

Transcribed from a presentation delivered at a CrossFit Health event in Scotts Valley, California, on Oct. 13, 2019:

Thank you, Zoë, and thank you to Greg and Karen and — and everyone for inviting me to give this talk. So over the last number of years, four years with Virta Health, we've been out there talking to two physicians and doing continuing medical education and — and really kind of formal presentations. So, I wanted to have a little bit more fun with that — with this — with this one in terms of the way we present it. So rather than sort of giving a straightforward talk about a clinical trial, I thought we would — we would talk about debunking myths and just reorganize things in a little bit more of a fun way. And I know I am standing between you all and lunch, and so, I have — I do have a lot of material, but I'm going to blast through it really fast. And there's no need to take notes, because I'll make all these slides available on SlideShare and get the information out there so that folks can see it.

So there's really only one goal for this talk, and that's to arm you to answer any question about ketogenic and low-carb nutrition approaches. And so, the reason that this is important is that the public is really now, in the last few years, finally paying attention, and the defenders of the status quo really are nervous about some of what they're seeing. So, this is the way, if you do Google Trends, that the sort of diets fluctuate every year. So between 2004 and 2012, looking at Weight Watchers is just one example of a diet that people search for. Every January it spikes, right? And so, the only thing that's kind of interesting that happened between 2004 and 2012 was the rise of the term “vegan,” which then passed Weight Watchers. But then something else happened here in — in February of 2012 along the very bottom line. You see that? You see a blue line? And that actually is the term “keto.” And — and so “keto,” short for nutritional ketosis or for the ketogenic diet, is the number-one diet search term of 2018 and 2019, but it really kind of came out of nowhere. This coincides in some regards with the work we're doing at Virta where we published our first paper in March of 2017 and our one-year results in — in spring of 2018. But you can see that keto passed Weight Watchers in 2017, passed vegan in 2018, and now it's on this sort of January trend of spiking every January as the number-one diet search term.

So, this is, you know, this is all about kind of public perception, and so, this could just be a fad. But look at the science behind this as well. So between — since 2000, the PubMed references for ketogenic have increased 860%. So there's a lot of science behind this. People are publishing a lot of papers on this topic.

Okay, so the outline for this talk is a little bit of an introduction and a little bit about the Virta Indiana University Health Trial. And this is just to kind of get you some background of kind of what you need to know before we get into these keto myths.

And — and then we'll go through — I wrote a blog over the summer about top-12 keto myths, and then I started on my file cabinet, just putting up sticky notes of kind of, you know, all of the other myths that I was hearing out there. So there was another 12 and then there was even more, so, but hopefully we'll have a lot of fun doing this.

Okay, so a little bit of an introduction. So why care about this at all? And what I've been working on for the last four years at Virta is on Type-2 diabetes and how to treat that. Over 10% of U.S. adults have diabetes. That's mostly Type-2 diabetes. Over one-third have pre-diabetes, and so about half of U.S. adults have some degree of chronic metabolic disorder including insulin resistance, and it's costing the U.S. economy over \$300 billion annually. And then this is also internationally, too. There's over 400 million people worldwide living with — with diabetes. And so, at Virta we got started a number of years ago to tackle this, and I wanted to put the acknowledgments slide up, up front rather than have it at the end as we're rushing out for lunch. And so I wanted to thank the team that's been part of this research at Virta and Indiana University Health and our other academic co-authors and collaborators, especially my co-principal investigators, Dr. Sarah Hallberg, who I believe you all had out here last year speaking, along with Steve Phinney and Jeff Volek, who are co-founders of Virta. And then, of course, our tremendous clinical trial participants. We couldn't have done this work without them.

And so, I think it's important to have financial disclosures, and so I've left Virta this summer, but I am a shareholder. And so, it was a company founded in 2014, headquartered in San Francisco. It's a nationwide telemedicine provider and full-stack technology company focused on the reversal of Type-2 diabetes, now working — practicing medicine in all 50 states, working with thousands of patients and dozens of self-insured employers and health plans. I also chair the scientific advisory board of a new startup called Readout Health that's in — in St. Louis, and it is a company working on helping customers with real-time biomarkers.

So my own journey to ketosis actually began a couple of years before I found Virta, back in 2012. And this is my family at my father's retirement party from the Field Museum of Natural History in Chicago. But as Zoë mentioned, I was part of the venture capital group at a crop protection company, and my sister made the comment to me that fall, she said, "Hey, you know a lot of the corn that you guys grow goes into high-fructose corn syrup and — and why is that a good thing?" And so I looked into that and started reading papers on corn syrup, and that led me to reading papers on sugar, and that led me to reading Gary Taubes' book, and I kind of went down the rabbit hole into this world of nutrition. And — and I discovered a lot of things that I was doing wrong and a lot of misconceptions that I had dating back to medical school.

