Peter Attia MD Keypoints — Nutrition, Gut Health & Fasting

Peter Attia MD Keypoints

Episodes in this pack: 17

380 The seed oil debate: are they uniquely harmful relative to other dietary fats?

Guest: Layne Norton
Date: 2026-01-19 · Duration: 2:25:58
URL: https://www.youtube.com/watch?v=iB49uq-t1UM

KEYPOINTS

• This was meant to be a pre-registered 'courtroom' debate; when the opposing expert withdrew, Attia steelmanned the anti-seed-oil case himself.

Over about a year, both sides were to pre-submit every paper so nothing could be asserted that couldn't be checked live. Attia stated his lean upfront: he doesn't see much here. Norton noted his own possible bias ran the other way—he trained in a low-carb-leaning lab and was funded by the National Dairy Council, Cattlemen's Beef Association and Egg Board.

• Attia framed four arguments that seed oils are uniquely harmful.

(1) Some old RCTs that swapped saturated fat for polyunsaturated fat lowered cholesterol but not mortality. (2) Linoleic acid makes LDL more oxidisable and fuels arachidonic-acid inflammation. (3) Industrial refining—heat, hexane—adds harm. (4) Evolutionary mismatch: linoleic-acid availability rose from under 3% of food to roughly 10%, and tissue levels more than doubled.

• The 'harmful' RCTs are confounded by trans fat from margarine.

In the Minnesota Coronary Experiment (1966–73, ~9,000 institutionalised patients), the polyunsaturated arm used corn oil and margarine. Margarine then contained about 25–40% trans fat, which is clearly atherogenic and now effectively banned. Each 30 mg/dL fall in total cholesterol came with roughly 22% higher mortality. Results waited about 13 years for publication. Patients could also check themselves out of wards, and average exposure was only 1–2 years.

• Saturated and trans fats pack straight, making stiffer particles; cis double bonds kink and loosen them.

Trans bonds keep chains straight like saturated fat but still carry an oxidisable double bond—'the worst of both worlds.' Membrane fluidity matters downstream for LDL-receptor recognition and for how readily particles aggregate in the artery wall.

• When trans-fat-confounded trials are removed, swapping PUFA for saturated fat reduces risk.

Lumping all trials together gives a null effect. Ramsden's reanalysis removing omega-3-confounded trials shows a trend to harm—but still includes trans fat. A 2017 analysis excluding trans-fat trials found roughly 29–31% lower risk. Norton insists on 'logical symmetry': if you remove one side's confounders, remove the other's.

• Mendelian randomisation shows lifelong LDL exposure is causal and dose-dependent.

About a dozen variants affecting LDL clearance, production or absorption all give the same effect. Each 1 mmol/L (~39 mg/dL) lower LDL brings about 50–55% lower cardiovascular risk, with R above 0.9. That consistency makes pleiotropy unlikely. CETP variants underdeliver because cholesterol falls more than apoB. The same genetics showed LDL has no causal link to cancer.

• Statins give ~22% per mmol/L, not 50%, because of timing, not hidden harm.

Statins usually start around 40 or later, after decades of exposure; genetic variants act from birth. Norton uses compounding-investment and 'truck rolling downhill' analogies. He runs LDL around 150 despite a high-fibre, low-saturated-fat diet, and started a statin at 40.

• Linoleic acid doesn't measurably raise arachidonic acid or population heart disease.

Cohorts of roughly a million people, and tissue biomarker studies that avoid recall error, link higher linoleic acid to lower cardiovascular disease. Conversion to arachidonic acid seems saturated, so eating more doesn't feed forward. Healthy-user bias would blunt a harm signal, not flip it to protection.

• Oxidation mostly happens inside the artery wall, so fewer particles getting in beats slightly more oxidisable particles.

Under 1% of plasma LDL is oxidised; particles clear in hours and plasma is rich in antioxidants. Once apoB-particles under ~70 nm cross the endothelium and bind proteoglycans, an estimated 30–80% may oxidise over weeks. PUFA-rich LDL is fewer in number, less prone to apoB modification, and less prone to aggregation than saturated-fat-rich LDL. Saturated-fat LDL is acted on by sphingomyelinase, making ceramides that drive clumping. Antioxidant trials failing fits this picture.

• Refining residues are far below harmful doses, and refining actually lowers oxidation products.

Hexane boils at about 69 °C and is steam-stripped under vacuum. Residues run around 0.05–0.5 ppm, often undetectable. Norton calculates about 11,340 kg of oil at once for even mild hexane effects, and hexane doesn't bioaccumulate. Refining cuts peroxides 5–10-fold and lowers aldehydes. It adds about 0.5% trans fat and some polymerised triglycerides.

• The ancestral argument cuts both ways.

Modern beef isn't ancestral either, and cardiovascular disease rose largely because people now live long enough to get it. The Hadza, our best ancestral proxy, have LDL around 50–70 mg/dL, with only one individual found above 100. 'Natural' isn't a reliable guide to longevity.

EXAMPLES

• Sydney Diet Heart Study

About 500 men after a heart attack moved from 16% saturated fat and 6% PUFA to 10% and 15%, using safflower oil and safflower margarine. There were 37 deaths versus 28 (CI about 1.03–2.8), the only significant harm signal, again with heavy trans fat.

• Rose Corn Oil trial

About 80 patients, with cardiac deaths of 1 (control), 3 (olive oil) and 6 (corn oil); hazard ratio 4.64, CI 0.58–37. Olive oil 'tripling' deaths shows the noise.

• Finnish Mental Hospital Study

A crossover of two hospitals, about 1,200 people, six years on each diet: 9% saturated and 14% PUFA versus 18% and about 4%. No trans or omega-3 confounding; about 41% fewer cardiovascular events. Weakness: randomised by hospital, not individual.

- **LA Veterans study and STARS**
  About 850 veterans for nearly nine years showed 18% lower risk (CI 0.56–1.21). STARS tracked plaque progression rather than events.
- **Frying-oil caveat**
  Thin layers of oil, or oil reused all day, generate oxidised and trans products within 20–30 minutes. A 5 cm depth oxidises far more slowly than 1 cm.

OTHER RELEVANT

- **If you avoid seed oils, still cut saturated fat**
  Use olive or avocado oil and leaner proteins, eat plenty of fibre, and measure apoB.
- **Don't treat lard-fried fries as health food**
  Both options are poor; marketing 'tallow' or 'no seed oils' mainly persuades people to eat more. Neither guest could say which is worse for occasional fries without trial data.
- **Mind the substitution effect**
  Cutting seed oils often helps because you cut chips, cookies and junk sauces—not because of the oil. Canola in a home salad dressing is fine.
- **Major in the majors**
  Norton notes Americans average about 3,500 kcal a day and under 20 minutes of activity. Obesity, fitness and strength carry far larger mortality effects than oil choice. Attia's verdict: we're 'majoring in the minor.'
- **Read the study, not the hot take**
  Weigh converging lines of evidence—mechanisms, cohorts, clean RCTs and Mendelian randomisation—over any single surprising trial.

375 - The ketogenic diet, ketosis, and hyperbaric oxygen: weight loss, cognition, cancer, and more

Guest: Dominic D'Agostino
Date: 2025-12-08 · Duration: 2:25:27
URL: https://www.youtube.com/watch?v=jW0cVEgW9YY

KEYPOINTS

• Dom D'Agostino came to ketosis through Navy oxygen-toxicity research

Navy SEALs use closed-circuit rebreathers with near-100% oxygen to avoid bubble trails, but below about 50 feet oxygen toxicity becomes possible and at ~100 feet a diver may seize within minutes. Oxygen acts as a stimulant: it drives glutamate release, inhibits the enzyme converting glutamate to GABA and bursts reactive oxygen species. Because ketogenic diets control seizures when drugs fail, D'Agostino pivoted to ketones; Duke trials now push volunteers in chambers to an EEG seizure and compare latency under dietary, supplemental or combined ketosis.

• Nutritional ketosis is defined by blood BHB above 0.5 mM

Fasting suppresses insulin, mobilizing fatty acids that the liver turns into beta-hydroxybutyrate and acetoacetate, which fuel the brain. The original epilepsy diet was ~90% fat; modern versions are 60–70% fat with more protein, because restricting protein stunted kids' growth. D'Agostino calls it the most researched diet with an objective biomarker, with 'pleiotropic' effects on metabolism, neuropharmacology and epigenetics.

• Ketogenic therapy works where seizure drugs fail

In drug-resistant pediatric epilepsy about two-thirds respond; of those roughly a third get 95–100% control, and 10–15% are 'super responders' who stay seizure-free after one or two years on the diet. Adults respond less (~30–40%), partly adherence. In brain slices, sodium BHB silenced evoked seizure activity and made neurons more resilient to toxins.

• For weight loss: high protein, fiber-carbs, and count calories

D'Agostino's mistakes list starts with not tracking. He recommends 20–30% protein (he eats up to ~220 g at 220 lb), up to 50–100 g carbs if about a third is fiber (broccoli, cauliflower, avocado, cucumber, asparagus — not carrots, tomatoes or most peppers), and a 10–20% calorie deficit. Tracking apps showed him eating ~4,000 kcal when he believed 3,200; 'calories don't matter on keto' is false.

• Watch lipids and certain genotypes

A strict keto diet sent his LDL and apoB soaring; he has an NPC1L1 variant, so a small dose of ezetimibe controls it. He's seen LDL and triglycerides rise and HDL fall in some people, especially APOE4 homozygotes, and urges tracking ApoB, LDL, triglycerides, HDL, A1c and insulin. Early on, cutting protein from ~250 g to 70–80 g cost him strength.

• Esters, salts and 1,3-butanediol are not the same thing

1,3-butanediol, a NASA-era food preservative, is metabolized by alcohol dehydrogenase like ethanol; ~150–200 mL/day for therapeutic ketosis doubled his liver enzymes over two weeks and can make people 'drunk stupid'. Esters bind BHB or acetoacetate to butanediol for a fast double peak. Salts ionically bind BHB to sodium, potassium, calcium and magnesium; he argues hypertension risk is tied to sodium chloride, not sodium BHB.

• Rapid ketone spikes trigger insulin and crashes

Rising above about 1.5–2 mM quickly prompts a counter-regulatory insulin release; two hours after a big ester dose people can be both hypoglycemic and low in ketones. Salts don't produce that effect in his experience. He says higher isn't better: above 2–3 mM from supplements approaches 'energy toxicity' and acidosis, and animals above 6–7 mM on some esters died. 1 mM BHB supplies roughly 10% more brain energy.

• D- and L-BHB behave differently

Meters and continuous ketone monitors measure only D-BHB. D is burned quickly for fuel; L is metabolized three to four times slower, accumulates in the brain and retains signaling effects such as NLRP3 inflammasome suppression. Pure D-BHB monoester didn't help seizures in his models; a 1:1 BHB-acetoacetate mix (redox balance) did.

• Cancer: a metabolic adjunct, still lacking trials

A 49-author framework led by Thomas Seyfried proposes a glucose-ketone index of 1–4 plus drugs targeting glucose and glutamine for glioblastoma. Pressed by Peter, D'Agostino concedes it won't cure GBM, the goal is extending survival, and there are no RCTs; funding now favors adjuncts to CAR-T and checkpoint inhibitors. Peter suggests pancreatic cancer may be a better first model.

• Alzheimer's: a fuel-rescue rationale with patient selection

Brain glucose use declines with age while ketone uptake is preserved (Stephen Cunnane's dual PET work). Acute ketone elevation improves cognition in impaired people, but long-term randomized amyloid outcomes are pending; D'Agostino would select patients with marked glucose hypometabolism.

EXAMPLES

• Keto Start salts on a road trip

One packet (6–10 g BHB, ~1 g electrolytes, 50/50 D/L) kept his measured D-BHB at 1–2 mM for four to six hours with sharp focus; true total may be roughly double. His wife advises the brand; he says he has no financial stake.

• Carbs in Greece, six pounds lighter

Tripling or quadrupling carbs on a Greek trip while swimming and walking daily, he came home six pounds lighter — evidence, he says, of metabolic flexibility.

• The Newport case and AC-1202

Samuel Henderson's 2008 caprylic-triglyceride product improved MMSE scores; Mary Newport gave her husband coconut and MCT oil, documented in a long case report co-authored by Veech.

• Hyperbaric oxygen protocol for acute concussion

Within 48–72 hours: about 2 atmospheres, 60–90 minutes, 3–5 days a week, up to 40 sessions. Peter calls that 'a job' and remains on the fence; soft chambers reach only ~1.3 ATA.

- **USF's $30 million sham-controlled trial**

  A DoD study in veterans with PTSD and brain injury uses a sham that pulses pressure at start and end, with assessors checking blinding, because a prior DoD study used hyperbaric air as control and both arms improved.

