The Tim Ferriss Show Transcripts
Episode 65: Dr. Peter Attia, Part 2
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Peter Attia: I'm going to do something that feels incredibly awkward.

Tim Ferriss: Hello ladies and gentlemen, boys and girls, this is Tim Ferriss and I am walking in flip-flops down the sidewalk in San Francisco where the birds are singing. I just passed by, kind of headficked and slalomed around. There appears to be a homeless guy or startup founder doing slow-motion karate chops on a tree either tripping his balls off or coming up with the next billion dollar company, who knows. In any case, all is right with the world. This episode is a follow up episode with Dr. Peter Attia. This is by popular demand. As soon as many of you listen to Episode 50, which was the first episode with Peter, that was Dr. Peter Attia on Life Extension, Drinking Jet Fuel, Ultra Endurance, Human and More, immediately after that you asked for a round two. So many many of you submitted hundreds of questions. Those were voted up, and he answers the top 10 to 15 of those in this episode. Why does it always sound like Beirut during wartime in San Francisco? God dammit people.

Anyway, this is a really really fun episode. It's hilariously awkward for Peter in the first few minutes. Give him four to five minutes to really get into the flow and I promise you this is well worth a listen. I learned so much about blood testing, and I know a lot about it already. I learned so much about the supplements he takes and why and the supplements he does not take and why, how he thinks about long term ketosis, the value or lack of value in it, and on and on and on. So please enjoy. You can always find show notes, links, all that good stuff at fourhourworkweek.com/podcast, and without further ado, please have fun with Peter Attia.

Peter Attia: I'm going to do something that feels incredibly awkward so I ask you to bear with me, which is basically sit here and have a monologue with myself for the next hour or so as I answer at least a subset of these questions. So hopefully this isn't as awkward for you as it is for me. All right, so basically looking through a list of a couple hundred questions that you have posed, and what I'm going to try to do is address about ten or 11 or so. So let's start. First question, which is submitted by someone that says, "Cinema." I don't know if that's the person's name, but it says,

"What are the top five biological tests, blood work, hormones, etc., everyone should get?" this is a tough question, because I don't know the answer to it in the sense that I think there are different, you know, the top five for one person are probably different than the top five for the other. So I'd have to know a little bit more about the risks that a person faces, right? Meaning, are they more at risk for cardiovascular disease? Are they more at risk for cancer? Are they more at risk for neurodegenerative disease down the line? Or are they dealing with an acute problem at the moment? You know, they have really horrible energy or really poor sleep or excess amount of body fat or something.

And so you have to know a little bit about which of those things the person wants to determine if you could only have five tests. Now with that said, let me take a crack at it through my lens, which is a lens of preventing death. So these aren't necessarily the tests you'd order if your goal is to make somebody feel better in six weeks or six months even, but this is probably the five most important things I would order to mitigate the long-term death, basically to extend longevity. So the first thing I'd want to know is I'd want to know somebody's APOE genotype, and the reason I'd want to know that is though it doesn't determine your fate, it certainly helps us understand out of the gate what diseases you may be more or less at risk for. So the APOE gene codes for proteins that are involved in the metabolism of cholesterol, but in particular they play a really important role in the development of cardiovascular disease and Alzheimer's disease. And so knowing somebody's APOE status allows you to determine what you need to do to mitigate those risks, both through nutrition, but also through pharmacology.

There's nuance to this as well. Somebody with an APOE-4 4 or APOE-3 4, which are variants on the wild type which is a 3 3, these are people I will always want to make sure, for example, that they have desmosterol levels that are maintained. Desmosterol is a cholesterol that we synthesize. I'd also want to be thoughtful before putting them on medication that could interrupt with cholesterol synthesis in the brain and things like that. Okay, the next thing I'd want to know, and these two sort of go hand in hand is LDL particle number, via NMR, and LP a particle number, also via NMR. So NMR is a technology that can count the number of lip protein particles in the blood, and the LDL particle, as its name suggests, counts all of the LDL particle. So an LDL particle is a particle that is defined as a lipoprotein with an APOE-B 100 APOE lipoprotein on it. These are the dominant particles that traffic cholesterol in the body, both to and from the heart, by the

way, and to and from the liver, but they sort of gain their fame because these are the ones that traffic sterols into the subepithelial space where it leads to atherosclerosis. And we know, I would say beyond any shadow of a doubt, but some might dispute that. We know beyond any shadow of a doubt that the higher the number of those particles, the greater you are at risk for cardiovascular disease.

So I like to know that, and again, that tells me where to focus on reducing it. Some people have that number elevated because of genetic reasons, and other cases it's very lifestyle driven. Now the subset of that is this thing called LP a. So LP a is another LDL particle, but it also has another apolipoprotein on it called apolipoprotein a. Now I know what you're thinking, which is, "Could they come up with worse names?" And the answer is, "Maybe." But nevertheless, the LP a particle is perhaps the most atherogenic particle in the body, and while it's included in the total of LDL particle numbers, I definitely want to know if somebody has an elevated LPL a particle number, because that in and of itself, independent of the total LDL particle number, is an enormous predictor of risk, and something we've got to act on, but we do so indirectly. In other words, diet, drugs don't seem to have any effect on that number, so we pull the lever harder on other things.

Let's see, that's one, two, three. Okay, the next thing I think it's worth doing on pretty much everybody, if you're trying to evaluate their risk of metabolic disease or just figure out what's going on at the moment, is a very simple test called an OGTT, an oral glucose tolerance test. And while simple in concept, it's sort of a pain to administer which is why most people don't get it done the way I would like it done, which is a time zero, time one hour, and time two hour test that looks at insulin and glucose. So out of the gate you have a glucose and insulin level, you drink the 75 gram sort of nasty cola-like drink that contains 75 grams of glucose in it, and then one and two hours later you have this repeat blood draw. And why I think this test is important, especially is what you see at the one hour mark. A lot of people skip that and they just go straight to the two hour mark, but that one hour one is where we see the early warning signs. So a lot of people don't meet the criteria for diabetes, meaning they have a normal hemoglobin A1C and they don't have a glucose over 200 in response to this test, but when they start to get very elevated levels of insulin at that one hour mark, and elevated is sort of a subjective term. I would define elevated as anything over 40 to 50 on the insulin, and that's subject to the lab, that's based on the lab, that I use.