And so, this is the way that I used to eat. I thought it was healthy but I was eating toast with jelly and banana for breakfast, and that was the start of the day of glucose-insulin rollercoaster, which had me having post-breakfast munchies and post-lunch food coma. And so, I changed the way that I ate. And so, starting in 2013, now coming up on seven years, I began to eat much more like this: non-starchy vegetables, lots of eggs now from our farm, oily fish, meat, including liver bouillon, olive oil, other high-oleic oils, nuts and seeds, nut butters, chocolate, and coffee. So that's — that's a lot of what I eat. And — and I measured as — for a year did morning and evening blood glucose and ketones and could track and knew when I was in or out of ketosis, usually. Around two millimolar beta-hydroxybutyrate in the morning and around one millimolar of beta-hydroxybutyrate in the evening. And so people ask me, why did I, you know, go to all this effort. Did I see any health improvements? I didn't have an issue with diabetes or obesity, but I did see positive benefits and one of them was in terms of hypertension. I was running close to 140 over 90 prior to starting this, and that drops sharply down to — I now run around 110 over 70 in terms of my blood pressure.

Okay, so some quick definitions. One is around this concept of diabetes reversal. And when Virta talks about diabetes reversal, or others talk about it, what do we really mean? And there really are. It's not just around ketogenic diets and low-carbohydrate diets. There are three different approaches that will effectively reverse diabetes: bariatric surgery, very low-calorie diets, and low-carbohydrate, including ketogenic, nutrition. And really we think about this as making patients informed that they have a choice. They don't need to see Type-2 diabetes as a chronic progressive disease. They can actually choose to undertake reversal. And there's a difference between remission, which has a strict requirement in terms of getting diabetes out of the A1C over 6.5 out of the diabetic range for hemoglobin A1C, but doing so in the absence of pharmacological or surgical therapy. At Virta we use the term “reversal” because we oftentimes will leave metformin in place. About 60% of our patients continue on metformin, and so we don't use the term “remission.” We instead use the term “reversal,” defined as not using drugs that are specific for diabetes because metformin is now widely used for the treatment of pre-diabetes as well. And so that's kind of the — the terminology around reversal versus remission. And then low-carbohydrate nutrition. That — a very low-carbohydrate nutrition, less than 50 grams a day. Ketogenic usually requiring less than 30 grams a day and resulting in an elevated level of beta-hydroxybutyrate above baseline. And then there's low-carbohydrate nutrition, which would be higher than a ketogenic level, but generally less than 100 grams per day. And you'll see papers, though, where they'll talk about low-carbohydrate nutrition when they mean 40% carbohydrate, and you know, that is not by any means low-carbohydrate nutrition. We generally mean less than 100 grams of total carbohydrate a day. Okay, and then nutritional ketosis. It's a metabolic state where the body is predominantly fueled by dietary fat or body fat, and it occurs when carbohydrates

are limited and ketones are produced as part of fatty acid metabolism in the liver. And actually, in fasting, ketones will provide about 60% of the brain's energy, and we'll talk more about these other topics.

All right, so that's a little bit of an introduction. And then I'll take you through just a few slides on kind of what was the Virta Indiana University Health Trial, and what we did we learn, and what do you need to know before we get into myths around ketosis. All right, so the Virta-IUH trial began in the summer of 2015, and over six months we recruited nearly 500 participants to an intervention group that we call the CCI, or continuous care intervention, and then 87 individuals in a usual care group who continued with the 2015 American Diabetes Association standards of care. And just some baseline characteristics for these individuals: They — average age in the mid-50s. Average body mass index of 40. Average weight of 257. Average time with diabetes of 8.4 years, so not just newly diagnosed. These are people with long-standing disease, some with 20 years with diabetes or more. About two-thirds of the individuals were women. And the way that we provided care with — with this group was we built what we called the — the continuing care intervention, or Virta remote care platform, and included one-on-one interaction with a health coach, 24/7 access to a health coach team, telemedicine relationship with a physician, an online patient community, resources online for extensive nutrition education and individualization of the nutritional advice. And then biomarker tracking so that people initially were measuring not only weight but also glucose and ketones on a daily basis and getting that as feedback as to whether or not they were seeing success with their intervention.

And we've published, now, six papers from that trial with another five or six papers that are in process. And so, I should say that I have included references here. There's over 70 references in this slide deck.