OTHER RELEVANT

- **Track food, ketones and lipids**

  Use an app occasionally, measure blood (or breath acetone with something like Keto Air), and check ApoB, triglycerides and insulin.

- **Transition over four to six weeks and bridge with ketone electrolytes**

  Keto causes sodium and water loss and a brain energy gap; ketone salts can ease the 'keto flu' and practitioners report better adherence with a gradual start.

- **Aim for 1–2 mM, not more**

  Pair a salt with MCT for sustained levels; avoid big ester or butanediol doses, especially in elderly people or those with liver disease.

- **Use fasting situationally**

  He now does five-day 'sardine fasts' and fasts for focus days or flare-ups rather than as a daily default.

369 Rethinking protein needs for muscle and longevity, and the benefits of creatine & sauna use

Guest: Rhonda Patrick
Date: 2025-10-20 · Duration: 2:01:15
URL: https://www.youtube.com/watch?v=VhbpSc6pKRQ

KEYPOINTS

• The 0.8 g/kg protein RDA is a minimum based on flawed methods; the true floor is closer to 1.2 g/kg.
The RDA came from nitrogen-balance studies that suffer from incomplete urine collection, nitrogen lost by other routes, and varying nitrogen-to-protein ratios across foods. Stable-isotope studies using 13C-phenylalanine oxidation put the requirement 30–50% higher, around 1.2 g/kg. Surveys suggest adults average about 0.9 g/kg (men) and 0.8 (women)—at the flawed RDA, not the corrected floor.

• There's no amino-acid reserve except muscle.
Fat can be stored almost without limit and glycogen buffers carbohydrate, but skeletal muscle is the only amino-acid 'tank.' Falling short means breaking down muscle immediately—what Attia calls an unforced error.

• Anabolic resistance is driven more by inactivity than by age.
Given the same protein dose, adults 65+ get about half the muscle protein synthesis of young adults, so they need roughly double the protein for the same response. But older people who resistance-train respond like young people. Luc van Loon's one-leg-cast study showed the immobilised leg became anabolically resistant while the trained leg didn't. Only about 32% of adults, and 22% of older adults, resistance-train.

• Sarcopenia arrives in steps, not as a smooth slope.
Population curves average out what individuals experience: a surgery, fall or flu causes weeks of immobility and muscle loss that older people never fully regain. Repeated hits push people past a 'disability threshold.' Attia says frailty, alongside cognition, largely determines the quality of your last decade, so build muscle 'headroom' at 40–60.

• Above 1.2 g/kg, more protein still adds lean mass, with diminishing returns.
Stu Phillips' meta-analysis of about 49 resistance-training trials found adding protein up to roughly 1.6 g/kg gave about 27% more lean-mass gain and 10% more strength than training alone. Benefits taper toward ~2.2 g/kg—Phillips' 'wringing a washcloth' analogy. Intakes around 3 g/kg add little, but neither guest knows of human data showing harm in healthy people.

• Attia's rule: aim for 2 g/kg so your bad days still land at 1.6.
Real life means missed meals and pasta nights. Because the downside of falling short is larger than the upside of overshooting, aiming at 1.6 means bad days fall to 1.2 and aren't made up. He notes David Allison's public call for harm data has met 'crickets.' The worst result he's seen is that high-protein IV nutrition in ICU patients showed no benefit—not harm.

• Use target body weight, not current weight, if you carry a lot of excess fat.
A 300 lb person whose healthy weight is around 220 should calculate from 220. Higher needs apply in calorie deficits and body recomposition ("e2.2 g/kg), heavy training, pregnancy and adolescence.

• The mTOR fear misreads where leucine goes in active people.
Only calorie restriction and rapamycin extend life in yeast, worms, flies and mice, both by lowering mTOR, and leucine strongly activates mTOR. But exercise increases leucine transporters so amino acids go into muscle, where you want mTOR on. Lab mice are sedentary, warm, fed freely, and never face catabolic illness. Attia likens mTOR to inflammation or cortisol: on when needed, quiet otherwise.

• Creatine: 5 g/day saturates muscle; 10 g/day may be needed to raise brain levels.
The body makes about 1–2 g a day and meat supplies more; vegetarians benefit most from supplementing. About 5 g a day saturates muscle in 3–4 weeks without loading. It works by recycling ATP so you can do more reps—it doesn't build muscle for a couch potato. Patrick cites a German dose-response study where brain creatine rose only at about 10 g, because muscles take up the first 5 g. Studies using 5 g may wrongly show no brain effect.

• Creatine's cognitive benefits show up mainly under stress.
Gains appear with sleep deprivation, exams, aging or neurodegeneration—the brain uses about 20% of calories at under 2% of body weight. Small studies show sleep-deprived subjects given about 20–25 g kept, or even beat, baseline processing speed. A pilot gave 20 g in Alzheimer's patients with improved cognition. Patrick says the literature is still small and you can't hang your hat on it.

EXAMPLES

• Attia's recomposition year
Eating one meal a day for calorie restriction, he still drank whey shakes outside the window. That kept him in a calorie deficit but an amino-acid surplus.

• Tirzepatide in Attia's practice
About 15–20% of patients use it, with DEXA scans before and after. He favours slow, steady low doses—most benefit by 5–7.5 mg—and avoiding yo-yo cycling. Two lean patients with unexplained beta-cell dysfunction saw near-normal glucose-tolerance tests within about three months on 2.5 mg without weight loss.

• Creatine gummies
Third-party testing found essentially no creatine in about 95% of gummy products. Patrick looks for NSF certification; Creapure is fine but not essential.

• Sauna and dementia (Finnish data)
Laukkanen's cohort linked 4–7 sessions a week at about 175–179 °F for 20+ minutes to roughly 66% lower dementia risk than once weekly. A separate Finnish study found higher risk among people going above ~200 °F, around 212 °F.

• Hyperthermia for depression

Charles Raison's single session raising core temperature about 2 °C produced an antidepressant effect lasting six months versus a sham. Ashley Mason's 4–8 sessions in a head-out infrared bed (~85 minutes) are extending that work.

OTHER RELEVANT

• Practical protein targets

Never go below 1.2 g/kg. Aim for about 1.6–2.2 g/kg if training, older, dieting or on a GLP-1, where easy-to-digest shakes help.

• Practical creatine use

Take creatine monohydrate powder, 5 g doses in water, about 10 g a day; Patrick uses 15–20 g when jet-lagged. Kids: about 0.1 g/kg. Ask your doctor for cystatin C, since creatine raises creatinine and can falsely suggest kidney trouble.

• Sauna dose

About 175–180 °F for 20 minutes several times a week raises heat-shock proteins about 50%. A hot bath at about 104 °F, shoulders down, for 20 minutes is comparable. Infrared at about 140 °F likely needs roughly double the time. Attia dropped from ~190–200 °F after hearing the >200 °F dementia signal, and a sauna hat helps.

• Exercise remains the master lever

Protein and creatine support training, not replace it. Olympic athletes, often eating "e2 g/kg, live about five years longer than average.

368 The protein debate: optimal intake, limitations of the RDA, & whether high-protein is harmful

Guest: Dr. David Allison
Date: 2025-10-13 · Duration: 2:01:10
URL: https://www.youtube.com/watch?v=k2qZT8OQRjc

KEYPOINTS

• Protein is the latest macronutrient to be demonized, in a predictable cycle of food villains.
Obesity researcher and methodologist David Allison (now at Baylor's Children's Nutrition Research Center) says food carries culture, identity, religion and economics, so people keep hunting for 'angels and demons' among fat, carbs, seed oils, phytoestrogens and now protein. Enthusiasm for protein is driving sales, which provokes people who dislike others 'taking the easy way out'. Both he and Peter disclose ties to David Protein; Allison also lists beef and pork industry funding.

• The 0.8 g/kg RDA was a nitrogen-balance survival threshold, not an optimum.
It came from nitrogen balance studies in lean, sedentary young men weighing about 65–70 kg. Nobody claimed it was ideal or an upper limit. A 1928 Polish study kept two young adults in nitrogen balance for 6 months on almost nothing but potatoes, without diabetes or weight gain, but that says nothing about older adults, pregnancy, injury recovery or training. Allison's conclusion: almost nobody should aim for just the RDA.

• Allison's target for thriving: about 2 g/kg/day, spread across meals.
He sees three zones: too little; a 'known superior' zone up to roughly double the RDA, with no evidence of harm in any group except rare cases like PKU or a specific protein allergy, even in kidney disease; and above about 2 g/kg, more uncertainty and diminishing returns but no demonstrated downturn. Peter's clinic advises 1.6–2 g/kg (about 1 g per pound), and settles for about 1.2 for lifelong vegetarians who struggle to get more. Don Layman would add roughly 30 g per meal.

• 'Trustworthy' depends on data, methods and logic, not on who funded the work.
Allison separates being trusted (others' judgment) from being trustworthy (process). Critics without good arguments turn to ad hominem attacks and innuendo. He argues scientists should aim to build trust in the scientific process, even at the cost of losing particular arguments.

• Nutrition trials are chronically underpowered because food isn't patentable.
Drug trials enroll tens of thousands because patents and FDA requirements justify billions in spending; nutrition RCTs are tiny by comparison. Allison guesses total US spending on research into the effects of food, across all commodity groups and companies, is under $1 billion a year. That's why most nutrition scientists piece together industry and government funding. He'd shift money from expensive observational epidemiology, which yields little new information, to randomized trials.

• Studies showing a plateau in muscle protein synthesis are misread when applied to trained people.
Untrained people max out muscle protein synthesis at lower intakes, just as a sedentary person gains hugely from three 30-minute workouts a week that would do almost nothing for Peter. Allison's analogy: using such data to cap protein is like telling a student 10 minutes of algebra a day is enough to master it. The ICU parenteral-nutrition trials showed no mortality benefit from more protein, but no harm either, and don't generalize to people shopping for dinner.

• No compelling human evidence shows higher protein causes harm, so the burden of proof should shift.
Observational studies point both ways and protein intake is heavily confounded by social class. Allison also distrusts mouse data: benefits of protein and calorie restriction show up mostly at 22 °C, which is chronic cold stress for a mouse, rather than at thermoneutral 27–30 °C. His black-swan argument: after searching thousands of ponds with drones and binoculars without finding a black swan, it's reasonable to stop worrying about them for practical purposes.

• 'Ultra-processed' is a social construct that's too broad to describe what a food does in the body.
The NOVA classification lumps meal-replacement shakes, Big Gulps and IV nutrition together. Allison quotes food scientist Joe Schwarcz: a substance's effect 'depends on its molecular structure, not its ancestry'. Nearly everything is processed (pasteurized milk, cheese, wine), and 'natural' foxglove and hemlock are poisons. Avoiding ultra-processed food might work as a rough rule of thumb, like shopping the perimeter of the store, but it says nothing about cause. He prefers David Kessler's 'ultra-formulated'.

EXAMPLES

• A Frito-Lay–funded snack trial.
Allison's group compared chips and snacks fried in corn oil, low-fat versions, and traditional saturated/trans-fat versions. With calories controlled, the corn-oil versions came out best on cardiovascular biomarkers, saturated/trans fat was worst, and low-fat was worse for triglycerides. Critics such as Marion Nestle attacked the funding rather than the design.

• Kelly Brownell's 1990s speech to food executives.
At a meeting convened by Michael Mudd of Kraft, Brownell said social change needs a villain, 'and guess who it is? You.' Allison sees that as the start of food-industry villainization, with 'ultra-processed' as its latest form.

• 'A heart attack on a plate'.
Michael Jacobson of the Center for Science in the Public Interest held up fettuccine Alfredo on national TV in the early 1990s. Allison's point: scientists who later say 'science evolves' should have expressed uncertainty in the first place.

• The Hall–Ludwig crossover debate.
Crossover designs, which give each participant both diets in sequence, save money and suit metabolic-ward throughput (Kevin Hall's case), but carryover effects can never be absolutely ruled out (David Ludwig's critique). Allison sides with accepting them as limited but valid evidence, as with epidemiology.

• Policy has mostly failed against obesity.
School programs, farmers markets, menu calorie labels, nudges and parent training show no large effects across meta-analyses. Smoking policy succeeded partly because you can quit smoking entirely but can't quit eating. Allison's long-shot research bets are general education, financial security and parenting, citing Moving to Opportunity and the Abecedarian study.

OTHER RELEVANT

- **Aim for about 1.6–2 g/kg/day, spread across meals.**
  The RDA is a passing grade, not an A. Above about 2 g/kg there are diminishing returns and opportunity costs: money, attention, and crowding out foods like fruit or the carbohydrate that fuels training.
- **Judge a study by its population.**
  Before applying a finding to yourself, ask whether you're bigger, older, more trained or chasing a different goal than the people studied.
- **Judge foods by composition and calories, not processing labels.**
  High-protein bars and shakes aren't harmful because they're processed. Any rule of thumb only helps while you actually stick to it, and marketers will route around it. Allison's own favorite protein: chicken gizzards.
- **Low-dose GLP-1 drugs may become a population-wide default.**
  Allison raises a polypill-like idea of broad, subsidized access to GLP-1 drugs, given how limited non-drug public health measures have proven.