I know that that person is hyper insulinemic even if not while fasting, and that's a harbinger for sort of the metabolic problems that we're trying to ward off. Let's see, one more. I think it would be a toss-up for me. It really does depend on what the person is at risk for. I like to see a person's IGF 1 level, insulin like growth factor one. We know that this is a pretty strong driver of cancer, so if we have a person who is at risk for cancer or who themselves is a survivor of cancer, we really want to do everything we can through diet, both the type of food and the amount of food that they consume, to keep IGF 1 levels low. So I guess that would probably make my top five list. Okay, next question. This is by someone named Bezo. It says, "In the fitness community, it is widely accepted that carbs after workouts help enable protein synthesis with the anabolic window, but I've seen studies disprove this. What have you seen and what do you know in regards to this theory?" So okay, so the question basically is should people eat carbohydrates following weight training to promote anabolism within the muscle? At least, that's the way I'll try to answer the question. So I think the short answer is it depends what you are optimizing for. So if you are a body builder, or if you are somebody who's primary objective is to increase hypertrophy, which is just the technical term for muscle size, then yes, I think there almost assuredly is a benefit from consuming carbohydrates and/or whey protein.

Remember, whey protein is going to spike insulin as well. It's an already relatively simple form of amino acids that's quite insulogenic. And so I'm not – Actually, that's not true. I am actually aware of a study that I believe tried to compare carbohydrate versus a whey isolate, and unfortunately I can't recall the difference between them if there was one. But the point is, they're both quite insulogenic. So yeah, if your goal in life is to sort of increase the size of your muscles, then I think that's going to be a positive thing to do. Keep in mind that for some time now body builders have used insulin, just straight up insulin, as a "performance enhancing drug." I say performance enhancing, because really, I don't know what performance means in body building. But in as much as they'll use anabolic steroids, they'll certainly use insulin in a building phase, not a cutting phase. Because remember, insulin is anabolic to fat and muscle. So unlike testosterone, which is of course anabolic only to muscle and it's catabolic to fat. So what's the flip side of that? The flip side of that is if you're somebody like me, for example, who, I mean, could not care less about the size of his muscles, then no, in fact, the answer is I don't do that.

In fact, I'm at the point now, you didn't ask this question but I guess since I'm on the topic, I don't even consume whey protein post-workouts anymore. So when I lift weights, which I do twice a week, I do it basically fasted, just drinking water, and post-workout I consume nothing. Now what I acknowledge is I am missing out on the opportunity to increase muscle size, muscle mass, potentially even strength with the slight breakdown of muscle, but you see, I don't care about that as much as I compare about a few long-term things I'm tweaking that involve some sort of caloric restriction that I like to do. So again, neither one is right nor wrong, but it's really a function of what you're optimizing for. Okay next question. This is by someone named Hapax. It says, "In the previous Tim Ferriss interview, you mentioned discussing what supplements to take, but ran out of time. What are your top 10 supplement recommendations, and do you describe to periodization even for everyday supplements such as vitamin D?" I mean, I'm certainly happy to answer what supplements I take. I'm not sure how relevant it is to the listener because there's few things that I believe just taking out of the gate for everybody. In other words I sort of, with my patients at least, take a very tailored approach to what they should or shouldn't take. So what do I take? I take vitamin D, I take a baby aspirin, I take methyl folate, I take B-12, I take EPA and DHA Omega 3 fatty acids, and I take berberine. I think that's all I take, and you could argue baby aspirin is not really a supplement, but I count it as one I guess. Okay, so why do I take those? What do I not take? I do not take a multivitamin, I do not take vitamin A, I do not take vitamin C, I do not take vitamin E, I do not take vitamin K, although I have flirted with vitamin K a little bit and I have some interesting thoughts on that for certain people.

Oh, I also take a probiotic, which I do actually periodize, and I actually deliberately cycle the dose of that throughout the week. So on the ones I do take, the reason I take them is basically all I'm managing to certain levels. So I have target levels for vitamin D, and I can't get to them without supplementing, so I supplement. I have an MTHFR mutation, which means, and these are not that uncommon by the way, so it's not like I'm a two-headed freak, but that mutation means I don't do a good job methylating folic acid, and so as a result, I take methylated folate to get around that problem. I also can't seem to get my B12 levels to where I want them to be. I can get them into the "green zone," but I aspire to actually have a slightly higher level, so I need a very low dose of that supplement. And again, to the point about periodization, I do take my vitamin D every day. I sometimes double up on days that

I know are going to be brutally stressful. On the methyl folate and the B12 and I also take B6 for another reason, I do actually rotate those, but that's less because I believe that periodization is necessary and more just to minimize the number of pills I take a day, and because I don't need them every day I generally only take them twice a week.

And again, I'm doing this to titrate to a very specific dose. So I'm really using my blood levels to determine how much or how little I need of these. I think the only one I haven't addressed is berberine and baby aspirin. So baby aspirin I take because my aspirin works test lights up. What that means is, if I'm not on a baby aspirin, I pee into a cup, the lab does a test on that to determine how sticky my platelets are, the answer is very sticky. So a baby aspirin, which is just a quarter dose of an aspirin, actually inhibits the functionality of platelets in a way that doesn't lead to massive bleeding if I get a cut, but takes the "edge" off that feature. And actually what I will do there is I will increase that to a full aspirin, meaning four baby aspirin, any day that I'm doing a cross-country flight, which is usually once or twice a week. So most days I'm just taking a baby aspirin, any day that I'm flying, because I want to minimize even the smallest chance of a blood clot, I'll take four of those.