Okay so what were the kind of “take home” points of providing this continuous care intervention with nutritional ketosis? We had 262 patients with Type-2 diabetes that were in the intervention, and over the course of the first year, 60% of them met our definition for diabetes reversal. So of those who finished the first year of the trial — 83% finished the first year of the trial — 60% of them got their hemoglobin A1C under 6.5 without the use of diabetes-specific medications — over a 1% drop in hemoglobin a1c — 94% reduction or elimination of insulin, 12% average weight loss and improvement in cardiovascular disease risk factors. And so, here's what the drop in the A1C looked like. And shown in blue is the continuous care intervention or Virta group, and then the usual care group is shown in gray. And this went along with a rapid reduction in the use of medications, resulting in over \$2,000 in savings on average per patient in the first year in medication cost reduction alone. Most of that, you can see — most of the medication reductions occurred in the first two months. And depending on where people started with their hemoglobin A1C, the

higher than they started the bigger their drops. So you can see on the left-hand side in blue that for those who started were relatively well-controlled, with A1C of 7, it dropped to about 6. For those who started with an A1C over 9 — the average was a 10.29 — and had dropped over three percentage points down to 6.84. And it's sustained. So we've now published the two-year outcomes this summer in — in *Frontiers in Endocrinology*. And we see a little bit of a rise, but most of the reduction in hemoglobin A1C that we saw at one year is retained at two years, and we see a continued reduction in insulin resistance and a continued high rate of diabetes reversal out at two years. And we've now extended the trial out to five years. A number of our patients wanted to continue on, and so most — actually most of our patients are going to continue on with us out beyond two years.

This is just looking at the medication reductions by class. So at two years, 67% of diabetes prescriptions were eliminated, 100% elimination of sulfonylureas, 91% reduction or elimination of — of insulin. And you can see, again, the steep decline in medication use in the first two months of the trial. And then one question that we get is, "Okay, you had 60% of folks were able to reverse their diabetes at a year. What happened to the other 40%? Were they off track?" And actually, most of them did very well. So most of them saw, on average, one percent drop in A1C, 45% of meds eliminated, 23-pound weight loss, 21% reduction or elimination of insulin use. They just didn't meet our metric for full diabetes reversal.

Okay, so that gives you, kind of, a little bit of background on the trial, and so now we'll get into sort of the myth buster part of this. All right, and I'll try to go fast. So, myth number one is the idea that this is not sustainable, that you can't sustain diabetes reversal, that you can't sustain long-term carbohydrate reduction or — or ketosis. We actually found that the majority of our patients were able to get into ketosis as measured by a beta-hydroxybutyrate, and that even after two years there, the average beta-hydroxybutyrate level was substantially above the — the baseline where people had begun. Seventy-four percent of our patients finished two years of the trial even with extensive tracking demands that were required of the trial. And in commercial practice where we're practicing medicine nationwide, where there's less onerous demands on folks, the retention is even higher. It's over 90% at a year and over 80% at two years. And this is what the beta-hydroxybutyrate levels look like. They were still elevated over 50% over baseline at two years. The levels of ketosis are highest in the first couple of months as people are getting established. And then people individualized, so we're not just tracking ketones; we're also tracking glucose, we're also tracking weight, mood, hunger, energy and cravings. And so we can kind of tell whether people are on track or off track. We can tell how much dietary diversity are they able to incorporate. Some people can have higher levels of carbohydrates and still stay on track, so not everybody needs to be in full ketosis at all times. But still, they see an elevation of ketones beyond where they started. And then — And then in terms of weight, people still doing very well at

two years in all dietary interventions and behavioral interventions. You see weight regain — or and we see this as well, but it is not as substantial as seen in most interventions. People actually still had 12% weight loss at two years, and about half the patients had lost 10% of their weight or more at two years. And so, to compare that kind of curve of weight loss and weight regain, this is what it looks like compared to a lot of other interventions, both with caloric restriction as well as other low-carbohydrate interventions. You see A1C increases, weight increases, and what we see in the Virta intervention is — is less — less, so the Virta shown in blue versus the other lines.

Okay, so, I'll go even faster now. So myth two is that ketosis will cause diabetic ketoacidosis. That's not the case. There were no DKA events in the trial. I should mention that we usually de-prescribe SGLT-2 inhibitors, because these are associated with euglycemic DKA, which we don't want to miss, and so we usually get rid of those medications. Just, again, to state that nutritional ketosis is not diabetic ketoacidosis. Nutritional ketosis usually has a beta-hydroxybutyrate level between 0.5 and 3, and it's not associated with — with acidosis, whereas DKA usually has very high beta-hydroxybutyrate levels above 10 millimolar and is associated with a metabolic acidosis.