324 Metabolism, energy balance, and aging: the impact of diet, calorie restriction & macronutrients

Guest: Eric Ravussin
Date: 2024-11-04 · Duration: 2:18:52
URL: https://www.youtube.com/watch?v=UVGBfrfPq98

KEYPOINTS

• Metabolic chambers measure energy expenditure with remarkable precision.

Ravussin, who spent 15 years at the NIH intramural program and 2.5 years at Eli Lilly before 24 years at Pennington Biomedical Research Center in Baton Rouge (about 500 researchers, roughly $80 million a year), explains indirect calorimetry: measuring oxygen consumed and CO2 produced reveals total calories burned, and the ratio (respiratory quotient) shows fuel—about 1.0 for carbohydrate, 0.7 for fat, ~0.82 for protein. Pennington validates its chambers against each other within 3% for O2 and CO2.

• Body weight is regulated, and energy intake dominates.

As weight creeps up, resting metabolic rate and the cost of moving rise, partly braking further gain. Ravussin himself went from 69 kg when he married in 1975 to about 77 kg. Still, from the 1980s to 2010 the average American gained about 10 kg (22 lb)—a tiny daily imbalance compounded over 30 years. He sees intake, not expenditure, as the main driver.

• People differ substantially in metabolic rate even after adjusting for size.

In measurements of about 150 people's 24-hour energy expenditure and resting metabolic rate, large variability remained after accounting for body composition—one reason identical diets yield different results.

• Exercise alone is a weak weight-loss tool because appetite compensates.

Peter notes an hour of hard cycling burns about 750–800 kcal, but eating quickly afterward can easily add 1,000 kcal in 20–30 minutes. Ravussin says generic advice like 150 minutes a week of moderate-to-vigorous activity 'doesn't work in general' for weight loss, though exercise has other major benefits and early-life habits matter.

• Macronutrient swaps barely change energy expenditure.

In a tightly controlled metabolic-ward study discussed in the episode (~16 people housed for a month with frequent chamber stays), switching from roughly 45–50% to under 10% carbohydrate at equal calories increased expenditure by only around 100 kcal/day—statistically significant but below the ~150 kcal hypothesized. Ravussin notes the body holds only about 500 g of glycogen (~100 g in liver, 300–500 g in muscle).

• Ultra-processed food may drive overeating via protein dilution.

Ravussin notes ultra-processed foods are about 12–13% protein versus the 15–18% we need. Under the protein-leverage hypothesis—first shown in insects and rodents—we keep eating until we hit a protein target, overshooting calories when protein is diluted.

• Biosphere 2 sparked the CALERIE study.

From 1991–93 eight people lived sealed in Biosphere 2; food ran short and they lost about 15% of body weight, with physician Roy Walford—author of a calorie-restriction textbook—among them. Ravussin found their energy expenditure stayed about 200 kcal/day below predicted, evidence of metabolic adaptation, and later partnered with Walford.

• CALERIE tested 25% calorie restriction for two years in non-obese adults.

Participants were women 21–47 and men 21–50 with BMI 22–27.9. More than 5,000 were screened to enroll about 225, randomized 2:1 to 25% restriction or ad libitum. Retention was spectacular: about 95% in controls and 82–85% in the restriction group. The main grant was $10.4 million in 2003, later about $13 million.

• Actual restriction fell short of 25% but still produced meaningful weight loss.

Measured with doubly labeled water, restriction was about 20% for the first 6 months, about 15% at one year and about 12% averaged over two years—cutting roughly 500–600 kcal from about 2,400. Weight loss averaged about 12% at one year and 10.4% at two.

• CR improved markers of 'secondary aging', with hints on primary aging.

Healthy participants saw remarkable improvements in cardiometabolic risk markers, inflammation (including hs-CRP) and other measures, plus signs of more efficient mitochondria and reduced thymic fat. Whether primary aging slows is uncertain.

• Open questions: muscle, sarcopenia and lasting effects.

Peter asks what happens to muscle mass decades later if lean people stay 10–12% lighter into their 70s and 80s; Ravussin says we don't have an answer. A CALERIE Legacy study is following participants from 2005–08 to see if any benefit persisted; many still use what they learned.

• Self-reported diet data are a core weakness of nutrition science.

Ravussin and Peter discuss how food-frequency questionnaires and recall are unreliable. Newer studies use tools such as a small camera mounted on glasses to record what people eat; one module of a large study involves about 10,000 people, with daily records over 10-day periods. Peter asks whether samples are banked for future biomarkers; Ravussin sees AI and better tools transforming how intake is measured and enabling more personalized nutrition and public policy.

EXAMPLES

• The six-month pilot

Four arms: ad libitum, 25% CR, 25% deficit split between 12.5% CR and 12.5% more exercise, and a low-calorie diet (about 800 kcal) to lose 10% then maintain.

• Peter's view on CR

Peter says no health benefit would justify the unhappiness of cutting calories 20–25% for him personally; Ravussin notes some participants loved watching body fat fall, e.g., from 15% to 12% on DEXA.

• The CR Society

About 200 self-imposed calorie restrictors exist; Ravussin is familiar with but hasn't studied them.

- **A cheap study**
  $13 million on a roughly $28 billion NIH budget is under a tenth of a percent, Peter notes, for one of the most important human CR trials.

- **Living in 2024**
  Peter: he'd rather be the most average person in 2024 than the most important person in 1400—our obesogenic environment is the cost of abundance.

OTHER RELEVANT

- **Focus on intake for weight; exercise for health.**
  Exercise is invaluable but easily out-eaten; plan post-workout meals rather than eating fast.

- **Prioritize protein.**
  Aiming for adequate protein may curb overeating, particularly in diets heavy in ultra-processed food.

- **Don't expect metabolic magic from low-carb.**
  Macronutrient shifts move expenditure by perhaps 100 kcal/day; adherence and total intake matter more.

- **Consider moderate, sustainable restriction.**
  Even ~12% CR improved markers in healthy people, but watch muscle mass and quality of life.

- **Expect metabolic adaptation after weight loss.**
  Biosphere 2 and CALERIE both showed expenditure falling more than body-size changes predict; maintaining loss requires planning for that lower budget.

314 Rethinking nutrition science: obesity treatment, GLP-1 agonists, protein, & better research

Guest: David Allison
Date: 2024-08-19 · Duration: 2:06:56
URL: https://www.youtube.com/watch?v=ilMWQBb_qVY

KEYPOINTS

• Decades of obesity research have produced little public-health progress.
Allison, a statistician and obesity researcher who began his career around 1991 at the New York Obesity Research Center, says clinical treatment improved moderately but public-health efforts achieved virtually nothing. Peter uses an aviation analogy: if planes fell from the sky more often every decade, nobody would claim we understood aerodynamics—yet obesity has risen steadily despite enormous effort.

• The 'epidemic' was declared from NHANES data in the early 1990s.
NHANES III (roughly 1988–94) midpoint data released around 1991 showed what looked like a jump and the word 'epidemic' took hold. Allison notes skinfold data show less of a jump and an earlier, more gradual rise; historical data on 18th-century British naval cadets, French cadets and Civil War soldiers help show long-run trends.

• The environment changed, not our genes.
People ate ad libitum 50, 100 or 200 years ago without today's obesity rates, so something environmental shifted. Peter notes type 2 diabetes rose by roughly a log-fold in his lifetime. Allison points to multiple plausible contributors, including air conditioning—a buffet is more tempting at 110°F in Austin if you're cool indoors—and is wary of single-cause zealotry, including from low-carb advocates.

• Classic public-health tools like 'nudges' have shaky evidence.
Eat-less-move-more messaging, school programs and nudges have weak data. Cluster-randomized school-based childhood obesity trials tend to be quite poor in quality. After repeated failures, Allison argues, we should say 'enough' and change approach.

• GLP-1 success forces a paradigm shift—but we didn't get fat from a GLP-1 shortage.
The drugs work, which some in public health resist because it seems to imply lifestyle doesn't matter. Allison wants a balanced approach: pharmacology plus realistic environmental change, while studying the mechanisms we still don't fully understand. Long-term safety is uncertain because no one has taken them for 40 years.

• Risk means uncertainty, not just known probabilities.
Following FDA thinking, Allison stresses safety involves unknowns. That shapes the debate over whether someone 'subjectively 10 pounds overweight' should take GLP-1s versus someone with a BMI of 40 and diabetes, where benefits clearly outweigh unknowns.

• Peter declines GLP-1s for himself despite their appeal.
He'd love to be 10 pounds lighter and never hungry, and the drugs improve glycemic control, but after watching many patients he doesn't accept side effects like the heart-rate increase for a cosmetic goal; for 40 pounds of medically significant excess, he'd take it 'any day of the week'.

• 'Healthy food' depends on the goal.
Someone wanting to be 10 pounds thinner, lift 10 more pounds or live 10 years longer may need different diets, so Allison dislikes blanket healthy/unhealthy labels.

• Protein needs are probably above the RDA, but thresholds are uncertain.
The RDA of 0.8 g/kg probably isn't optimal. Allison questions claims that 20–30 g per sitting is required to be anabolic—a sigmoid curve is plausible but not proven. A study co-authored by Luc van Loon using up to 100 g suggested the old 40 g ceiling may apply only to fast-digesting whey.

• Upper limits for protein are poorly established.
Claims that more than about 3 g/kg risks kidney damage in healthy people rest on thin evidence. 'Rabbit starvation' reports go back a century; one or two men ate only meat for 6–12 months and were fine, and a 1928 study put two Polish men on nothing but potatoes for six months, also fine—'semi-anecdotes', not RCTs.

• Physics-style humility: we may not understand obesity mechanisms for decades.
Allison compares obesity science to other fields where progress was steady because the underlying science (physics, chemistry) kept improving and being applied. He imagines a future, perhaps 30 years out, where obesity rates fall back toward levels of 50–100 years ago—driven partly by drugs—even while we still don't fully understand the mechanisms, much as the 1970s 'population bomb' fears were defused by agricultural advances rather than by the solutions people then proposed.

• Bias in trials is subtle and often misunderstood.
Allison distinguishes genuine bias from selection inherent in a goal—being cut from a basketball team for being short isn't 'bias' because height is intrinsic to basketball. In nutrition RCTs, he urges clear definitions before labeling a study biased, and notes funding source alone doesn't determine quality.

EXAMPLES

• Danish conscripts
Denmark recorded heights and weights of virtually every 18-year-old male conscript for over 100 years—a rare long-run dataset on obesity trends.

• Feeding-tube experiments
Classic 1960s studies by Theodore Van Itallie and Sami Hashim let people feed themselves through a tube without seeing how much they ate; obese and lean participants responded differently, informing ideas of appetite regulation.

• Viagra's origin

Allison recalls sildenafil was developed for something else, and erections were noticed as a side effect—an example of serendipity in drug discovery.

- **Trial costs and CROs**

  An RCT can cost from over $100,000 to far more; pharma studies are usually run by hired contract research organizations, not the company itself.

- **Obesity and Energetics Offerings**

  Allison's free weekly curated list of about 100 links reaches over 100,000 people, accepts no commercial support and flags when findings are 'in mice'.

OTHER RELEVANT

- **Judge obesity interventions by data, not ideology.**

  Allison urges openness to drugs and to environmental change, and skepticism about cherished programs that haven't worked.

- **Match medication decisions to medical need.**

  The case for GLP-1s is strongest for significant obesity and metabolic disease; for small cosmetic goals, unknown long-term risks weigh more.

- **Aim above the protein RDA, spread across meals.**

  Higher intakes appear safe for healthy people, though minimal per-meal thresholds aren't firmly proven. 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.

- **Read nutrition headlines skeptically.**

  Ask whether it was in mice, observational or a well-run randomized trial. 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.