Okay, so the last one is berberine. So berberine is a vegetable extract that actually is kind of a natural mimicker of metformin on one hand, which is to say it activates AMP kinase, and what the net effect of that is, and I'm sorry I'm going a little quick. We could obviously spend an hour just talking about why AMP kinase activation is important in health, but suffice it to say one of the net outcomes is the suppression of hepatic glucose output, which maintains lower levels of insulin and therefor lower levels of IGF 1, which is something I place a huge premium on. The other thing that berberine does that metformin does not do is it inhibits PSCK9. So PCSK9 plays a very important role in the metabolism or breakdown or processing of lipoproteins, those LDL particles, and about 10 to 15 percent of the population if I have my numbers right, and I might be a bit off, tend to over express PCSK9, and we have a genetic test for this that I frankly don't do that often in people. I tend to just put them on berberine, and if their LDL particle level drops on berberine by 10 to 20 percent, then I know that they're an over expressor of PCSK9. If they have no response, then I know that they're not, but they still may benefit from it from a glycemic and insulin level.

So anyway, that's where I am on the supplement front. Okay, next

question. This is from Gabbi in Toronto, my hometown no less. "The evidence both pro and anti keto seems conflicting. Should the ketogenic diet be seen as a short-term intervention or a long-term lifestyle, and what can be done to minimize any potential downside to keeping it long-term?" Gabbi, this is a question, I think I'm selecting all the questions I don't know the answers to, because, well, okay. So let's start with the hardest part of this. Is there evidence of any society that has subsided, or any group of our ancestors or any culture, that has lived entirely on a ketogenic diet in perpetuity? Now this is a controversial topic, and I'm not an expert in it, so I don't know the answer, right? But I've read everything that I can get my hands on, and I think I'm comfortable saying I don't know.

Now historically, people have suggested that the Inuit lived perpetually in a ketogenic state. I'm not convinced that that's correct. I think they probably spent part of their time in ketosis but may not have been in ketosis full time. The other culture that often gets mentioned as a full time culture of ketosis are the Maasai, though I've never seen supporting evidence for that, and I have my doubts because the Maasai, to the best of my understanding, bordered more on carnivore than omnivore, and it would be, to my estimation, very difficult for a pure carnivore to be in ketosis, because that's just too much protein consumption and as you probably know, if you've experimented with ketosis, you've got to really be, you have to titrate that protein level down quite low in addition to the carbohydrate level. So basically, let's take that off the table as, do I have any sort of natural experiment that I can point to that says, "Being in ketosis in perpetuity is the way to go?" And I think the answer is I personally don't. If somebody does, it'd be great to post about it and post to some sort of credible literature on it. So assuming the answer is no, that doesn't mean the answer to your question is no, right?

So when we start with what are the pro and anti keto data, I guess the question is they're all surrogate data, right? In other words, nobody's done a long-term study that says, "We're going to take a group of people, we're going to randomize them, half of them are going to go on a ketogenic diet, half of them are going to go on a fill-in-the-blank diet, and let's see who lives longer." So we'd want to do that, and we haven't done that. And even if we did that in animals, by the way, it's not clear it would be a particularly relevant experiment, given especially mice, which we have a fondness for doing experiments in. Mice, being natural herbivores, probably wouldn't be a great model for this. So when people say this study is pro versus anti keto, they're usually doing it based on

proxies. You know, body weight, cholesterol numbers, triglycerides, markers of insulin sensitivity, etc. And you're right, I think the data are generally conflicting, though I would always sort of, on any data, challenge people to make sure they read more than the abstract. So I've read probably a dozen studies that claim to be ketogenic diet studies, and then you read the methods and you look at the results and you realize no, actually these were studies that were putting patients on a low-carbohydrate diet, and these people weren't in ketosis.

Their beta-hydroxybutyrate levels didn't register high enough to really answer the question you're asking. And so if they find no difference between the arms, I don't know what conclusion we can draw from that. So, I mean, we could obviously spend a lot more time just discussing the sort of literature on this. I think others have already documented that pretty well, right? So there are a lot of documented examples of ketogenic diets being very safe and effective treatment at least over the short-term, by that I mean less than a year, for type II diabetes and obesity. I don't really follow the keto literature that closely, so I've also seen sort of bio marker studies on this, but I don't think I've seen anything longer than a year. So what does this mean to you? Well, I spent two and a half years in ketosis, and people ask me why am I not in ketosis today? So I haven't been in ketosis for a little over a year, at least not consistently.

I do get into ketosis at least once a week, just generally as a result of a fast that I'm doing, but long gone appear to be the days when, for just months and months and months I would not get out of ketosis. I would just continue to consume very very low amounts of carbohydrates, very very modest amounts of protein, and high amounts of fat. I will say this; I actually felt at my best on a ketogenic diet, and to this day I feel at my best when I'm either consuming hypo amounts of calories coupled with a ketogenic type of calorie, or not. But the main reason I think for me to move away from it to basically a diet today, which is sort of higher in carbohydrate than it has been historically but still lower in carbohydrate than it would be to the general population, is basically one of just a kind of craving I've really had for more fruits and vegetables. So doing that, it's pretty hard to stay in a ketogenic diet, and I think that going forward, I would probably stay in a diet that maybe cycles into and out of ketosis, but it's less about me believing that there's a long-term harm to being in ketosis, and more about me sort of scratching other itches in terms of experiencing a broader array of foods.

That's not as crazy as it sounds, maybe having a bit of a reminder of what it is I enjoy about that. So I apologize. I feel like I did a pretty crappy job on this question. I don't think I answered your question about the downsides to keeping it long-term, which I think is an important question. I guess the point is, I don't know the answer to that at the population level, but at an individual level, it's pretty clear when a ketogenic diet doesn't work. And I guess I should make that point as well. I've probably put two dozen patients on ketogenic diets for whom it became obvious to me within two months if not less that this was not a good diet for this person. So when you put somebody on a ketogenic diet and their CRP goes through the roof and they actually increase adiposity and their homocysteine goes up and their uric acid goes up and their LDL particle number goes up, I mean, I'm having a hard time justifying why this person should be on a ketogenic diet. And I think for some people that's just the case. I have some hypotheses about why, but I don't know the answer.