Okay, ketosis will not cause hypoglycemia. There were no instances of systematic — of of — hypoglycemia while patients were in ketosis, and in other trials, the only time that you'll see hypoglycemic events are where people are using medications like insulin or sulfonylureas. And in terms of clinical management, in the trial we did report one patient had hypoglycemia. That patient was no longer following dietary changes, had gone back on insulin, and was using insulin above the prescribed dose.

Okay, myth four: Ketosis will deprive the brain of required glucose. This is one we hear all the time. This is false. Blood glucose levels are not low in ketosis. The liver produces plenty of glucose by gluconeogenesis. And actually, the brain metabolizes ketones in preference to glucose, and this is shown very nicely in this PET study, that if you look at labeled acetoacetate following the administration of a ketogenic diet, you'll see — you'll see that in the brain, and you'll see actually less use of glucose by the brain following the administration of a ketogenic diet. And actually, ketosis is used to treat brain disorders such as epilepsy, and more recently, showing efficacy against migraine as well as improved cognitive performance.

We hear all the time that ketosis will impair the heart and cause vascular damage, and we don't see that this is the case. We actually see that the ASCVD risk score improves. We looked at a large number of cardiovascular risk factors. And one thing I'll show you in the upcoming couple of slides is I'll cite a couple of papers that are using animal models as opposed to clinical studies. And I've put an asterisk next

to those in — in brown, just to note those, as Zoë was saying, in terms of levels of proof that these are more understanding the mechanism of action as opposed to being a high level of clinical proof. So animal models with incorrectly formulated ketogenic diets are actually responsible for many of the keto myths. And if you correctly formulate a ketogenic diet, it actually extends lifespan and healthspan in mouse. And so those animal model papers are all marked for you.

So we see an ASCVD risk score, and so the setup for these next couple of slides, or you'll see scattered throughout the myths, are that an improvement in a risk factor shows a movement to the right, a negative is movement toward the left, and the intervention is shown in blue, and the usual care group is shown in gray. So we see this 12% improvement in the ASCVD risk score. That's an amalgam of a couple of different factors. If you actually break them out, we actually looked at 26 different cardiovascular risk factors. We showed statistically significant improvement in the intervention group in 22 out of 26 risk factors versus zero out of 26 in — in the usual care group. That includes markers for hypertension, atherogenic dyslipidemia, chronic inflammation, as well as fatty liver. Now, I mentioned just in passing that this study of ketogenic diets for congestive heart failure is a very interesting one. Most — most of this work has still been done in animal models, just a little bit of work in humans, but indicating that ketones are actually a preferred fuel in the failing heart. And that this changeover to the use of ketones as a fuel and in heart failure is actually adaptive, and adaptive as opposed to a maladaptive response. So look — Look for more clinical trials to see if ketogenic diets might be useful in congestive heart failure.

So the lipid profile. We actually see that patients improve in their triglycerides and HDL, and while the calculated LDL rose, we see no change in the mean LDL particle number by two different methods: by measuring Apo B as well as measuring LDL-p by NMR lipoprofile. And then the type of LDL particle shifts toward a more favorable large buoyant LDL. And this isn't just our trial. A large number of trials have shown that in the use of a low-carbohydrate or ketogenic diet, there is no increase in — in the Apo B LDL particle count. So we see this improvement in atherogenic dyslipidemia. We see an improvement in the LDL profile with the exception of the calculated LDL. And one kind of point about that is that while the mean LDL doesn't change, there is a lot of scatter in this, and this is seen not just in the low-carbohydrate or ketogenic group, but it's seen in the usual care group as well, in this histogram. So while our LDL-p decreased 5% in terms of its mean, you'll see that histogram, that distribution in both the blue and the gray, we see this — this decline in the number of small LDL particles as well as a decline in the number of large VLDL particles that corresponds with the reduction in triglycerides.

All right, so the next keto myth is that ketosis will cause inflammation. We actually see the opposite. We see a reduction in inflammation as measured both by a 39%

reduction in one year in high sensitivity C-reactive protein, and 9% reduction in white blood cell count. Our patients and surveys are pointing to — report improvement in joint function with reduced pain. And other clinical trials have seen this as well. So this is our data on the reduction of hsCRP, as well as white blood cell count. We see this reduction at both one and two years. And — And then this, another study from 2008, looking at a large number of inflammatory markers saw a decline in inflammatory markers with the use of the ketogenic diet as opposed to a low-fat diet, and so why might this be? So one indication of mechanism is that beta-hydroxybutyrate is actually an inhibitor of the NLRP3 inflammasome. And so there have been a number of studies now looking at this mechanism of how inflammation — chronic inflammation may be reduced in these with the ketogenic diet. And then beta-hydroxybutyrate is also an endogenous — an inhibitor of the endogenous histone deacetylases, reducing oxidative stress.