299 Optimizing muscle protein synthesis: protein quality and quantity, & the key role of training

Guest: Luc van Loon
Date: 2024-04-22 · Duration: 2:38:39
URL: https://www.youtube.com/watch?v=AVOKWvYJM-c

KEYPOINTS

- **Muscle stays responsive to training and protein at any age.**
  Van Loon, a professor at Maastricht University in the Netherlands who has spent around 30 years and about €30 million in research funding on muscle and protein, says you don't need to start at 40 to have good muscle at 80—muscle remains responsive at 70 and even past 100, though starting earlier is better.
- **Stable isotope tracers reveal what happens to the food we eat.**
  Carbon-13 has an extra neutron and is stable. Feeding labeled carbohydrate shows its oxidation via exhaled 13CO2; labeled amino acids such as phenylalanine show incorporation into muscle. His lab even produced 'intrinsically labeled' milk and meat by infusing tracers into cows—one experiment cost more than €50,000 in tracer.
- **Exogenous carbohydrate oxidation tops out around 60–70 g per hour from glucose.**
  Glucose alone is oxidized at about 1–1.1 g/min; adding fructose, which uses a different transporter, can push it to 1.3–1.4 g/min in high-output athletes. Glycogen storage is roughly 100–200 g in the liver and 300–350 g or more in muscle, though trained athletes can store more.
- **Your body recycles far more protein than you eat.**
  You synthesize about 300 g of protein daily but eat perhaps 70–100 g, so roughly 230 g of amino acids are recycled from your own tissues each day. Muscle proteins are fully turned over in about 50–100 days—'in 50 to 100 days you have a new arm'.
- **The '20 grams per meal' figure comes from whey studies—and may underestimate needs.**
  Studies found 40 g of whey didn't stimulate muscle protein synthesis more than 20 g over about four hours, so 20 g became the standard on packages. Body size matters (more for 120 kg, less for 50 kg), and with mixed whole-food meals, 30–40 g per meal may be more appropriate.
- **A 100 g protein dose showed the 'ceiling' isn't real over longer periods.**
  In his study comparing 0, 25 and 100 g of intrinsically labeled protein (mostly casein—milk is about 80% casein, 20% whey), the 100 g dose produced a larger and much longer anabolic response over 12 hours, and oxidation of excess protein had been overestimated. Digestion of a full meal takes 2–3 hours, versus peak amino acids within 30–75 minutes from a shake.
- **Typical intake is modest; targets for muscle gain are higher.**
  Healthy Americans eat about 1.1–1.3 g/kg/day; Peter suggests 1.6 g/kg or more for building muscle. Spreading it—20 g at breakfast, lunch, dinner and an evening snack—reaches about 80 g for a typical person.
- **Presleep protein uses the overnight fast.**
  Dinner at 5–6 p.m. and breakfast at 8–9 a.m. leaves about 15 hours without food, a period of muscle loss risk—'that's stupid'. Protein ingested before sleep, even delivered via nasogastric tube at 2 a.m. in early studies, is digested and incorporated overnight. Evening exercise plus 40–60 g of protein boosted overnight synthesis.
- **Disuse rapidly destroys muscle, and hospital nutrition makes it worse.**
  Immobilizing a leg loses about 220 g of muscle in a week, with declines in oxidative capacity. Healthy elective-surgery patients ate only about 0.5 g/kg during four hospital days—a third of guidelines (ASPEN suggests 1.2–1.5)—and lost about 1.4 kg. Of people over 65 with hip fracture, 15–30% die within a year, and about half of survivors never regain prior function.
- **Older muscle shows anabolic resistance.**
  Michael Rennie's group coined 'anabolic resistance' around 2005; van Loon's lab took nearly 10 years to confirm it. Older adults need more protein per meal and resistance exercise to get the same response, though cross-sectional young-versus-old comparisons limit conclusions.
- **Glycogen recovery and endurance fueling have been rethought.**
  Van Loon notes that with adequate carbohydrate, glycogen can be fully restored after exercise, unlike the old beliefs Peter grew up with as an endurance athlete. For ultra-long events, aiming for over 1 g per minute for 20 hours would be punishing on the gut, so practical intake is lower. Endurance cyclists perform hundreds of thousands of low-force repetitions at 80–100 rpm, none as hard as a heavy lift—different stimuli with different protein needs.

EXAMPLES

- **Peter's glucose during exercise**
  Peter recalls a test where his glucose started around 80 mg/dL and never went above 100 during hours of exercise while consuming carbohydrate, and insulin stayed under about 11—showing insulin-independent glucose uptake by working muscle.
- **Time-restricted eating pitfalls**
  Peter describes a 2–7 p.m. eating window (19-hour fast) that makes reaching 1.6–1.8 g/kg nearly impossible; van Loon suggests 25 g whey shakes at 8 and 11 a.m., then meals at 2 and 7 p.m.
- **Ten grams of essential amino acids**
  About 10 g of EAAs equals roughly 20 g of protein—consistent with dose-response studies.
- **Exercise insulin sensitivity**
  Effects of a session on insulin sensitivity last up to about 48 hours, which is why diabetics are advised to spread 150+ minutes across the week; van Loon considers that a minimum.

OTHER RELEVANT

- **Eat 30–40 g of protein per meal from whole foods.**
  Distribute across 3–4 occasions, including a presleep serving. 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.
- **Prioritize protein and movement during illness or hospitalization.**
  Even a few days of bed rest with low intake costs significant muscle. 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.
- **Start training at any age.**
  Muscle remains responsive into very old age; resistance training plus protein counters anabolic resistance.
- **Fuel long endurance efforts with mixed carbs.**
  Glucose-fructose blends allow higher carbohydrate oxidation, though GI tolerance limits very long events.
- **Don't fear 'excess' protein at one meal.**
  Van Loon's 100 g study suggests a large protein meal isn't simply wasted; the body extends the anabolic response. Still, for practicality he favors distributing protein, and his team calls a single 100 g dose an unrealistic amount for most people.

283 Gut health & the microbiome: improving and maintaining the microbiome, probiotics, & more

Guest: Colleen Cutcliffe, PhD
Date: 2023-12-18 · Duration: 2:48:48
URL: https://www.youtube.com/watch?v=th3UwC10EZU

KEYPOINTS

• The microbiome is seeded at birth, peaks early in life and loses diversity with age.

Colleen Cutcliffe is a biochemist who worked in pharma and DNA sequencing before co-founding the microbiome company Pendulum. She defines the microbiome as all the bacteria, viruses, fungi and yeasts living in and on us. The womb is nearly sterile. Initial seeding comes largely from passage through the birth canal, then breast milk, food and environment expand diversity. Diversity peaks around the years 'when you could eat whatever you wanted,' then declines with age. She considers the '10-to-1' ratio of microbes to human cells questionable. Their importance lies in what they produce, not their numbers.

• There aren't really 'good' and 'bad' bugs. Context decides.

Bacteria are independent organisms that can divide every 10–15 minutes, so they evolve fast. That speed drives antibiotic resistance, but it also lets your gut community adapt to what you feed it. After a week of eating abroad your microbiome can look very different. Many healthy people carry Clostridioides difficile at low levels without harm. Peter compares this to calling cholesterol 'good' or 'bad.' The Human Microbiome Project, a one-time snapshot of more than 10,000 people, showed people differ hugely at the strain level, with more overlap in function.

• Butyrate from fermented fiber is one of the most important things gut microbes make.

In the oxygen-free distal colon, bacteria ferment fiber we can't digest into short-chain fatty acids, ultimately butyrate. Colon cells are the only cells that use butyrate as their main fuel, and low butyrate is associated with poor colon health, including colon cancer. Butyrate also triggers receptors on gut L cells that release GLP-1. Colleen says recommendations are roughly 20–30 g of fiber a day, far above what most Americans eat. Peter notes his daily green drink supplies vitamins and polyphenols but not meaningful fiber.

• C. diff shows the power of restoring a gut ecosystem.

Antibiotics act like 'a nuclear bomb' on the microbiome. If a resistant C. diff strain survives, it multiplies unchecked and can become fatal. More antibiotics cure it only about 70% of the time, by Colleen's figure. Fecal microbiota transplant (FMT) re-establishes competition and succeeds about 99% of the time. Colonoscopic delivery works better than capsules, likely because freeze-drying loses diversity. She says the FDA once tried to halt FMT but reversed course after an outcry from patients and doctors. The risks: unknown pathogens, and donors' metabolic traits may transfer, including case reports of new obesity after transplant.

• FMT is a 'messy drug.' The goal is to isolate the strains that matter.

Transplants from lean to obese mice, or human microbiomes into mice, reliably shift body weight, and FMT has been tried in type 2 diabetes. But a single donor's stool changes with travel, diet and antibiotics, so dosing can't be standardized. Pendulum's premise was to identify specific beneficial strains and manufacture them reproducibly. Akkermansia is a strict anaerobe that a single oxygen exposure can kill. Contract manufacturers kept sending back dead batches, so the company built its own roughly $10 million plant.

• Many probiotics barely deliver live organisms.

Most products contain Lactobacillus and Bifidobacterium, which tolerate some oxygen and are easy to grow. Manufacturing involves growing cultures in large vats, centrifuging, then freeze-drying, which kills a large share: for hardy common strains Colleen estimates about 50–80% survive, and early on her company sometimes lost 90%. Cheap capsules may dissolve in stomach acid, while enteric-coated or time-release capsules reach the gut. She argues CFU counts can overstate live, active cells, so Pendulum reports 'active fraction units' (AFU) counted by flow cytometry. Its products should stay refrigerated.

• Akkermansia drives GLP-1 release in three ways.

Akkermansia muciniphila, linked to bariatric surgery work by Lee Kaplan at MGH, has a surface protein (Amuc_1100) that signals L cells via TLR2. It secretes a protein called P9 that stimulates L cells, and it makes propionate, which Clostridium butyricum and related strains convert to butyrate, activating receptors that trigger GLP-1. It also maintains the gut's protective mucus layer. Unlike injected semaglutide, this would produce meal-timed, physiological GLP-1 pulses, so Peter and Colleen agree it wouldn't produce drug-level weight loss.

• The company's 76-person pilot trial found modest glucose benefits, with clear caveats.

Colleen describes a double-blind, placebo-controlled pilot in people with type 2 diabetes, with three arms. Over 90 days, a five-strain formula including Akkermansia lowered A1C by about 0.6 points versus placebo and reduced glucose spikes on an oral glucose tolerance test by 34%. A subset without Akkermansia didn't reach statistical significance. Diet wasn't logged. After a 30-day washout, about 15–20% kept Akkermansia levels. Colleen is the company's CEO. The product costs about $165 a month, a lower-dose version $49. Further data are mostly customer reports, an unblinded cravings pilot, and about a dozen investigator-led trials using donated product.

EXAMPLES

• The hyena researcher.

An antibiotic hunter convinced of hyenas' antibiotic-rich mouths refused antibiotics after being bitten, signed waivers, and reportedly never got infected.

• Diet soda swaps.

Peter has seen some patients' weight and metabolism improve after replacing six daily Diet Cokes with soda water, while his wife thrives on one every other day. Colleen calls evidence on sweeteners and the microbiome conflicting and proposes crossover trials.

• Akkermansia predicting diet response.

In a study of a high-fiber diet that Colleen cites, people starting with more Akkermansia improved more in BMI, waist-to-hip

ratio, A1C and weight. The finding is correlational.

- **Estrogen recycling.**
  Some gut microbes remove the tag marking estrogen for excretion, potentially raising circulating levels. Colleen calls microbiome-menopause research very early.

OTHER RELEVANT

- **Eat much more fiber.**
  Vegetables, fruits and well-delivered fiber supplements feed butyrate-producing strains.
- **Treat antibiotics as a major disruption.**
  Use them when needed, but recognize they can wipe out the gut ecosystem.
- **Scrutinize probiotic claims.**
  Look for human trial data, live-cell delivery and appropriate capsules. Very few supplements are tested.
- **Weigh the source.**
  Much of the product discussion comes from the company's own founder and its small pilot study. Larger independent trials are still pending.

224 Dietary protein: amount needed, ideal timing, quality, and more | Don Layman, Ph.D.

Guest: Don Layman
Date: 2022-09-26 · Duration: 2:14:12
URL: https://www.youtube.com/watch?v=BqmG2y4IeY8

KEYPOINTS

• Muscle is an organ of metabolism as well as movement

Don Layman, a professor emeritus of nutrition, grew up on a farm in the 1950s and has studied protein and muscle for decades. He sees muscle as doing two jobs. The first is mobility: most people who die after 65 die from some consequence of immobility, such as falls, fractures or hospitalization. The second is metabolism: skeletal muscle is the main site of insulin action and holds 75–80% of the body's glucose storage capacity. From that view, he says, you should plan a diet around muscle and around protein first.

• The RDA is a minimum to prevent deficiency, not an optimal intake

The 0.8 g/kg RDA comes from short nitrogen-balance studies, often seven days long, in college-age students. The method measures nitrogen and multiplies it by 6.25, assuming protein is 16% nitrogen, so it counts anything containing nitrogen. The estimated average need is then raised by two standard deviations to cover about 97.5% of people. Layman says every essential amino acid also has metabolic roles at intakes far above that minimum. Leucine activates mTOR, arginine supplies nitric oxide, lysine feeds carnitine, and cysteine is used to make glutathione.

• Protein quality varies widely

Animal proteins and most isolates, including soy isolate, are about 95% or more digestible, while raw plant sources may be only 60–70% available. On DIAAS, the digestibility-corrected quality score, Layman ranks whey isolate at about 100%, a ribeye at about 96%, soybeans at about 80% and shredded wheat at about 40%. A cereal label claiming 4 g of protein is still just nitrogen × 6.25. Of roughly 7,000 foods in the USDA database, about 4,000 have amino acid profiles and fewer than 300 have DIAAS scores. Layman is working on a simpler score based on three amino acids: leucine, lysine and methionine.