And so if you're not in that camp, if everything is moving in the right direction, if you're in the camp that I was in where my biomarkers are at their finest when I'm on a ketogenic diet, I guess I'd ask what's the alternative? Is it going back to a standard American diet? Is it cycling in and out? That probably gives you your answer. Okay, next question. This is by – I can't read it. Someone in New York. "In the previous talk, you mentioned you perform bloodwork on yourself at home. Do you see this becoming possible for the average person? What worthwhile test metrics are possible or on the horizon for average self-testing people?" Do I see this being possible for the average person? Probably not. And just to be clear, it's not like I have the lab inside my house. I just have the centrifuges and all of the equipment, so any day that I want to draw my blood I just have my wife draw my blood and I spin it and package it and send it to my lab with my paperwork, and I guess because I'm a doctor I can do that, so I guess you would need a slip from your doctor if you wanted to do that in a centrifuge and someone to draw your blood.

So in essence, yes. I think anybody who is obsessive enough could do what I'm doing if they had somebody who could draw their blood, they had a doctor who was willing to give them an unlimited number of lab slips, and they had all of the equipment to do this. That said, and I don't think that's that interesting, by the way. I think what is interesting is stuff that a company like Theranos is doing. So Theranos is a company in the Bay Area founded by a woman named Elizabeth Holmes, who I don't know by the way, but she's sort of this young prodigy. And basically

what they're doing is, at least to the best of my understanding, is creating this sort of black box that allows you to use just a thimble, less than a thimble, really the amount of blood you would use in a blood glucose meter. But instead of just getting glucose or just getting ketones, which is pretty much what we get on those tests today, to get just a much much broader array of tests. And I think the question is, will those devices be the things that people own?

I think not, but I think their goal is to have those things potentially at a CVS, where you can go in and you can sort of put a finger prick of blood onto a strip and you can get a wide array of things. So I think those things aren't that far away. I do wonder if one of the bigger hurdles to that is sort of the legal stuff. Obviously if you see what the FDA and 23 and Me have gone through, you could argue, "Well okay, that's just because it's genetic testing. Would the government be as concerned if people are getting blood tests without their physician acting as middle men or women?" I don't know the answer to that question. It's certainly beyond my pay grade. Now your second question is what worthwhile tests or metrics are possible on the horizon for the average person? Well, I think the sky is the limit here. Again, now I differentiate between the average person versus me. I mean, I just think of this more broadly as what's on the horizon? I mean, I think everything. I just read a paper a week ago that showed pretty convincing data – again, it's epidemiologic data, or it's cohort-based data rather, not epidemiologic – suggesting that plasma levels of APOE might be actually more indicative of the risk of neurodegenerative disease and Alzheimer's disease in APOE genotype. That's amazing to me.

So the first thing I did when I read that paper was I sent it to the chief scientific officer and lab director of Health Diagnostics Laboratory, to find out, "Hey, do you think you'll be able to offer this test one day?" And to my surprise, he responded and said, "Yes. We collect this data, we just didn't know anybody cared about it." And so I find myself often surprised when I want something done that somebody has already thought of it and they're just waiting to know that there's a demand for it. Okay, next question. This is from Craig in LA. "I've heard from several well-respected people in biology and medicine that not drinking alcohol at all may be the best bio-hack out there. Do you agree? I may cry." You know Craig, I was just asked this question at a conference last week, and I'll try to remember what I said, though I'm sure I was funnier and more eloquent then than I will be able to be now. I'll start with something that may be viewed as controversial. I have never seen convincing evidence that the

addition of alcohol confers a health benefit. So I know what you're thinking. "Oh, come on, I've heard that if you can drink two glasses of red wine a day, it reduces your risk of heart disease, blah blah blah blah blah." And I'm saying I don't buy those data.

I think that for some people, ethanol alcohol, up to reasonable doses, no harm. And you have to determine what your toxicity level is. Obviously at some dose everybody is harmed by it, and in that sense we come back to this model of what I call the toxicity model. So let me explain that, and then I'll come back to what the implication is for Craig and everybody else who's wondering if they should drink. So in pharmacology there's this idea, and I've blogged about this once, but since I doubt anyone's read it, I'll revisit it here. So in pharmacology, we have this thing called an LD 50. LD stands for lethal dose, to 50 percent of the population. So let's take a drug that everybody understands, like Tylenol. So Tylenol has an LD 50. Now we don't know exactly what it is in humans, because the only way you can find that out is to try and kill a whole bunch of people with Tylenol and figure out what was the dose that killed half of them, but we know exactly what it is in animals, and it's been extrapolated that in humans, it's probably between 10 and 20 grams. So let's just for argument's sake say it's 15 grams. What that means is, if you had a room of 1,000 people and you gave everybody 30 extra strength Tylenol, in three days half of them would be dead. And I say in three days, because that's about how long it takes to undergo liver failure and death from an acute ingestion of Tylenol.

So okay, so that's interesting, but how does that pertain to our alcohol question? Well, if you took that same group of 1,000 people and you gave everybody five grams, you might actually knock off one person. You wouldn't probably in 1,000 because that's too small a sample, but play with me on this one, right? If you gave six grams, you might knock off a few more. By the time you get up to 15 grams, remember, you've knocked off half the population, and if you crank that up to 20 grams, maybe 2/3 of the people have died, and if you went up to 40 grams, maybe you'll kill everybody except two people. So there's a distribution. It is often not bell-shaped, by the way, but nevertheless there is a probability distribution that basically says, "Eventually you'll kill everybody with anything," and by the way, there's an LD 50 for water, there's an LD 50 for oxygen. There's nothing that's not toxic if given in high enough doses. So let's go back to the ethanol question. So there's a pretty well-known LD 50 for alcohol, but that's for what I call acute toxicity.