All right, so how you guys holding up in terms of — we're gonna go — I'll go even faster.

So, there are a lot of myths out there. So one is that ketosis will cause hypothyroid. We don't see this. We actually see that the thyroid hormone T4 was unchanged. We actually see a numeric though not statistically significant decrease in TH — TSH, whereas you would expect in the condition of an underactive thyroid that you would have an increase in TSH in order to stimulate more thyroid hormone production. There were no cases of symptomatic hypothyroidism in our trial, and this is consistent with other low-carbohydrate clinical trials.

There's a myth that the ketosis will harm the liver and increase liver fat based on rat studies. We actually see that liver function was greatly improved by multiple markers of non-alcoholic fatty liver disease, both at one and two years. So the — the liver fat score improved, the liver fibrosis score improved, and this has been seen in other trials of ketogenic and low-carbohydrate diets as well. So here's what we see in terms of the Virta or continuous care intervention treatment on — on the left, showing a reduction in ALT enzyme, a reduction in steatosis, a reduction in fibrosis at one year versus no change in the usual care group.

Okay, there's a myth number 10 that ketosis will harm the kidneys. We're kind of going after all of the organs. We actually see that the glomerular filtration rate improved. There were no cases of worsening kidney function in our trial, and other trials have seen the same — the same thing: an improvement and no harm in kidney function.

Myth 11: that ketosis will cause muscle loss. We actually see, while there's a 12% or about a 30-pound weight loss by DEXA scan, that most of that weight loss is body fat, including abdominal fat. It's not — not mostly lean tissue. There's another trial

actually out of Spain that's looked at this very nicely in a lot of detail and shown that 87% of the weight loss is fat mass, and that of the non-fat loss, it includes a small amount of lean tissue as well as water. And there was no change in muscle strength in that study.

There's a myth that ketosis will cause loss of bone mineral density. We don't see this. So at both one and two years, there was no change in spine mineral density. Again, this other trial out of Spain looked at this as well. There was no change in bone — bone density in their trial.

All right, so that's 12 down. Let's do another 12. All right, ketosis is just a fad — this is false. Ketosis is not the standard of care. Actually, if you'd said this in 2016, you'd be right, but that has changed, and so let me walk you through that. So ketosis is not a fad. So both fasting inducing ketosis, as well as carbohydrate restriction is an ancestral eating pattern. It — the Native Americans, the Inuit, the Masai — there were, depending on availability of energy sources around the world — different ancestral populations used everything from a high-carbohydrate to a high-fat diet depending on what was available in their environment. And fasting ketosis has been a religious practice for treat — and for treatment of disease since ancient times. The actual first indication in the medical literature that carbohydrate restriction could be used for diabetes was in the early 1800s. And that continued to be in the medical literature up until, in the 1920s, well it — where it eventually fell out of favor with the availability of insulin, and then in the 1950s with the diet-heart hypothesis. And actually, more diabetes trials have examined carbohydrate restriction than any other dietary pattern. There have been over 30 RCTs and meta-analyses, as well as 10 other trials. This is more than DASH, or Mediterranean, or plant-based, and I provide here a number of the recent meta-analyses.

So this has been around for a long time and been well studied. And now, finally, in 2019 — and this has been just tremendously exciting for us — the American Diabetes Association has changed both their standards of care and their nutrition consensus statement to incorporate very low-carbohydrate nutrition as an established eating pattern for the treatment of Type-2 diabetes. And so, this hasn't been just the — the ADA. The European Association for the study of diabetes has changed their standards as well. And then, actually, this was preceded by a statement from the Veterans Administration in the Department of Defense in 2017 — also changing their standards of care to incorporate low-carbohydrate nutrition for diabetes treatment.

Okay, myth 15: The benefit is just all about weight loss. That actually is not the case, and there's a very nice study out of Jeff Volek's lab that I'll walk you through. It's showing that you see benefit even in the absence of weight loss. And then, the follow-on from "It's just all about weight loss" is "And all of that weight loss is water."

That actually is not the case. So while natriuresis causes water loss early in ketosis, this clinical trial out of Spain that I mentioned, with a 20-kilogram weight loss over four months found that it was 87% fat mass, 8% water mass, and 5% lean mass.