• At high enough intake, the protein source matters less

Layman's rule of thumb: at about 120 g of protein a day, the split between animal and plant probably doesn't matter, because you will cover your essential amino acids. At 50 g it matters enormously. So a plant-based eater aiming for about 125 g is probably fine, while a vegetarian eating 56 g is 'going to get in trouble'.

• Older muscle is less responsive, but more protein can make up for it

Muscle proteins turn over with half-lives of roughly 15–16 days. The body makes about 300 g of new protein a day while most Americans eat about 80 g (women about 70, men about 90), so most of it is recycled. With age, a given dose of protein triggers less synthesis than it does in a 16-year-old. Layman says raising intake from 0.8 to about 1.6 g/kg can bring a 65-year-old's muscle protein synthesis response up to that of a 20-year-old.

• Protein is an absolute need, so never set it as a percentage of calories

A 75-year-old woman eating 1,200 calories still needs about 100 g of protein, which is 35–40% of her calories. Setting fat at 30% and carbohydrates at 50% and leaving protein with the remainder gets it backwards. Layman says you should set protein first and build the rest of the diet around it.

• The first meal of the day matters most

After an overnight fast, protein synthesis is suppressed and muscle is catabolic until a meal provides about 3 g of leucine, which is roughly 30 g of high-quality protein. Layman advises 40–45 g at the first meal and again at the last meal, with smaller amounts between. In his study of people averaging 37 years old, 90 g split 30/30/30 beat 10/20/60. He now thinks the ideal might have been closer to 40/10/40.

• Big meals aren't wasted, but muscle has a ceiling per meal

You will digest and absorb 100 g of protein at a meal, despite the myth. However, muscle can use only about 25–60 g of it per meal depending on quality, and the liver uses the rest. Total daily protein still matters. A very large lifter needing 250 g would do better with four or five meals than two, but Layman says that's about total supply rather than the leucine–mTOR signal.

• Higher-protein diets help weight loss mostly by preserving lean mass

Layman's trials ran from 12 weeks to 16 months, the longest multicenter one with about 120 subjects. Calories were equal, and the higher-protein group lost about 8 lb more, roughly 6.5 lb of it fat. He estimates an energy advantage of about 170 calories a day, enough to explain the difference. For anyone over 40, losing lean mass during weight loss matters, and he says that's when protein becomes critical.

EXAMPLES

• Ruminants upcycle protein

For every 60 g of low-quality plant protein and nitrogen a ruminant eats, Layman says it can produce about 100 g of protein with a balanced amino acid profile. He uses this to argue that cattle play a role in producing quality protein.

• Peter's shoulder surgery

Unable to squat or deadlift after shoulder surgery, Peter lost 10 lb in three weeks, some of it water. Five months later he still hadn't fully regained his muscle mass, and he uses this to show how quickly muscle is lost and how hard it is to rebuild.

• Plant 'milk' and plant 'meat'

Layman points out that many nut milks have about 1 g of protein per 8 oz versus about 8 g in cow's milk, and he calls labelling them milk 'pure deception'. On plant-based meats like Beyond and Impossible he has limited knowledge. Lab-grown meat is described as unlikely to be feasible on energy, cost and sanitation grounds.

• Kids need small amounts

Children grow efficiently on snacks of 8–10 g of protein. A small child may need only about 40 g a day, so parents needn't push adult-sized portions.

- **Why industry funds this research**
  Layman explains that NIH has generally left applied food research, such as comparing whey and soy, to industry. That forces researchers to turn to dairy councils and other industry bodies for funding.

OTHER RELEVANT

- **Front-load protein**
  Make breakfast, or your first meal, 40–45 g of quality protein, and do the same with your last meal.
- **Count grams, not percentages**
  Set an absolute daily target (Layman cites about 1.6 g/kg for older adults) and build meals around it. This matters most when cutting calories.
- **Be skeptical of epidemiology on 'high' protein**
  Studies often call 1.2 g/kg 'high' and define low as under 0.8 g/kg or 10% of calories. 'High-protein' groups also often eat more calories overall, so protein is 'along for the ride'.
- **If plant-based, eat more total protein**
  Aim for about 125 g a day and choose higher-quality sources to cover leucine and lysine.

222 How nutrition impacts longevity | Matt Kaeberlein, Ph.D.

Guest: Matt Kaeberlein
Date: 2022-09-12 · Duration: 2:43:50
URL: https://www.youtube.com/watch?v=4sqyGwqyAao

KEYPOINTS

• Human nutrition science is structurally hard to do well.
Kaeberlein and Attia note that because people age so slowly, longitudinal studies of today's 70-year-olds rely on data and methods from 40 years ago; much nutritional epidemiology is decades old. Both have grown less dogmatic: healthy people eat very different diets, from protein-hungry ancestral patterns to ketogenic diets, often sharing little besides leafy vegetables.

• Calorie restriction is the oldest, most robust longevity intervention in animals.
Experiments date to the early-to-mid 1930s. In mice, CR extends lifespan substantially — the largest effect Kaeberlein has seen is about 65% restriction producing about a 65% lifespan increase in Weindruch and Walford's graded study. CR mice also have less age-related disease and preserved function in heart and immune system, which he finds more compelling than epigenetic clocks.

• CR has real costs to muscle and strength.
Calorie-restricted mice lose body weight and grip strength — normalized grip strength drops on the order of 30–35%. Attia argues few humans would view losing 30% of weight and 30% of strength as good; Kaeberlein agrees the human trade-off is uncertain.

• The monkey studies disagreed.
The Wisconsin rhesus study (2009) reported CR animals outlived controls with fewer age-related diseases; the NIA study (2012) found no lifespan difference. Wisconsin controls ate a diet with about 28.5% of calories from sucrose, a key reason for the divergence; a later reconciliation paper tried to explain it. The 30–40-year experiments can't realistically be repeated. Kaeberlein reads the overall monkey data as suggestive that CR improves health in primates, with the lifespan question unresolved.

• Much of the 'fasting' benefit may be calorie restriction — and vice versa.
Lab CR mice eat their ration quickly, so they also fast most of the day. Studies that fed mice continuously found about two-thirds of CR's benefit came from fewer calories and one-third from the fasting period. Kaeberlein's 2021 Science review argued much intermittent-fasting and time-restricted-feeding literature conflates the two.

• Starting CR late helps far less; rapamycin works late.
Most evidence suggests CR started past about 15 months in mice (like a 40–50-year-old human) yields little benefit. In a 2019 study of 800 female mice switched between diets, late CR had small effects. By contrast, the NIA Interventions Testing Program — rapamycin nominated by Dave Sharp — found robust lifespan extension starting at 20 months, about a 60–65-year-old human, published 2009.

• mTOR inhibition didn't cause the expected muscle loss.
Because mTOR drives muscle protein synthesis, researchers expected rapamycin and CR to accelerate sarcopenia. Lab animals didn't show that, though Kaeberlein cautions against extrapolating.

• Protein restriction extends lifespan in mice, but humans are another matter.
Restricting total protein or specific amino acids — methionine, tryptophan, branched-chain amino acids — extends mouse lifespan, possibly via different mechanisms, including FGF21 released on low-protein diets. Steve Simpson's nutritional-geometry work explored these ratios.

• Protein needs probably rise with age.
In the Levine/Longo epidemiological study, lower protein was associated with lower mortality before 65 but higher mortality after. Because death rates climb nonlinearly after 65, Attia's own modelling suggested high protein's net mortality benefit begins around 50. Attia targets about 1 g per pound of body weight — over twice the 0.8 g/kg RDA — in roughly four 40 g meals.

• IGF-1 is probably not very informative after about 50.
An IGF-1 receptor antibody in old mice (Nir Barzilai and Yousin Suh) gave roughly a 14–15% median lifespan extension. But Attia argues that a fit person with slightly higher IGF-1 and a younger immune system likely has lower total cancer risk; lowering IGF-1 from high levels may cut cancer risk without the reverse being symmetric.

• Function and exercise matter most.
So-so epidemiology suggests 30–50% of exercise's full benefit comes from going from nothing to about 15 MET-hours per week. Attia emphasizes that frailty dominates life after 75: living to 100 cancer-free is pointless if you're an invalid for 25 years.

EXAMPLES

• Intermittent ketogenic mice
One lifelong ketogenic diet study in mice showed no lifespan effect, but an intermittent version — keto every other day or every few days, normal diet otherwise — gave about a 15% increase.

• Organ shrinkage with fasting
Within 24 hours, fasted mice show dramatic reductions in organ size followed by rapid regrowth on refeeding — also seen in fasting-mimicking diet work.

• The 80/20 principle
Attia credits Tim Ferriss for the idea of getting 80% of results with 20% of effort — relevant to nutrition, where getting basics right matters more than fine-tuning.

• Whole foods vs. protein bars
Kaeberlein argues eating a simple whole food is inherently less risky than a protein bar with 14 ingredients, given how little is known.

• Reverse-feeding experiment

Attia asks whether anyone has fed CR and control mice at the same frequent intervals — every two hours — to remove the fasting component. Kaeberlein says at least one study did something similar, which is where the roughly two-thirds calories / one-third fasting split comes from; he stresses this is mouse data and human eating patterns differ.

OTHER RELEVANT

- **Don't rely on calorie restriction for longevity.**
  Mouse benefits are large when started young, but human costs in muscle and strength may outweigh gains, especially in midlife.
- **Prioritize adequate protein as you age.**
  Spread protein through the day; Attia's 1 g/lb target is his practice, not a universal prescription.
- **Be skeptical of fasting hype.**
  Benefits attributed to time-restricted eating may largely reflect eating fewer calories. 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.
- **Build function now.**
  Even modest exercise captures a large share of the benefit; strength and fitness protect against late-life frailty.
- **Judge interventions by function, not just biomarkers.**
  Kaeberlein prefers evidence that a heart or immune system still works like a young one over shifts in epigenetic clocks or lab markers, which may not translate to outcomes.

205 - Energy balance, nutrition, & building muscle | Layne Norton, Ph.D. (Pt.2)

Guest: Layne Norton
Date: 2022-05-02 · Duration: 3:17:33
URL: https://www.youtube.com/watch?v=R-Ltg1dl2jM

KEYPOINTS

• Energy balance governs weight, but it isn't linear arithmetic.
Norton rejects the idea that burning 2,500 and eating 2,000 calories guarantees a pound lost per week indefinitely. Water, glycogen, gut contents and adaptive changes in expenditure distort the scale: a 200-lb person can read 196 or 204 on any day. He tells clients to treat it like the stock market and watch the trend.

• Not all calories you eat are absorbed or retained.
About 5–10% of energy is lost in faeces. The thermic effect differs by macronutrient: from 100 calories of fat you net about 97–100, from carbohydrate about 90–95, and from protein only about 70–80. Even celery has calories; there's no 'energy-negative' food.

• Resting metabolism is the biggest slice of expenditure.
For most people BMR is about 50–70% of total daily energy expenditure — about 55–60% for Norton. Indirect calorimetry estimates expenditure via the Weir equation, heavily weighted to oxygen consumption. Attia's measured BMR sits consistently around 1,900–1,950 calories.

• NEAT varies hugely and adapts.
Non-exercise activity thermogenesis explains much of why some people resist weight gain. In Levine's 1995 overfeeding study, people were fed about 1,000 calories above measured needs; one participant barely gained weight because spontaneous activity rose to compensate. After losing 10% of body weight, NEAT can fall by up to about 500 calories a day.

• Fitness trackers badly overestimate exercise burn.
A 2018 study of about 20 devices found they overestimate exercise energy expenditure by 28–93%, so a reported 500 calories might really be 260–400. Calorie intake is also routinely underestimated: 50 versus 20 grams of oil on a salad is invisible but adds hundreds of calories.

• Weight-reduced bodies fight back.
Formerly obese, weight-reduced people have lower BMR than never-obese people of the same size. Norton cites John Speakman's work on set-point ideas: evolution penalized getting too lean more than getting too fat, since famine was a real threat until the early 1900s.

• Habits matter more than the 'X's and O's'.
A systematic review of people who maintained weight loss found no single superior diet; consistent behaviours and habits mattered most. Many people do well Monday to Friday, then add pancakes, alcohol and poor choices on weekends.

• Ketogenic diets don't meaningfully raise expenditure.
The rigorous inpatient study run by Kevin Hall with Rudy Leibel, Eric Ravussin, Steve Smith and others found only a small increase on low-carb — about 57 kcal/day, near the detection limit — not the 250–500 promised. Above about 65–70% of VO2 max, ketogenic diets appear to impair performance.