That's not really what this question is about, but I want to just make sure I clear this up, because this will be a confusing point. So the acute toxicity is, if we have 1,000 people in a room and we make everybody drink 24 beers, assuming they don't puke, or we could just say, "Look, we'd give it to them intravenously," so we take that off the equation, yeah, you'll kill some fraction of them. So now let's take that off the table and say, "No, no, we're not talking about acute toxicity. We're talking about chronic toxicity. So at a high enough level of alcohol, everybody is going to get cirrhosis, right? But interestingly at a low level of alcohol, long before people are getting drunk, there are a lot of people who experience horrible side-effects. Now, the second point worth making here is it's not always due to the alcohol. So there are a non-trivial subset of the population for whom the tannins within wine cause vasomotor effects, horrible flushing, horrible GI effects, and basically anything over about a sip of wine and they're not doing well. And I don't mean, like, they're ill, I just mean they're having basically an inflammatory response that's sub-optimal. And the same is true for many people drinking beer. And so I guess, to answer your question, Craig, the thing I always recommend to patients when they ask me this question is do an elimination reintroduction test to find out what's true for you. Because at the end of the day, you're asking this question probably not because you care about it at the meta level, but probably because you want to know the answer for you.

Should you be drinking alcohol? And if so, how much can you get away with? And the best way to answer that is basically, knock it out of your system for one month, make no other change, by the way, and then slowly reintroduce it and take your alcohol of choice. So if you're a red wine guy, go zero wine for a month, make no other change otherwise, and then reintroduce a glass a day, and you'll get a sense, "Do I feel better, worse, or the same?" And if the answer is, "I feel a little worse," then you think you know. And if you don't feel any different, then you're probably okay. Okay, so anyway, I think I've harped on that enough. I think you get the point. Okay, next question is from Kirby in Austin, Texas. "You have mentioned passing a glucose test with flying colors after being in ketosis. Matt Lalonde has stated long-term ketosis would induce insulin resistance. Do you think your results are anomalous, and would you discourage carb carbolysis?" Okay, so yes, I did several types of tests while in raging ketosis. First and foremost, I did what was called the gold standard, which is either a euglycemic clamp or insulin suppression test.

I did the insulin suppression test at Stanford. It was administered

by the team of Gerry Reeven. Gerry Reeven is a fellow who basically coined the term "syndrome X," which later became described as metabolic syndrome. He's perhaps one of the most thoughtful people on insulin resistance. And I apologize if I'm repeating myself. I may have already talked about this on a podcast, but if not – If I have, skip the next three minutes. So the way that test works is you show up in the morning, overnight fast, they hook you up to two huge IVs. So 14 or 16 gauge IVs, one in each arm, and they give you insulin in one and glucose in the other. And the dose of glucose and the dose of insulin is determined by your body weight and your surface area. And they've done this in thousands of patients for about 35 years now, so they have this pretty well dialed in. And let's say your starting glucose was 90, which I think mine was. What they're going to do is follow you for the next six hours with this constant infusion of glucose and insulin, and they check you every 30 minutes, and where you end up when you hit a steady state of glucose determines how good you are at glucose disposal, which is really the best metric we have for insulin sensitivity.

So the higher your glucose at the end of that test, the less able you are to dispose of glucose, the more insulin resistant you are. And they had just published a series looking at 440 or so non-diabetic patients undergoing this test, and I believe that the range of glucose levels at steady state varied between as low as 75 to 80 and as high as 400. So obviously that person at 400 is basically pre-diabetic, and that person at 75 is very insulin sensitive. So I had a very bizarre experience there, which is my glucose started to go down very quickly. So the post doc who was running my test quickly realized that I was very insulin sensitive, or to be more specific, I was very able to dispose of glucose, and so they actually broke protocol and lowered my insulin level. And my glucose level kept falling, and by the way, so did my ketone levels. So I walked into the test with a glucose of, I don't know, 90, and a ketone level of like two and a half millimolar, and I very quickly started to go down in glucose, down in ketones, and the test ended pretty badly. Basically at about 90 minutes, my glucose was in the 40s, I was starting to become symptomatic, they stopped the insulin, gave me more glucose, but then I really fell off a cliff.

My glucose got down to 32, ketones were near zero, now I was profoundly symptomatic. That's actually the closest I've ever come to biting the big one doing one of my goofy self-experiments. Because they had to bolus me with pure dextrose, it's called D50, the IV infiltrated, the whole thing was a total disaster, but luckily in the end, they rescued me, and the punchline

is I guess I'm the most insulin sensitive person they'd ever measured. As part of that, I also did an oral glucose tolerance test a couple of weeks later, and the results there were quite similar. So I started out at a glucose of, I don't know, 90, or maybe 89 I think, and an insulin level of maybe four and at one hour the glucose was up to maybe 105 and the insulin was up to like 15, and at two hours glucose was in the 70s and insulin was maybe down to six. So again, that would be a great example of gluco-disposal. Okay, so what is Matt Lalonde talking about? Well, what Matt is talking about is there are many people, and I have a hypothesis why, for whom that's not true. You put them in ketosis or you restrict carbohydrates and, in fact, they appear to be insulin resistant.

And what we believe that is something called physiologic insulin resistance. So when you restrict carbohydrates, your body, specifically your muscles, your liver, and maybe even your adipose tissue, your fat tissue, although I don't know the answer to that question, may actually get to a point where they say, "Look, we're going to become really resistant to the effect of insulin because we want to preserve any remaining amounts of glucose for the brain." So when you take somebody who's been in that state, whose brain is getting about 60 percent of their energy from glucose, 40 percent from ketones, the muscle basically says, "I'm not going to use up any of this glucose. I'm going to rely entirely on ketonin free fatty acid." And then when you dump on that person a huge degree of glucose, it just skyrockets. Because the brain isn't going to dispose of that quickly. The rapid disposal of glucose is glycogen mediated. It's hepatic glycogen and muscle glycogen. And to be honest with you, that is a much more common response than the one I've just described.