And so the study — this is a really wonderful study, and it's a randomized-order study, holding weight constant in people with metabolic syndrome, and found significantly more participants reverse their metabolic syndrome following the low-carbohydrate diet for just four weeks, whereas this is not seen in a — a low- — a high-carbohydrate or moderate-carbohydrate diet. So I'd encourage you to read that paper.

Myth 17: Ketosis will cause “keto flu.” I'm going to show you a number of slides on electrolytes. And so electrolyte or salt management actually can avoid most if not all of the symptoms that are associated with the transition to ketosis, including fatigue, headaches, and weakness.

And myth 18: that you'll have constipation. So again, salt management can avoid most if not all the symptoms, including constipation. So let's go through electrolytes for a little bit. So we generally are recommending for our patients that they aim for around 5 grams of sodium per day and getting that from either salt in their food, or from broth or bouillon. And so, in high-carbohydrate diets, insulin actually signals the kidneys to retain sodium. And so, when you switch over to a low-carbohydrate diet, you take away that insulin signal and sodium will be excreted, so natriuresis. And so, you need to replace that sodium. And likewise, we recommend potassium, either dietary or supplement, and magnesium, either dietary or supplement. So getting salt right turns out to be a big deal in terms of avoiding side effects of ketosis.

So then, okay — So we're recommending a lot of sodium. That must be a problem, right? So myth 19: So ketosis will require too much sodium. So while the U.S. Dietary Guidelines recommends low sodium, 2.3 milligrams, actually multiple studies have now shown by tracking sodium excretion, which matches pretty closely with — with intake, that low salt consumption actually is increasing mortality, and that higher-salt intake is actually advisable. So I'll just read this quote here from what we recommend in terms of clinical management: “One of the biggest challenges that we encounter in managing people following a ketogenic diet is to get them to pay adequate attention to their sodium and potassium intakes. Part of this stems from the past 50 years of salt demonization, in which we were taught that the less sodium intake the better.”

Okay, so then myth 20: If you're taking in all this extra sodium, you must be getting hypertension. Well, actually we see the opposite. So just walking through that in a little more detail, there's a very nice study in *New England Journal of Medicine* in 2014

and then a follow-up to that in *Lancet* in 2018, the PURE Study, looking at over 100,000 people in 17 different countries showing that there's this U-shaped or J-shaped curve associated with sodium, and that if you get the levels too low, you're actually not improving things, you're actually making the mortality worse — whoops.

And then, likewise with potassium, there actually is an increased risk associated with low potassium as well. So, getting enough dietary potassium is important. And then blood pressure. We saw actually, as we told people to get on a ketogenic diet and increase their sodium intake, their blood pressure went down. We saw the systolic reduced from 132 to 126 — sorry — and diastolic decreased from 83 to 79. And there's a nice study out of the U.K. from Unwin and colleagues in recent months also showing even a sharper decrease in — in blood pressure. And in both cases, both our trial as well as their trial, a decrease use of antihypertensives.

Myth 21: Ketosis will cause adrenal fatigue. There's no evidence that ketosis inhibits adrenal function. However, sodium restriction — again, back to salt — sodium restriction during ketosis will trigger adrenal activity through the renin angiotensin aldosterone system. So it is advisable not to overly restrict sodium when in ketosis.

And then also, myth 22: Ketosis will cause gallstones and requires a gallbladder. So actually, gallstone formation is associated with very low-calorie liquid diets that lack fat. So where there's not a stimulation for the gallbladder just to empty, that's where you're much more at risk of gallstones. And we have many patients on a ketogenic diet who do not have a gallbladder, have had that previously removed, and so in terms of management — clinical management, if there's an issue with fat tolerance, you can improve that through the use of fat in emulsions, as well as to spread fat intake out throughout the day.

Okay so myth 23 — and Zoë talked about this a little bit, not in the context of ketosis, but in the context of other nutrition including carbohydrates versus fat — is nutritional epidemiology studies. So it's important to point out that in these nutritional epidemiology studies, no one has really looked at it — at a ketogenic diet. These people whose — who are tracking their foods in these — in these studies have been much more kind of within the mainstream of dietary consumption. And while some studies based on food surveys have extrapolated higher mortality with higher fat diets, other studies have reached the opposite conclusion, and in clinical trials, replacing saturated fat with polyunsaturated fat or carbohydrates has not improved mortality.

And then myth 24: that ketosis requires meat consumption. While most of our patients are omnivores in terms of their food consumption, we do have a large number of vegetarians who follow a ketogenic diet and are part of Virta. And we

even have people who are vegans, and we've provided instructions for how to follow a ketogenic diet on — if you're a vegetarian or a vegan.