• Protein needs for muscle are higher than the RDA, and the mTOR fears are misplaced.
Norton suggests about 1.6–2.4 g/kg of lean body weight to maximize muscle protein synthesis. He argues cancer-linked mTOR signalling stems from chronic, dysregulated insulin signalling in insulin resistance — not pulsatile rises after protein meals — and that 'high protein' in cancer meta-analyses often means just over 70 g/day or 1.2 g/kg.

• Train close to failure, not always to it.
Most sets for advanced lifters should be around RPE 7–8, a few at 9, rarely 10. Hypertrophy close to failure is similar to absolute failure, but failure creates disproportionate fatigue. A 6–15 rep range lets you accumulate volume efficiently.

• Muscle gain is slow even when done right.
Net muscle protein accretion is perhaps 5–10 grams a day at most; since muscle is about 70% water, that's roughly 26 lb of muscle per year as a theoretical ceiling, and much less in practice.

• Fat loss can be done in sprints.
Rather than one long diet, Norton cut back to his old 205-lb weight class over about a year using short fat-loss sprints — two or three weeks of an aggressive 750–1,000-calorie deficit — followed by breaks. For gaining, trained people put on lean and fat mass roughly 50/50 or 40/60, which is why he keeps surpluses small.

EXAMPLES

• The 50-year-old woman
A hypothetical 135-lb (about 60 kg) woman in menopause at 30–35% body fat eats only 50–60 g of protein a day. Norton would raise it to around 100–120 g, spread across meals, and aim for about 10 lb more muscle in two years — noting most people eat 65% of their protein at dinner.

• The trained 50-year-old man
For a 175–180-lb man in the low 20s body fat, Norton says 180–200 g of protein daily has no downside, with a slight surplus of 100–200 calories to gain muscle.

• Doubly labelled water vs. tracking
Norton's own tracked intake implied about 4,400 calories of expenditure; doubly labelled water measured about 4,200.

• Squatting to failure
Norton once squatted 480 lb for 14 reps, grinding the last so hard he couldn't rack the bar, and couldn't have managed another rep after 15 minutes' rest — fatigue far beyond the extra stimulus.

• Contest prep

He gets from about 14–15% to about 7% body fat, and the final push to very low levels takes 12–16 weeks because lean mass must be preserved; adipose tissue itself is about 13% lean tissue.

OTHER RELEVANT

- **Track trends, not daily weigh-ins.**
  Average weight over weeks before adjusting intake. 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.
- **Distrust tracker calorie numbers.**
  Don't eat back exercise calories based on a watch.
- **Prioritize protein and strength as you age.**
  Falls and frailty drive mortality after about 70–75; muscle and adequate protein protect against them.
- **Avoid proprietary blends.**
  Choose third-party-tested protein powders; 'nitrogen spiking' with cheap amino acids or creatine can inflate protein claims. Take creatine — about 5 g a day — on its own.
- **Watch weekends and alcohol.**
  Weekend eating can erase a weekday deficit. 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.

#156-Jake Muise: Humanely harvesting axis deer while alleviating its impact on Hawaii’s ecosystems

Guest: Jake Muise
Date: 2021-04-05 · Duration: 2:33:49
URL: https://www.youtube.com/watch?v=Fy1dMjULbXo

KEYPOINTS

• Axis deer are an invasive species reshaping Hawaii.
Muise, founder of Maui Nui Venison, explains that in 1868 King Kamehameha V had the deer brought from India, with the first animals arriving on Oahu and then Molokai. By 1898 newspapers estimated 7,000 deer already decimating upland forests. Lanai received deer in the 1920s and Maui in the 1960s, and private individuals secretly introduced them to the Big Island around 2010–2011.

• Their reproduction produces 'hockey stick' growth.
Gestation is about 238 days, similar to humans, and the population can grow roughly 33% a year. Of the roughly 15,000 animals Maui Nui has harvested and measured, about 89% of females were lactating or pregnant at harvest. Maui's population, about 60,000, is still emerging and could peak around 210,000; Molokai holds roughly 60,000–70,000 deer alongside about 7,000 people.

• Hawaii's deer densities dwarf the mainland's.
Muise says the densest US deer states have about six deer per 100 acres; established Hawaiian areas have about 25, at least three times higher. Lanai is roughly in balance at about 20,000 animals; Molokai is past capacity, with deer crowding roadsides.

• The deepest damage is to watersheds.
Native Hawaiians equated water with wealth, and the islands' layered forests capture fog and rain into aquifers. Native plants evolved without hoofed grazers, so deer strip the understory, worsening erosion and sediment runoff when big rains come. Downhill, they compete with cattle at roughly seven deer per cow, a herd of about a thousand can wipe out 10 acres of lettuce overnight, and they hop six-foot fences.

• Axis deer are among the hardest animals to approach.
Their senses are so acute that getting within 100 yards requires doing everything right, and even inside 50 yards they can dodge an arrow. Muise ties this to evolving alongside tigers in India.

• Field harvest at night under USDA inspection is the core innovation.
Maui Nui built its process around the 1930s-era Federal Meat Inspection Act, with an inspector present at night using thermal optics so precise the bullet appears as a tracer. Animals are assessed before harvest at up to about 200 yards; if they stand calmly, unstressed, the process proceeds. A brick-and-mortar plant is asked to operate at about 95% efficiency; Muise says they run at about 99.99%.

• Humane standards mean deliberately missing.
Shooters target a small zone in the brain and train to miss 30% of the time—a perfect night is 70% efficiency—and the miss is always high so no animal is wounded. New shooters are expected to shoot at about 50% to widen the safety margin, using a .308 at about 100–200 yards.

• No stress at harvest changes the meat.
Attia notes stressed animals produce cortisol and lactate that affect wild-game taste. With unstressed animals, rigor mortis proceeds gradually over 16–24 hours as glycogen converts and pH shifts, avoiding the color and texture changes of stressed meat.

• Venison tested as an exceptional protein source.
A typical axis deer is about 60 pounds whole carcass and yields about 50 pounds for human use, with hides, hooves and organs used too, including in pet food—Maui Nui's starting business. In testing Muise described, their venison came out about 33% higher in protein per ounce than the best regenerative beef.

• Total eradication isn't possible; managed balance is.
Aerial surveys let them manage density precisely, for example bringing one ranch from 6,000 to 2,000 deer. Muise says no deer left by 2030 is technically impossible, and recreational or subsistence hunting can't match commercial-scale harvest.

• Tracking collars revealed what the deer actually eat.
Maui Nui fitted satellite telemetry video collars that recorded in 10-second increments for 48 hours, showing the deer's diet directly. The footage confirmed what harvest data already suggested: the animals eat almost anything, including native plants that evolved no defenses against grazing, which is why their effect on forest regeneration is so severe.

EXAMPLES

• The Big Island hunt
Muise and partner Mike tracked deer secretly dropped in a 70-square-mile area, walking 12 hours a day, deploying camera traps and flying aerial thermal surveys covering about 10,000 acres an hour. The helicopter pilot who dropped the deer was sentenced to 300 hours flying with them. After three years they were confident they had the last one in that area.

• Airlifting cattle from lava
A fast lava flow about 500 yards wide trapped ranch animals. Over a week or two of missions they slung 40–50 cattle, including 2,000-pound bulls, on a 100-foot line beneath a helicopter.

• Volleyball to Molokai
A Canadian raised 14 hours north of Edmonton on moose meat, Muise came to Hawaii on a volleyball scholarship, hit a vertical leap above 40 inches, played professionally in Europe and missed the Olympic team by one spot.

• Feeding Hawaii during COVID

With food banks empty and tourism collapsed, Maui Nui donated about 50,000 pounds of venison, over 100,000 meals.

- **Returning to meat**
  People who hadn't eaten meat for 20 years have written to say they chose Maui Nui venison because of its humane harvest.
- **Skipping long shots to harvest more**
  Carrying a 200-pound buck over rough terrain from 200 yards leaves shooters exhausted, so the team learned they could harvest more animals per night by passing on deer beyond 200 yards—a lesson Muise says took thousands of animals to learn. Attia admits he couldn't carry his own buck for the first stretch.

OTHER RELEVANT

- **Ethical meat can serve conservation.**
  Harvesting invasive deer protects watersheds, native species and farms while producing food.
- **Stress at slaughter affects quality.**
  Calm, instant harvest improves meat texture and taste. 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.
- **Consider nose-to-tail use.**
  Using organs, hides and trim reduces waste and adds nutrition.
- **Look for data-driven management.**
  Muise credits nightly tracking of proficiency rates and aerial counts for precise, humane population control.

#94 – Mark Hyman, M.D.: The impact of the food system on our health and the environment

Guest: Mark Hyman
Date: 2020-07-08 · Duration: 1:50:28
URL: https://www.youtube.com/watch?v=DxbeLdVoYpU

KEYPOINTS

• Hyman frames ultra-processed food as a health, economic and climate problem at once

Hyman, a functional medicine physician, cites 11 million deaths a year worldwide from eating too much ultra-processed food and too little good food. He says 70% of US military recruits are rejected as unfit. He also cites a UN projection of 200 million to a billion climate refugees within the coming decades. In his view the food system connects chronic disease, healthcare costs, national security and the environment.

• Calories aren't biologically equivalent, he argues

Hyman's example: 750 calories of soda is a Big Gulp holding 46 teaspoons of sugar, while 750 calories of broccoli is 21 cups with 35 grams of fiber and no sugar. He says ultra-processed food now makes up about 60% of American calories, and that each additional 10% of calories from it raises death risk by 14%, as he reports the data. Peter adds that processed foods may hijack the body's normal appetite feedback loop.

• He says the food industry funds confusion

Hyman cites about $12 billion spent by the food industry on nutrition 'research.' He describes how Coca-Cola executive Rhona Applebaum set up the Global Energy Balance Network. He says it paid scientists including James Hill, with about $20 million in funding, to push 'all calories are the same' and 'exercise more, eat less.'

• Gut health sits at the center of his model of inflammation

Hyman says low-fiber, high-sugar diets feed harmful microbes, damage the gut lining ('leaky gut') and let food antigens trigger inflammation, noting that about 60% of the immune system is in the gut. He cites rodent experiments in which transferring stool from lean to obese animals changed their weight. He adds that stress alone can increase gut permeability.

• US health statistics he calls staggering

Hyman says 6 in 10 Americans have a chronic disease and 4 in 10 have two or more. One in two has prediabetes or type 2 diabetes, about 75% are overweight, and most states are near 40% obesity, whereas no state had 20% when he finished medical school. He says 80% of the world's type 2 diabetics now live in developing countries, and some ethnic groups face higher risk at lower body weights.

• Policy works, and the tobacco playbook is being reused

Hyman points to Chile, where a senator who was also a doctor pushed through warning labels on unhealthy foods, marketing limits and a soda tax. He says marketing restrictions and labels had about four times the impact of the tax. Peter recalls that requiring anti-smoking ads alongside cigarette ads led tobacco companies to pull their TV ads. US adult smoking fell from about 50–55% in the mid-1960s to about 18%.

• Fertilizer and tillage degrade soil, Hyman argues

Hyman says global fertilizer use is 400 billion pounds, sevenfold higher than 40 years ago yet two-thirds as effective. It is made from fracked natural gas, emits nitrous oxide, which he calls about 300 times more potent than CO2, and runs off into roughly 400 ocean dead zones, including one the size of New Jersey in the Gulf of Mexico. He claims a third to 40% of excess atmospheric carbon comes from lost soil.

• Regenerative agriculture is his proposed fix

Regenerative farming means cover crops, rotation, minimal tillage and animals or legumes for nitrogen. He says it rebuilds organic matter, holds water and can match yields. Peter notes that US corn yields were flat at about 20 bushels per acre from the Civil War to World War II, then climbed to about 200 before GMOs arrived. GMOs, added perhaps about 10% more, a figure Peter says may be debatable.

• Glyphosate: Hyman is alarmed and Peter isn't convinced

Hyman says glyphosate is 70% of agrochemicals used, weeds are becoming resistant, there are about 14,000 lawsuits, and animal studies show microbiome and epigenetic effects. He says his own urine glyphosate was at the 50th percentile on a Great Plains Lab test. Peter eats similarly but says he is far less confident that glyphosate causes human disease than that tobacco causes lung cancer, because the data haven't convinced him.

EXAMPLES

• Gabe Brown's North Dakota farm

Hyman says this farmer, battered by hail and bad weather and close to bankruptcy, switched his roughly 5,000 acres to regenerative methods and says he has built 29 inches of soil. He uses no chemical inputs and is profitable, while the average farmer loses money and relies on subsidies.

• Impossible Burger versus regenerative beef

Hyman cites a Quantis life-cycle analysis: the Impossible Burger beat a factory-farm burger but still added about 3.5 kg of carbon per burger. A regeneratively raised beef burger removed carbon on net. He objects to scaling GMO soy monocrops sprayed with glyphosate.