So I'll share with you another anecdote. So a friend of mine who's been on a very low carbohydrate diet, not sure if he's quite ketogenic, but he's been on a very low carbohydrate diet for about three years, called me in a panic about a month and a half ago because his brother needed a kidney transplant and he was a match for him, but went to do an OGTT and "failed" because his glucose didn't, he had a horrible OGTT. His glucose went up. And they said, "I'm sorry, you cannot give a kidney to your brother because we worry that you're basically pre-diabetic." And he calls me up and he's obviously distraught and said, "How can this be happening?" And I said, "Tell me a little bit about your diet. Okay, got it." So I said, "Look, repeat the test, but just make sure that in the three days prior, you consume about 150 grams of good carbohydrates. I'm not saying go out and eat potato chips, but in

the three days before, go out and have some rice, have some potatoes, have the sort of things that are a high quality carbohydrate, and what you need to do is basically let your muscles realize over three days, 'Hey, by the way, glucose is on the horizon. You don't have to shut down.'" And he sent me a very very kind note about a month later saying, "Oh my god, I'm just getting out of the hospital now. The operation went well," implying obviously he redid the test, he passed with flying colors, and he had just donated a kidney to his brother. So a very happy ending for him, but of course it sort of pissed me off to think that the doctors didn't know this in advance.

So now to the question why did I not have that experience? And I've done so many of these tests that it's pretty consistently true. The only thing I can think of is that because of the quantity and intensity of my exercise, I think I walk around in a state of relative glycogen depletion, and as such, there must be a certain threshold where below a certain amount of glycogen, your muscles are just primed to take in glucose. And I suspect that's what's going on in me, and the other few people I've tested who are on very low carbohydrate or ketogenic diets, who pass OGTTs with flying colors. So I hope that answers that question. Okay, the next question is Ohedna, I think, in London, "You've mentioned before that you eat a ketogenic diet because it works for you. How would someone figure out if it's a good or bad idea for them? What are the markers you check?" Okay, so I guess I kind of already answered this one in the question that Gabbi asked. So how could I sort of synthesize that so I don't go on too much more?

So it works for me. I think the reasons why I described it works for me make sense. How does this diet not work for you? Well, people who start to just put on massive amounts of fat, which, I think it happens. I think there are just people for whom you put them on a ketogenic diet, and they blow up. That's generally a bad sign, right? It just says that your body prefers the currency of glycogen to that of fat, and absent doing something hypo caloric, maybe a hypo caloric ketogenic diet, something is not going right. The other thing is, biomarkers that really go to hell in a handbasket, and I always do worry when someone's LDL particle number goes through the roof on a ketogenic diet. I will actually comment on that specific case on my blog shortly. Because that's, in and of itself, an entire topic around troubleshooting the skyrocketing LDL particle number on a ketogenic diet, which I feel like I'm now becoming one of the people who sees that a lot, and I'm getting better at appreciating what some of the nuance is there. But it is complicated, and it comes down to managing levels

of sterols. So understanding cholesterol synthesis versus cholesterol reabsorption, and you can get clues about that.

There are also, and this is too soon for me to say because I don't think my N is large enough, but I do think that there are certain APOE genotypes that do more or less better on a high fat diet versus not. The thing I would wrap this in, the bow I would wrap this all around, is be careful to distinguish between hypo caloric and hyper caloric ketogenic diets. They don't have that much in common, aside from their names. So physiologically, to put somebody on a hypo caloric ketogenic diet, most people respond really well to that when they have an acute metabolic issue you're trying to resolve. The u-caloric or iso-caloric or even hyper-caloric ketogenic diet, meaning basically an ad libitum ketogenic diet, which is like, "Yeah, just stuff your face with ketogenic foods," that's one where all best can be off. There are a lot of people that really don't do well on that diet, and I've sort of described what that phenotype looks like. And conversely there are kind of people like me who got away with it.

I mean I just, I could mainline fat when I was on a ketogenic diet, and it just didn't matter. But I'm starting to believe that people with my phenotype are actually in the minority. And by the way, there also appears to be a big gender difference. I have noticed that on balance it is easier for me to succeed on ketogenic diets than women. It's not an across the board rule, but it's just sort of a general theme. Okay, the next question by Christian in Montreal, Canada. I love the Canadian contingency here. "When Dr. Attia mentioned that cardio isn't good for you, does he mean intense cardio, or even regular folks jogging? How do I get a good VO2 max then?" Okay, so there's really two questions here, but they're good ones. So no, I do not mean that exercise is bad and that you shouldn't be out there walking or jogging or doing all these things. What I'm talking about is the type of cardio activity that puts an undue stress on the heart in terms of cardiac output. So what does that mean? So, and again, apologizing if I've – I've already forgotten what we talked about on the last podcast, but obviously we must have talked about this somewhat or this wouldn't be coming up.

So at rest we have a cardiac output that's modest, right? So someone my size might be four or five liters per minute. Meaning as I sit here, my heart is putting three to five liters per minute of blood throughout my body. And it accomplishes that by a certain rate, how many times it beats, and a certain stroke volume, how much blood gets pumped with each beat. The product of those is

your cardiac output. When you exercise, when you really push the limits of what you're doing aerobically, anaerobically, and the sweet spot, by the way, where you're going to get maximum cardiac output is sort of at that threshold level, you are increasing that cardiac output significantly. So a well-trained athlete could get to 30, even more than 30 liters per minute. And you get part of that increase through an increase in heart rate, but a lot of it comes through an increase in stroke volume, which means that the heart has to expand.

It has to open much wider to accompany the blood volume to pump that blood. And it's that expansion, if sustained for long periods of time, that results in deformation of the electrical system within the muscle of the heart, in particular on the right side of the heart, because the right side of the heart is less muscular than the left and more susceptible to this stretch injury. And what we then see are electrical errors. Basically we see electrical failures, electrical system failures of the heart down the line. So there was actually a prospective cohort, so it wasn't a randomized assignment. We're never going to get an answer to this question in humans on a random assignment. But there was a prospective cohort study, the Copenhagen cohort, that looked at people running, and it stratified them by duration and speed. Okay? So how far do you run a week and at what pace? And it turned out to reproduce virtually all of the previous literature on this, which is basically a U-shaped curve, an inverted U-shaped curve. Sorry, let me be clear, an inverted U-shaped curve.