Okay, so we've done two dozen myths. Are there any more? Surely there couldn't be any more? There are. All right, let me do a time check. We're gonna go even faster.

Myth 25: Ketosis will increase cancer risk. There's no evidence of this. In fact, several dozen trials are currently examining ketogenic diets as adjuvant therapies to chemotherapy. For instance, there's some very interesting work going on right now in Cornell in New York on PI3 kinase inhibitors and how you can use ketogenic diets to counteract a rise in insulin.

There's the myth that ketosis will increase circulating fat, saturated fat. Certainly, if you have all this saturated fat in your diet you must have a lot of it in your blood. Actually that's not the case. In this same study that I cited earlier, Hyde et al., *JCI Insights*, 2019: In a randomized-order study, holding body weight constant, plasma saturated fatty acid levels were actually lowest during the low-carbohydrate diet despite higher saturated fat consumption. And this sounds like a paradox, but it's actually because you're burning fat for fuel.

Myth 27: Ketosis provides inadequate dietary fiber. And I hope I haven't stepped into a fierce debate here, but there is not evidence that the fiber is inadequate in a ketogenic diet. It's not an essential nutrient. A well-formulated ketogenic diet does provide about 12 grams of fiber per day from vegetables, nuts, seeds, versus the American Heart Association is recommending that people have 25 grams or more per day. So our recommendations are lower, but there's no evidence that there's an issue with that.

And actually, and then following on from that, if you have inadequate fiber, you must be messing up your gut microbiome. Again, there's no evidence that this is the case. While the microbiome does vary with diet, there's no evidence that ketogenic diets result in an inferior microbiome. And actually, the role of the microbiome may be somewhat different in the context of a high-fat or ketogenic diet in terms of one of the functions of having that fiber and those microbes is to produce butyrate to feed the colonocytes. And there's a good argument that beta-hydroxybutyrate in a ketogenic diet may be filling — fulfilling that same role. And so, here's an example of fiber on — in a well-formulated ketogenic diet over the course of breakfast, lunch, and dinner, and snacks. Works out to about 24 grams of carbohydrates per day, mostly from non-starchy vegetables. That's almost 13 grams of fiber.

Myth 29: Keto is environmentally unsustainable. And so keto has been kind of caught in this fight between animal and plant agriculture. And I would just state that the advantages of plant-based diets are often overstated in terms of their environmental impacts. There's a recent, very interesting study by White and Hall that removing all animal agriculture from the United States would only reduce the greenhouse gas emissions by 2.6% while resulting in nutrient-deficient foods. And so I'd encourage you to read that paper. Also, ketogenic diets can be formulated to be either animal or plant based depending on the preferences of the patient.

And then, the myth that ketogenic foods are too expensive. I would point out that among the three macronutrients, actually getting protein without fat and/or carbohydrates is the most expensive per kilocalorie. So, for instance, lean cuts of meat are more expensive than fatty cuts of meat. And ketogenic diets are not high in protein. They're high in fat, and they're moderate and protein in at 15-20% range. So we're not asking people to go out and buy, you know, expensive cuts of meat. There's actually no requirement for expensive processed foods. We actually discourage processed foods in a well-formulated ketogenic diet. There's no need for premium ingredients, and there's no need for keto supplements.

So this is what we recommend: individualized nutritional ketosis — highly personalized, including by the budgets of our patients. So talking with them about — about their — their — the cost of their food for their family. Also looking at their preferences, everything from omnivore to vegetarian and focusing on whole foods rather than processed foods. And again, it's not a zero-carb diet, so it's a low-carb diet.

Okay, so getting into the home stretch, and so — this one that could be an entire talk in and of itself, and there are others in the room that are much more expert in this — but the application of ketosis to exercise. It's false to just assume that it's going to interfere with exercise. There are examples of elite athletes following keto adaptation. Performance can exceed high-carbohydrate results. Actually Zach Bitter, just in the last two months, broke the world record in the 100-mile, and the world record in the 12-hour run. And he does that as a fat-adapted ketogenic athlete. So I would point out that keto adaptation in terms of athletic performance takes at least 12 weeks in terms of — you will see a dip in performance in the first few weeks as you begin a ketogenic diet, and then this varies by sport and by energetic needs. So I'm not saying that all athletes should be in ketosis. And so I'll show in the next slide actually, though, what actually happens in terms of peak fat oxidation, which is really fascinating.