• SNAP and soda

Hyman says food stamps can buy a two-liter soda but not a rotisserie chicken. By his estimate, 75% of SNAP purchases are junk food or soda. That includes about $7 billion a year, roughly 30 billion servings, on soda alone, in a $75-billion-a-year program feeding 46 million Americans. He says this contradicts the Dietary Guidelines.

• Why bread feels different in Europe

Peter noticed European bread and pasta didn't affect him the same way. Hyman's reasons include modern dwarf wheat bred under Norman Borlaug, which he says is more disruptive to the gut, and pre-harvest glyphosate spraying of non-GMO wheat. He

suggests heirloom grains like einkorn as an alternative.

OTHER RELEVANT

- **Hyman's 'Five R's' for gut repair**
  Remove triggers (gluten, dairy or grains for some people; parasites; yeast overgrowth); replace missing fiber, prebiotics and enzymes; reinoculate with probiotics, which he admits is 'still sort of a Wild West'; repair with nutrients like glutamine, vitamin A, fish oil, butyrate and polyphenols; and rebalance stress and lifestyle.
- **Buy organic where it matters most**
  Organic certification bans synthetic pesticides, hormones and antibiotics but allows 'industrial organic' monocrops. Use contamination lists to prioritize organic strawberries and celery and save on bananas and avocados. A regenerative organic certification has been proposed.
- **Hyman's top three changes if he were 'food czar'**
  Pay for food as medicine, including produce prescriptions and healthy government food purchasing. Reform SNAP, school lunches and the Dietary Guidelines. Back regenerative agriculture with policy and investment.

#83 – Bill Harris, Ph.D.: Omega-3 fatty acids

Guest: Bill Harris
Date: 2020-01-14 · Duration: 2:02:25
URL: https://www.youtube.com/watch?v=2Nz7nFlvx9M

KEYPOINTS

• Harris has studied omega-3s for over 40 years

After a PhD in nutrition in 1978, Harris did his postdoc with Bill Connor in Portland, Oregon. He has published over 300 papers on EPA and DHA, and founded OmegaQuant about 10 years before this conversation. Attia was introduced to him in 2011 through Tom Dayspring. Keep his testing company in mind when weighing his advice on testing.

• How fatty acids are named

The notation gives the number of carbons and double bonds: palmitic acid is 16:0 (saturated), oleic acid is 18:1. 'Omega' (or n-) tells you where the first double bond sits, counted from the tail end, so oleic is omega-9. Linoleic acid (LA, 18:2) is the main omega-6. EPA has 20 carbons and five double bonds, and DHA has 22 carbons and six. Fish oils are rich in omega-3s, and vegetable oils such as safflower, corn and sunflower in omega-6s.

• The 1980 salmon-oil study found an unexpected effect

Participants drank salmon oil straight, about 25 g of EPA plus DHA a day. Triglycerides fell from about 100 to 75 mg/dL, and cholesterol dropped modestly (around 250 to 230). Nobody had known fish oil lowered triglycerides, and the paper came out just as the US was entering its 15–20-year era of fat phobia. In patients with extremely high triglycerides, 18–20 g a day took levels from around 2,000 down to 250. In some people, LDL rose (for example from 120 to 140–150).

• Typical intake is tiny compared with traditional fish-eating diets

The average American gets about 100–250 mg (roughly 0.15 g) of EPA plus DHA a day, out of 80–100 g of total fat. When Bang and Dyerberg studied Greenland Inuit in the 1970s, they documented about 6–7 g a day. The body converts little plant omega-3 (ALA) into EPA and DHA: even 12 g of ALA barely raises EPA.

• The omega-3 index tracks status better than plasma

The index measures EPA plus DHA as a percentage of red blood cell membrane fatty acids. It reflects most tissues, including the heart, which Harris validated using biopsies from heart-transplant patients, though it reflects the adult brain less well. Harris targets 8–12%. The average American is around 4–5%, and some non-supplementers are at 2%. Attia's own index was about 10–11% (EPA 2.2%, DHA 8%). Harris has seen no clear adverse effects at higher levels. International bodies consider up to 5–6 g a day of EPA plus DHA safe.

• REDUCE-IT: 4 g a day of purified EPA cut cardiovascular events by about 25%

The trial included about 8,000 statin-treated patients with triglycerides of roughly 150–500 and other risk factors. They received 4 g a day of EPA ethyl ester (Vascepa) or a mineral-oil placebo. Events fell by about 25%. Attia notes that was a bigger effect than in the PCSK9-inhibitor trials, though REDUCE-IT also ran longer, about five years against roughly 2.2 for FOURIER and 2.4 for ODYSSEY. Critics question whether mineral oil was a truly neutral placebo. Japan's JELIS trial, published in 2007, had also used an EPA drug.

• VITAL found little effect at a low dose in low-risk people

Reported at the same meeting as REDUCE-IT, VITAL gave about 20,000–25,000 relatively healthy Americans one Lovaza capsule a day (about 850 mg EPA plus DHA). It missed its primary endpoint but showed roughly 20% fewer heart attacks, including fatal ones. Harris says that with low-risk participants and about a fifth of the REDUCE-IT dose, the two trials can't be directly compared.

• Harris doesn't think omega-6 is the villain

He dislikes the omega-6 to omega-3 ratio, because the same ratio can mean very high or very low levels of both, and it assumes omega-6 is bad. Americans eat about 15 g of LA a day but only about 0.1 g of arachidonic acid. Tissue arachidonic acid barely shifts with intake, which Attia calls a buffer or 'capacitor'. Harris is sorry to see oils bred to be low in LA (safflower went from 77% to about 15%) because evidence suggests higher LA is linked to lower risk. Attia pushes back, pointing out that humans ate little seed oil for most of history.

EXAMPLES

• '1,000 mg fish oil' is not 1,000 mg of omega-3

Prescription Lovaza is a 1 g capsule containing about 850 mg (85%) of EPA plus DHA as ethyl esters. It was approved at 4 g a day for triglycerides over 500. Raw fish oil may be only about 30% EPA plus DHA. Modern processing concentrates it, so check how much EPA and DHA a capsule actually contains.

• Three NEJM studies in May 1985

That month the New England Journal of Medicine published three omega-3 studies back to back. Harris calls 1985 a turning point for the field.

• Some people reach 8% from diet alone

Even among non-supplementers eating roughly one fish meal a week, some had an index of 8%. Genetics and absorption vary, so intake alone doesn't predict status.

• STRENGTH trial pending

AstraZeneca's Epanova trial (4 g of EPA plus DHA, about 13,000 patients, similar criteria to REDUCE-IT) was due to finish around October 2020. Attia and Harris planned to discuss it once results were out.

OTHER RELEVANT

• Measure, don't guess

Harris wants omega-3 status checked as routinely as cholesterol. The finger-prick test costs about $50. Aim for an omega-3 index of about 8–12%.

- **Prefer fish, supplement if needed**
  Eating fish is preferable, but taste, cost and ecological concerns make that hard for many people. EPA plus DHA supplements can get you there. Because there is no pure EPA supplement equivalent to Vascepa, the prescription drug may even be cheaper if insurance covers it.
- **Read the label for EPA plus DHA content**
  A typical good supplement has EPA and DHA in roughly a 60:40 or 40:60 ratio. Count the actual milligrams, not the 'fish oil' weight.
- **Don't rely on flax or ALA**
  Plant ALA converts poorly to EPA and DHA, so it can't replace marine sources.

#46–Chris Masterjohn, Ph.D.: Pathways to health and disease (NAD, sirtuins, methylation, choline...

Guest: Chris Masterjohn
Date: 2020-01-08 · Duration: 2:51:59
URL: https://www.youtube.com/watch?v=lv7ihoY8XyA

KEYPOINTS

• Without enough choline, fat gets trapped in the liver

Choline is needed to make phosphatidylcholine, which coats the VLDL particles that carry triglycerides out of the liver. Patients on intravenous feeding formulas that lacked choline developed fatty liver, mirroring rodent experiments from the early 20th century. Masterjohn's reading of those animal studies is that with enough choline, the liver can clear its fat whether the source is sugar, alcohol or fat.

• Choline needs may be far above typical intake

Masterjohn estimates average intake at about 300 mg a day. Some genetically predisposed people need as much as 1,200 mg, and labeling studies show triglyceride export from the liver in NASH (inflamed fatty liver) at about 25% of normal. He uses that to argue some people may need several times typical intake. Liver and egg yolks are the richest sources.

• Fatty liver has inputs and outputs

Fructose, alcohol and very high polyunsaturated fat intake drive fat into the liver, while choline governs how fast it leaves. Attia, who considers fructose molecule for molecule perhaps the biggest driver of NAFLD, notes that removing it usually also causes weight loss, which muddies the results. They discuss Miriam Vos's eight-week study in children, in which whole families were given the food, as a chance to separate the two.

• TMAO as a heart-disease villain fails first principles

Stan Hazen's Cleveland Clinic work linked TMAO, which gut bacteria and the liver make from choline and carnitine, to atherosclerosis in genetically engineered mice and to heart disease risk in people. Masterjohn and Attia point out that fish contains far more TMAO, perhaps hundreds of times more than you'd get from eggs or red meat, yet fish eating is consistently associated with better heart health. Attia sends patients who bring him the papers to Masterjohn's write-up, though he wouldn't rate the possibility of harm as zero.

• The liver stores and regulates NAD

Masterjohn compares the liver's NAD pool to glycogen: the liver keeps blood levels tightly controlled by releasing precursors such as nicotinamide for other tissues, much as it keeps blood glucose near 5 grams. This matters for understanding what NAD-boosting products can actually change in other tissues.

• IV NAD and oral NMN are unlikely to work as advertised

Cells can't simply absorb NAD from the blood, so Masterjohn suspects any felt effect of IV NAD is placebo or a nonspecific signal; Attia notes friends describe infusions as 'the worst feeling in the world'. Masterjohn would bet NMN isn't absorbed intact, because enzymes in the small intestine strip phosphate groups off everything we eat, as they do with riboflavin-5-phosphate.

• High-dose NAD precursors may drain methyl groups

Excess nicotinamide is cleared by attaching a methyl group (methylation), and studies show large increases in methylated nicotinamide in urine and blood with NR. Typical NR doses of 1,000–2,000 mg dwarf the niacin RDA of about 15 mg. In theory, every 1,000 mg of nicotinamide cleared this way could cut creatine production by up to 500 mg against roughly 2 grams made per day. Masterjohn suggests a lower dose matched milligram for milligram with the methyl donor TMG (trimethylglycine).

• Methylation centres on SAMe and homocysteine

Methionine becomes S-adenosylmethionine (SAMe), the universal methyl donor, leaving homocysteine to be recycled through MTHFR or the choline/betaine route, or broken down. Masterjohn says about 90% of methyl groups go to making creatine and phosphatidylcholine; creatine alone accounts for about 45%, and it's the first thing to suffer when methyl groups run short.

• COMT variants shape dopamine and temperament

COMT uses methyl groups to break down dopamine. Masterjohn says faster dopamine methylation is linked to mental flexibility and slower methylation to stability, popularly the 'warrior' and 'worrier' types. Normal variation is personality, while the extremes may raise psychiatric risk.

EXAMPLES

• A homocysteine that wouldn't budge

One of Attia's patients sat at 13–15 µmol/L (normal at his lab is about 9 or below) despite methylfolate and methyl-B12, doubled doses and 50 mg of B6 three times a week. Adding TMG cut his homocysteine roughly in half. Masterjohn reads the failure of B6 as a sign the problem lay in fasted-state recycling rather than fed-state breakdown.

• The TMAO biomarker meeting

Attia was one of about a dozen advisers at a two-day meeting held by a company deciding whether to offer TMAO as a new cardiovascular biomarker. Someone in the room noted that fish delivers more TMAO than any realistic amount of red meat and eggs could generate, and later observational data confirmed that fish eaters have higher blood TMAO. For Attia, that undercut the thesis on first principles.

• MTHFR strategy

Masterjohn's first priority for people with MTHFR variants is 900–1,200 mg of choline a day from food such as eggs, the step with the most evidence. Next comes creatine, about 5 grams a day of monohydrate, to reduce methyl demand, along with attention to folate and glycine.

• How the two take NR

Masterjohn was experimenting with about 75 mg twice a day, from 150 mg capsules split in half. Attia observed, while acknowledging it's anecdotal, that patients taking NR products consistently seemed to see marked improvement in even mild

rosacea.

OTHER RELEVANT

- **Prioritise choline from food**
  If you're at risk of fatty liver, or avoid eggs and liver, check your choline intake before reaching for exotic supplements. Masterjohn prefers phosphatidylcholine to choline salts when supplementing.
- **If you take NR, protect your methyl supply**
  Use modest doses, consider pairing with TMG, and watch for mood or energy swings, which Masterjohn says fit methyl depletion. Short studies of a few weeks can't capture longer-term effects.
- **Look past simple biomarker stories**
  Whether it's TMAO or 'normal' homocysteine, Masterjohn and Attia stress first principles and flux, meaning how fast things are made and cleared, over single snapshot measurements.

