; fiber and food matrix change the insulin and

fructose story versus juice with the same sugar grams.

OTHER RELEVANT

- **Treat ALT <25 and uric acid ~5–5.5 as action lines.**
  Do not wait for the lab flag at 42 or 7.0 if metabolic risk is the question you care about.
- **Strip packaged sugar before micro-managing macros.**
  If there is a Nutrition Facts label, interrogate added sugar and refined starch first; real-food patterns (regardless of named diet) are what Lustig sees work.
- **Protect kids' taste environment early.**
  Delay sweet drinks and pouches; keep introducing savory foods patiently. Epigenetic and preference programming in childhood is 'the gift that keeps on giving.'
- **Policy has to meet science—science alone has not moved the CPG oligopoly.**
  Lustig got a Master of Studies in Law because educating clinicians was only half the fight; farm-bill and labeling levers matter when ten firms set the default food supply.