The other — the other myth is that ketosis will deplete muscle glycogen. And the same study that I'll show in a second shows that there's no differences in muscle glycogen pre- and post-workout in high-carbohydrate versus ketogenic-adapted

elite athletes. And high fat oxidation is actually glycogen sparing. So — So Jeff Volek's lab looked at this a few years ago, this paper published in *Metabolism* in 2016. It compared 20 male ultra runners who were either on a low-carbohydrate ketogenic diet, or a high-carbohydrate diet for at least six months. And they found that in the low-carbohydrate ketogenic group, that their peak fat oxidation was 230% higher than the low-carbohydrate group. And this actually is resulting in rewriting of the textbooks in terms of what peak — peak fat oxidation in humans looks like, and so that's why it's glycogen sparing.

Okay, so myth 20 — myth 33, sorry: Ketosis will raise long-term risk of gout. That's not the case. So while uric acid shows a transient rise in the first few weeks of keto adaptation, probably because there's competition within the kidney between uric acid and — and ketones, uric acid levels were unchanged at one and two years in our trial, and no new cases of gout were observed. And other clinical trials have seen — seen the same thing, and there's actually a mechanistic paper in animals suggesting that ketosis could prevent gouty flares by inhibition of IL-1 β .

Myth 34: Ketosis will raise long-term risk of kidney stones. This is also false. There are papers that describe case series of kidney stones in ketogenic diets for pediatric epilepsy. We saw one case of a kidney stone during the entire trial. And there's no trials documenting a higher rate of kidney stones beyond baseline in adults in ketosis.

Okay, so these are crazy ones, all right? So you probably wondered when I was getting to this: What is keto crotch? So it does not exist. This was a term that appears to have been promoted by a public relations firm in February of 2019 as part of a paid media campaign to counter the keto trend, and I won't go through who all might be behind that.

Myth 36: Keto will cause keto bloat. Again, this does not exist. There's no evidence that ketosis causes bloating. However, in clinical management, whenever you make a dietary change you may see changes in — in your — your bowel function. So, instruct patients to be aware of irritable bowel syndrome that can occur upon introduction of any new food following any dietary change, not just ketogenic diets. These include FODMAP-containing foods, as well as sugar alcohols and other artificial sweeteners. So, you know, if you're getting off into kind of the, you know, crazy low-sugar processed foods, you could be causing bloat that has nothing to do with ketosis.

Okay, so, the sort of desperation myths. Okay, ketosis will confuse the public. This is an excuse. In other words, the experts are saying, "If we embrace the benefits of a high-fat diet, the last 40 years of nutrition guidelines and advice are in doubt." But there's good reason for doubt.

Okay, ketosis myth 38: Ketosis will undermine science. This is another excuse, okay? So you've seen early on in the talk, the increase in scientific publications. But in this recent last month on the unprocessed meat and processed meat, dietary recommendations came out of an international group showing that there was not evidence that people should be shifting away from the consumption of — of red and processed meat. And here was the reaction from one group of nutritional epidemiologists. They said, "The publication of these studies and the meat guidelines in a major medical journal is unfortunate. It's going to harm individuals' health, public health, and planetary health. It may also harm the credibility of nutrition science in erode public trust in scientific research. And it's going to cause confusion among public and health professionals — among the general public and health professionals." So these are excuses.

Okay, we get this one: You're gonna get rid of diabetes, but you're gonna get diabetes again because ketosis causes diabetes. There's no evidence of this. This myth is derived from poorly designed animal studies with improperly formulated high-fat diets.

And then the last one — you're probably waiting for the end. So myth 40: It's just better to stay with usual care. Safe, you know, stay safe. Well, usual care does not reverse diabetes. There's actually a large study, medical record review out of Kaiser Permanente of 22,000 adults. And they said, "The seven-year cumulative incidence of partial, complete, and prolonged remission was 1.47%, 0.14%, and 0.007%." So even allowing for metformin use as we do in our definition of diabetes reversal, these reversal rates in usual care are very, very low.

All right, so, a few conclusions: So, nutritional ketosis is a viable patient choice for the reversal of Type-2 diabetes. Low-carbohydrate nutrition patterns including ketosis have extensive clinical trial evidence for diabetes improvement, including our one- and two-year results. The ADA and other organizations have updated their guidelines to include low-carbohydrate eating patterns for Type-2 diabetes. In terms of clinical management, focus on electrolytes, especially in the first few weeks as people go through keto adaptation. Forty — eight of the 40 myths that I talked about are basically issues to do with salt consumption. Be informed, talk with your patients, debunk myths that are causing fear, and let patients know that they have a choice to reverse diabetes and that the decision is theirs. This is about empowering patients. Thank you.