#08 – Tom Bilyeu: nutrition, fasting, meditation, mindset, immortality, and fulfillment

Guest: Tom Bilyeu
Date: 2019-12-22 · Duration: 1:38:22
URL: https://www.youtube.com/watch?v=82jm5CA9PyQ

KEYPOINTS

• A 2013 meeting with Peter and Dom D'Agostino ended Bilyeu's fat phobia

Bilyeu, co-founder of Quest Nutrition, admits that even while running a nutrition company he believed 'fat makes you fat.' After Peter and D'Agostino visited, with Ron (one of his Quest co-founders) taking the first meeting, the mention of possible anti-cancer properties pushed him to try therapeutic ketosis. Since then he has eaten some version of high-fat, low-carb or fully ketogenic. He credits his habit of seeking disconfirming evidence: 'I want to know how I'm wrong.'

• His first ketosis attempt was miserable but fixed 15 years of wrist pain

He followed a 4:1 ketogenic ratio, with blood ketones above 3 and glucose in the low 60s, for about five days without knowing how to supplement. He calls it the worst experience of his life. But wrists he had iced up to twice a day for 15 years, leaving small burn patches, suddenly felt 'perfect.' He concluded fat mattered for cell membranes and inflammation, offered as his own interpretation.

• Before that, he lost 60 pounds on 'rabbit starvation'

For about two years he ate more than 80% of calories as protein, mostly steamed chicken breast with salt, at 1,200–1,500 calories a day. He went from 230 to about 170 pounds and was 'shredded,' but lost much of his strength. He describes moving from obsessing over size, to obsessing over aesthetics, to now focusing on performance.

• Bilyeu wants immortality; Peter tests whether that survives losing everyone

Bilyeu quotes Woody Allen on wanting to live forever 'by not dying.' Peter's thought experiment: would he accept immortality knowing his wife and friends will die? Bilyeu says yes without hesitation, and that he moved faster, not slower, once money removed any need to work. He and his wife chose not to have kids, and he rejects the 'deathbed regret' argument because your perspective changes with every phase of life.

• A fixed mindset nearly broke him; a growth mindset built Quest

With 990 SATs, he talked his way into film school, then botched his senior thesis film so badly that he stole the master copy. Classmates cut it into joke reels. Believing talent was innate, he was crushed until he began asking why he couldn't learn to tell stories better. A tech job meant to fund filmmaking for 18 months stretched on for years.

• He walked away from paper millions, and that is how Quest began

Bilyeu held 10% of a security software company worth about $22 million at its peak and was miserable. He told his partners they could sell it for a billion and he would take nothing. Instead they asked him to stay and build something meaningful, which led to Quest in 2010. He describes Quest as a food company aiming to 'end metabolic disease,' not a bar company.

• Money didn't change how he felt the next day

Bilyeu says he expected wealth to bring the reverence he once felt toward rich people and to wash out his insecurities. Instead it was like losing his virginity: great, but he was the same person. In his view money is 'inert' but enormously powerful when aimed at a clear problem, especially to direct capable people. He names Elon Musk as a role model.

• His formula for fulfillment is becoming someone you're proud of through hard skills used for others

Fulfillment ebbs and flows; it isn't a permanent state. Serving soup feels good, he says, but fulfillment is the Toyota engineer who used hard-won skills to multiply a soup kitchen's output. He defines power as the ability to manifest the world you imagine and cites Mother Teresa. Peter adds that it's hard to feel fulfilled without serving someone else.

EXAMPLES

• The magic genie question, across 1,500+ interviews

Bilyeu personally interviewed everyone Quest hired, from executive VP to janitor, more than 1,500 people. He asked what they'd wish for, with no curing cancer and no extra wishes. After nudging past 'a job' to 'money,' he says every single person named the same figure, one million dollars, which wouldn't even buy a house in LA.

• Quest University and the birth of Impact Theory

About 1,000 of Quest's roughly 1,400 employees grew up poor, like Rashon Jackson, a student Bilyeu remembered from college. Quest tried to treat 'making protein bars as your tuition' and helped one worker move into tech and later found a company. An internal show, Inside Quest, felt like a brand mismatch, so he spun the studio out as Impact Theory.

• Why he'd rather keep you four years than 20

Bilyeu says a happy employee for three or four years beats a resentful one for 20, and calls his motive frankly selfish. As a child he pretended not to see Easter eggs so his sister could win, saying he's 'wired' to enjoy others winning.

• Peter's sleep study example

Peter cites a University of Chicago study in which four hours of sleep a night for 14 days cut glucose disposal on a clamp by about 50%, making participants roughly twice as insulin resistant. He calls it 'one study' among several and now suspects sleep loss, not only diet, explains his metabolic decline during residency.

OTHER RELEVANT

• Bilyeu's routine

He eats high-fat, low-carb rotations of beef, chicken, lamb and pork, and cheats about twice a year. He alternates ketogenic weeks, when 16-hour fasts feel easy, with higher-protein weeks because extended ketosis 'softens' his muscles. His normal overnight gap is 14 hours, and he does one five-day water-only fast a year. He reaches ketones in the 3s but feels about 20% less energetic by day four, losing three or four pounds if lean versus ten pounds carb-fed, much of it water.

- **Protect sleep as a performance tool**
  For about 16 years he has been in bed by 9 p.m. on weekdays and woken without an alarm. His logic is that sleep makes waking hours more efficient.
- **Use breath meditation and abort bad lifts**
  Navy SEAL Mark Divine talked him into meditating. Diaphragmatic breathing before going on stage gets him to 'absolute zero' stress. In the gym he warms up to 315 pounds on the deadlift and aborts about one in five sessions if his sacroiliac joint or lower back feels off, a rule he also applies to squats.

#05 - Dom D’Agostino, Ph.D.: ketosis, n=1, exogenous ketones, HBOT, seizures, and cancer

Guest: Dominic D'Agostino
Date: 2019-12-17 · Duration: 2:43:21
URL: https://www.youtube.com/watch?v=q7kOs6bS1Hg

KEYPOINTS

• D'Agostino came to ketones through diving physiology and a lab accident.
His PhD was on how brainstem neurons sense oxygen and CO2. His postdoc built a hyperbaric atomic force microscope, funded through the Department of Defense, to image living cells under pressure. Around 2008–09, while testing different fuels in cell culture, he noticed cancer cells grew more slowly in 1, 2 and 5 mM beta-hydroxybutyrate (BHB) at the same glucose level, and sped up again when the ketones were removed.

• Cancer cells sit on a knife-edge of oxidative stress.
He describes a U-shaped curve. Tumor cells use elevated reactive oxygen species to grow, spread and invade, but because their mitochondria are dysfunctional, pushing oxidative stress further with high-pressure oxygen or chemotherapy can exceed their antioxidant capacity and trigger cell death. He says he saw this directly under the hyperbaric microscope, which no one had used for that purpose before.

• Seizures from oxygen toxicity limit Navy rebreather divers.
A closed-circuit Dräger rebreather leaves no bubbles, which allows stealthy dives, but D'Agostino says about 10 minutes at 50 feet of seawater can trigger a seizure in some divers. He puts brain oxygen pressure at roughly 2,000 times normal. Susceptibility varies with genetics, sleep loss, diet and illness. He notes seizures are likely underreported, because SEALs are known for hiding health problems that could get them removed.

• In his research, ketone esters greatly increased resistance to oxygen-toxicity seizures.
He says a ketone ester increases resistance by roughly 600%, and that exogenous ketones added to standard high-carb rat chow also protected against chemically induced and absence seizures in animal models. He thinks pairing a ketone ester with hyperbaric oxygen (HBOT) could make HBOT safer and more effective, though this is still a hypothesis for people.

• HBOT has about 14–15 approved uses and a powerful effect on stem cells.
Approved uses include decompression sickness, carbon monoxide poisoning, radiation necrosis, noise-induced hearing loss and diabetic wounds. D'Agostino estimates diabetic wounds make up over 90% of hyperbaric facility revenue. He says HBOT mobilizes stem cells about as strongly as drugs like Neupogen. Traumatic brain injury is the most controversial use, and he would want to test low-pressure HBOT soon after injury combined with ketones.

• Ketones act as signaling molecules, not just fuel.
Beyond replacing glucose for the brain, D'Agostino describes BHB acting as an HDAC inhibitor with epigenetic effects and suppressing the NLRP3 inflammasome in ways unrelated to metabolism. He began with the classic 4:1 ketogenic diet, about 90% fat, from the Johns Hopkins protocols, but reached only about 2–2.5 mM. He later moved to a modified diet with more protein plus MCTs.

• MCTs, especially C8, raise ketones because they go straight to the liver.
Medium-chain fats bypass the chylomicron and lymphatic route and travel through the portal vein to the liver, where they are quickly oxidized. He says two to three tablespoons can raise BHB to about 0.5–1 mM even on a high-carb diet, and pure C8 raises it about 20–30% more than a C8/C10 mix. Attia notes that stomach upset often limits the dose before ketones get very high.

• Exogenous ketones reliably lower blood glucose, and why isn't settled.
In rats, the maximum tolerated ketone-ester dose dropped glucose from about 140–150 to around 40 mg/dL, and doses above that made glucose spike. Candidate explanations include ketone-triggered insulin release, better insulin sensitivity (Richard Veech's view) and a shift in the liver's redox balance. Attia says a talk with Stephen Phinney convinced him nobody fully knows the answer.

• Salts and esters differ in chemistry, and D'Agostino isn't worried about racemic forms.
Ketone salts bond BHB ionically to sodium, potassium, calcium or magnesium. He calls them 'ketone electrolyte formulations' and limits magnesium BHB to about 1–3 grams per dose for digestive tolerance. Esters bond covalently, for example to 1,3-butanediol, which was researched as a spaceflight fuel. He says the D-form is the better fuel, the L-form lingers longer, and both suppress the inflammasome. He has seen no data suggesting racemic products are harmful.

• His 'press-pulse' idea for managing cancer metabolically is presented as experimental, not as advice.
Attia frames the question as a thought experiment with a clear caveat: D'Agostino is a PhD researcher, not an oncologist, and is speaking about a loved one who is still receiving standard treatment and losing. The 'press' is continuous metabolic stress: a calorie-restricted ketogenic diet, eating within about six hours, possibly low-dose metformin, and exogenous ketones. The goal is a glucose-to-ketone ratio of 1–2, versus his guess of 25–50 for a typical person. The 'pulse' includes chemotherapy, radiation and HBOT, which he argues may work better in that changed metabolic state.

EXAMPLES

• A seizure in the chamber
In a video D'Agostino shows in talks, a diver breathing 100% oxygen at 2.7 atmospheres has a violent tonic-clonic seizure. It stops as soon as he switches to air at the same pressure.

• Scheck's glioblastoma mouse study
D'Agostino cites Adrienne Scheck's work at the Barrow Neurological Institute. In the GL261 glioblastoma mouse model, a ketogenic diet combined with radiation made the radiation far more effective and cured the tumors in that model, which helped launch clinical research.

• HBOT dosing in his research

For his press-pulse approach he describes 2.5 atmospheres for 60 minutes three times a week, with rest days to allow adaptation. For glioblastoma, where seizures are a risk, he would start around 1.5 atmospheres. Pressure dissolves oxygen into plasma so it can reach poorly perfused, hypoxic parts of a tumor.

- **The 'ketone tolerance test'**

  He came up with this during the conversation: take a known dose of ketones and measure BHB, glucose and insulin at 30, 60, 90 and 120 minutes. Fat-adapted athletes clear ketones quickly, while one commercial packet can push some sedentary people to 5–6 mM.

- **The 'jet fuel' diester**

  The acetoacetate diester raises BHB and acetoacetate roughly 1:1, which he links to anti-seizure effects. It tastes so bad that even in capsules you can taste it, so he sees it more as a medical food or IV therapy.

OTHER RELEVANT

- **Track your glucose-to-ketone ratio, not just ketones.**

  In D'Agostino's framework the ratio matters more than ketone level alone. It is meant for therapeutic settings with medical supervision.

- **Dose exogenous ketones carefully.**

  D'Agostino says he starts to feel 'a little bit weird' once exogenous ketones push him above about 3 mM, even though he uses ketones well. Responses vary widely: in data people have sent him, one commercial packet sent some to 5–6 mM. He also notes that well above the tolerated dose in rats, glucose rose rather than fell.

- **Treat HBOT for unapproved uses with skepticism.**

  Attia notes how much off-label use there is, such as for mercury toxicity. The approved uses are specific, and HBOT itself can cause oxygen-toxicity seizures.