Which means that at very low levels of activity, the outcomes are not good, right? People don't live as long. At medium levels of activity, and again I don't exactly remember what medium was, it might have been something like 30 to 45 minutes a session four sessions a week I think might have been around the sweet spot at a modest level of activity, coupled with other types of exercise, you actually saw the longest or the best outcome, the most longevity. So that's no surprise, right? Those people are doing better. What is surprising is that at really high levels, so greater duration, greater intensity, we actually saw the curve fall down. So what's the net effect of that? The net effect of that is it's not clear that you increase your longevity by exercising like a maniac. And I don't know what else to say about that, so I think I've answered that question. Now to your question, "How do I get a good VO2 max then?" Now, that's kind of a loaded question, and I don't know how to answer that without taking like ten hours.

So the first question I would ask you is who cares what your VO2

max is, right? So what's the purpose of the VO2 max? Well, and I say this as a guy who used to be obsessed over his VO2 max. When I was in high school, I had a very high VO2 max. Now that I'm kind of an old guy it's not as high, but it certainly used to be something I cared about. The reality is, VO2 max is very sport specific. So the number itself really shouldn't be something you care about. So my VO2 max on a bicycle doesn't translate to running, right? If you put me head to head with somebody who was a runner with their VO2 max and I'm a cyclist with VO2 max, that guy would blow me out of the water because I don't run at all. Similarly, we know that VO2 max is only weakly correlated with performance, even in endurance sports, and that's very counter intuitive. Now there's something that's related to VO2 max that's highly correlated with performance, and that's called either PVO2 max in cycling or VVO2 max in running.

So in running, the velocity that you run at your VO2 max, not your VO2 max, is highly correlated with how you will perform, and similarly in cycling, the power, the amount of watts you put out at VO2 max is much more important than whatever your VO2 max is. Okay, so I won't go into that anymore, but I will say this. Nothing that I've said about the principles of training means you can't have a high VO2 max. Remember, VO2 max is something – How do you train for VO2 max? Like, if someone came along and said, "Peter, let's see if you can get your VO2 max back to 70. I'm going to give you six weeks to get your VO2 max up to 70 milliliters per kilogram per minute," I might actually still be able to do it if I just trained very specifically for it. So the first thing I would do is I would lose weight, right? I would probably drop three kilos. Out of the gate that helps you. And then secondly, I would train very specifically to increase my VO2 max, which is basically three to five minute intervals in the exact apparatus and position I will plan to be tested in.

And frankly, that's just kind of an artificial thing to do. So I can train that energy system naturally without any detriment to what we're talking about, because it's a relatively short duration, or I can train it artificially just to get the higher number on the test if I cared. So short answer is, you can still have a good VO2 max while adhering to the exercise principals of longevity. Okay. Oh, there's another question about VO2 max. I'm not going to address that. Oh, someone is asking, "When can we expect some results from the Energy Balance Consortium and any other New Sea results?" This is from Jeff in St. Louis. Jeff, the – So we've got a lot of feedback to that effect, and that's great feedback. So what we are doing, we're actually just launching a new website. In fact,

it might even be up right now. New Sea has a new website, and in the next couple of months what we want to do is put up a whole bunch of updates on the site, operational updates.

I mean for example, the EBC, the Energy Balance Consortium, the patients completed enrollment at the end of the summer, the data have been all analyzed, and the team is currently using that analysis to guide the design of the follow up study. So the follow up study will be designed by probably May or June, and the goal is to launch that at the end of the year. And the results of the EBC pilot study, the one that just finished as a pilot study, those will probably be submitted in the next month for an abstract, and then they will be submitted, and that will be, I think that will be an abstract for The Obesity Society, which presents in November, I believe. And then they'll also be submitted in manuscript form to probably one or two journals. So I'm not sure what the time lag is on that, but my guess is the abstract will be the first thing that hits, and that'll be in November. But this great feedback, and yes, we should absolutely be doing this for all of our studies, just so people will know exactly what the – You know, science moves at a pretty slow pace, even though at New Sea I think it moves as quick as it could possibly move.

All right, so NP from Seattle asks, "Please talk about hormone issues in general for men over 40. Regarding this, what are your thoughts on testosterone supplementation?" Well, I think in general, the hormone replacement topic is generally complicated. Remember, there are basically four hormone axes in the body. There's the sort of insulin system, which is basically the one that determines fuel partitioning. There's the adrenal system which copes to your response to stress, both acute and chronic, but of course it overlaps with the fuel partitioning system. Right? Too much cortisol, you're going to partition more towards fat. There's the thyroid system, which is primarily responsible for your metabolism, certainly your response to temperature, a bunch of things that figure into mood and other things like that, and then there's the androgen system, your sex hormones. And these behave quite differently in men and women, and they behave differently as we age.

So you'd asked a very specific question, so let's talk about men over the age of 40. So everyone is familiar with what menopause is, which is a condition that women typically go through in their late 40s, early 50s, where basically there is a loss of the two dominant androgens, estrogen and progesterone. And maybe at some point I can share my thoughts on hormone replacement

therapy in women and the role of androgen in women and how you decide should you be or should you not be on hormone replacement therapy. Hint, the answer is super complicated, and unfortunately gets distilled down into overly simplistic rhetoric. On the male side, it's referred to typically as andropause, which is sort of a play on menopause but referring to the androgen hormone.

Okay, so, boy, this is a loaded topic. It's a loaded topic because we live in a society where somehow we've let morality get in the way of science. So we just, we have this whole issue in our society about drugs and sports, and we somehow view cheating in baseball as the greatest crime that can exist, and I'm sure most of you realize this, there have been more congressional hearings on drugs in baseball or drugs in sports than there have been on virtually any important topic that should matter to Congress. Why drugs in baseball even gets in front of Congress is a mystery to me, let alone the number of times it's happened. Well, the net result of that is that basically there's a culture in medicine, sort of from the top down, that I think really tends to view hormone replacement therapy in men as a negative thing. And again, this is purely speculation, so I don't want to be taken to the cleaner's on this. I'm literally just sharing an opinion, which is when I read the literature, when I read the editorials and the commentaries, what I'm really seeing is, we have a bias against hormone replacement therapy in men.

Part of it may be justified, because I think the pendulum, when I look at sort of all the goofy testosterone commercials on TV, I think the pendulum swung too far. But the problem is, we've completely lost the nuance of it. So I absolutely think that testosterone replacement is a viable option for men in whom testosterone levels are deficient and symptoms justify the use. Now, the problem is, we have this belief that is not actually substantiated by rigorous science that, I think, overstates the detriment of that, right? So there's a very famous JAMA paper that came out six months ago, maybe a year ago, that was a pretty poor, poor meta-analysis of a bunch of studies that suggested that testosterone replacement in men increases the risk of cardiovascular disease. Now it might, but the data certainly don't suggest that. So the way they did their study, the way they did their meta-analysis, they did a whole bunch of stuff.

This actually could be another topic in and of itself. We could probably just do an entire segment on hormone replacement, but if hormone replacement in men results in an increased risk of heart

disease, it's actually not clear from the data. In fact, people are more willing to accept that hormone replacement therapy in men, testosterone therapy specifically, actually reduces the risk of prostate cancer, and when you get prostate cancer, you actually have a lower grade of prostate cancer. So the problem with all hormone replacement, and testosterone is no exception, is the numbers alone aren't significant. They're not sufficient to make the determination. So you have to treat patients based on their symptoms, and I also think that the way we treat patients has to be customized to them. So for example, it's not that interesting to me what a person's total testosterone level is, or even what their free testosterone level is. If I don't know what their estrogen level is, what their sex hormone bindings globulin level is, their DHEA and their DHT levels, I can't really determine –

And I'm assuming now we're dealing with a patient who is symptomatic, who clearly demonstrates the symptoms of low androgens. I'll probably have sort of six different ways that I would treat somebody, depending on their objectives, do they want to be on this for life? Is this a bridge? Do they want to maintain the ability to have kids and all these sort of things, fertility issues? So I think I've answered the broad level question, which is I think testosterone replacement therapy is a great tool in the tool kit, but like every tool, you'd better know how to use it, right? It's not just a hammer, it's a much more complicated tool, and unfortunately, there are probably just as many docs doing harm with this tool as there are docs who are afraid to pick up the tool. All right, so I feel like I'm at an hour, so this is kind of the last one. I don't want to kill people on this. So it's from Mike in Brisbane. "You're very productive. Do you have a standing weekly schedule for when you do each task? Do you have any unplanned non-productive time?"

Mike, yeah, I think I am a pretty productive person most of the time, though there are times when I feel highly unproductive. I am a list guy, and this has been a trait that I've had since I was in high school, and it's just more evolved now. Now there's a book, I think it's called *Getting Things Done*. I have not read it but I know people who have read it who tell me I sort of do what the guy describes. So if you're asking this question because you're personally interested in productivity, it sounds like that's a good book to read. I think it's called *Getting Things Done*, and the aficionada refer to it as just GTD. But briefly I'll just tell you what I do because it's probably a subset of that. So the first thing is, I'm maniacal about lists. So I carry this little leather folder with me everywhere and it has cards in it, like 3x5 inch cards. And I have a blue card, and the blue card is the top one in the little thing, and it

represents everything I have to do on a given day.

So I don't get to go to bed until everything on the blue card is crossed out. So it sounds crazy, but I have a little box beside everything. So if I haven't done anything, there's no checkmark through the box. When I've started the process or made some progress, if it's a two part thing, I put a hash through it, and then when it's completed, it gets the full X through it. And then beneath that I have a pink card. The pink card is everything that has to be done by Friday of the week. So I fill out a new pink card every Saturday morning, and that's my weekly task. And again, that's work related. Then I have a white card, which is personal tasks for the month. So like get my wife's birthday present, register the home warranty, switch out our car insurance, like just dumb stuff that has to get done that I don't want to forget about. And then I have a yellow card which is long-term work-related things. So these are things I'm not putting on deadline, but I find it very cathartic to be able to write stuff down, because it takes the stress away from me.

Because I find that a lot of people get sort of paralyzed by not being able to do stuff. They get overwhelmed with things. I'm in the same boat. I'm very prone to this. Yet when I put stuff down on paper, and any day of the week, any time of day, I can pull out my little cards and I can look at all the crap that has to get done, it actually alleviates my stress. Right? Because it's like, "Yeah yeah, you're not going to forget about it." Because I think most of our anxiety is worrying that we're going to forget stuff, not how much stuff we have to do. I think of the two, the former is worse. And look, if you go through Meyers Briggs testing, obviously I'm a J on the P J axis, and I'm probably an off the charts J. So I crave structure, I crave organization, I crave order. So to your second question, "Do you have any unplanned, non-productive time," I mean, I do every week, and I try to make that the time I spend with my kids. I try to basically, and I shouldn't say that, because it's still somewhat structured. Right? Like when I drive my daughter to drum lessons. I mean, there's a structure to that in that we have to leave at this time and we're going to do X, Y, and Z. But it's also a time when I'm sort of releasing my agenda. For example, and this is going to sound like I'm a psycho, but I don't schedule any phone calls during that drive. Like, I don't want to be on the phone when she's in the car, because that's our time.

And you might say, "Wow, what a martyr you are. What kind of sacrifice is that?" But that's how regimented my life is. I'm generally always doing something. I would probably benefit from

more unstructured time. I think part of the challenge is, many of you listening would probably appreciate this, is when you're trying to run a couple of companies, when you've got kids, when you're trying to maintain some level of fitness, everything tends to be quite structured. I think sometimes I want to dip into a period of sort of, "Let's do nothing for a day." I have not done – I typically don't do well in that setting. I get very restless doing nothing. I'm just trying to think. The last time I took a vacation, did something unstructured. Well, I'll put it this way: it's been long ago enough that I'm probably overdue for it. So anyway on that note, I will end this very structured interaction of answering questions. I hope this was what people found interesting. If it is, please let Tim know. Maybe we can do it again.

If not, please let me know why so I don't do it again. All right, thanks everyone.