# Diet Doctor Podcast
## with Trey Suntrup, PhD
**Episode 67**

**Dr. Bret Scher:** Welcome back to the DietDoctor podcast, I'm your host Dr. Bret Scher. Today I'm joined by Trey Suntrup. Trey is a little unique in that he is a PhD in physics, I can't say I have had any physics PhD's in this podcast so far, but stick with me. So, he got his PhD in physics at University of Santa Barbara, then he got into translational science and entrepreneurship, he did a fellowship in that at Washington University in St. Louis.

And since then he has been involved in different startups, different companies, to basically develop products, to bridge the gap between the science and translating it into things that we can use that make our lives better. Now he's working with a company, you can find more about them at mybiosense.com where they are working on ketone monitors.

And he was actually the lead author on a paper which as you'll hear provided more than two and a half times the data that already previously existed correlating blood and breath meters. So, he's got a wealth of knowledge about ketone monitoring in general and specifically about breath monitors.

So we're going to all that, we talk about the basics, about what ketones are, why we should measure them and then we go into details about the pluses and minuses and the intricacies of all the different testing methodologies and talk about what's coming in the future, how it relates to diet, how it relates to fasting. So hopefully this is true statement but everything you wanted to know and more about ketone testing coming up now with Trey Suntrup.

Trey Suntrup, welcome to the Diet Doctor podcast.

**Trey Suntrup PhD:** Hey Bret, thanks so much for having me.

**Bret:** My pleasure. I'm excited to talk all things ketone measuring and ketone monitoring. And you are sort of uniquely qualified to do this. I mean, you've got your PhD in physics. So that tells me you know your science, you know how to interpret science well, but you've also got years of experience in product development and translational science. So really sort of bridging the gap between what the science says and sort of the practical applications of things. And that's really what I want to talk about today. So you ready to dig in and get started?

**Trey:** Absolutely. Let's do it.

**Bret:** All right. So first let's talk about ketones. I mean, let's start from the basic, like what are ketones? Because we talk about ketones as if they're one thing. So many people just say ketones

and most people know the difference. But why don't we just take a step back and review the different types of ketones, how they're similar, how they're different, and then we can get into the monitoring process.

**Trey:** Yup. That sounds great. So I think from the very highest level, we can talk about two different types of energy substrates for the body, right? So two different types of energy. So on the one hand, you have glucose, which of course everybody is familiar with and is used to, and on the other hand, you have fat. So your body likes to burn glucose first, if it's available, right?

So if you're eating a lot of carbohydrate, you have a lot of-- your blood sugar's reasonably high, your body is going to burn that source first. Once that gets depleted and then once the stored glucose in your body or the glycogen gets depleted, you start tapping into your fat stores. So your body starts to metabolize fat for energy because there's no more glucose left to burn. And one of the byproducts of that fat metabolism process... there is this molecule called ketones, right? So as you say, there's really not one ketone, there's actually three. And they're produced in your liver as a byproduct of fat metabolism.

So as a molecule of fat is metabolized, your body produces a molecule called acetoacetate, right? So that's really the first kind of parent ketone we like to call it, right? So acetoacetate can turn into two different molecules. One of them is called beta-hydroxybutyrate and the other is acetone, right? So those are the three ketones.

And they're all related to each other in these kinds of really interesting ways that we can get into later. But those are the three primary ketone bodies. The important thing to remember is that of all the different ways to measure ketones, they're all sensitive to one of those three ketone bodies, right? So I don't know if you want to get into the different measurement methods yet or you want to talk a little bit more about the physiology, but those are the three ketone bodies.

**Bret:** Yeah, and I think that's important, and we definitely will get into that, how each one sort of has his own mode of measurement. And that can be important, but before we get into that, let's now talk about, okay, we know what ketones... we know where they come from, what they are, why do we want to measure them? Like what benefits is it for measuring a ketone body?

**Trey:** Yeah, that's a great question. So there's a lot of evidence that suggests that a healthy metabolism is one that can actually switch between this glucose burning state and this fat burning state. So I think a lot of folks know and appreciate that when, you know, you have an excess of glucose in your blood and you're always burning glucose, that there's some adverse effects to your body when you're doing that.

So there's an inflammation that occurs, high blood pressure, kidney disease, diabetes, all those things, when your blood sugar gets too high. In addition, you tend to gain weight, right? Because if you have all this excess glucose, your body eventually ends up storing this as fat and your fat stores build ups in your body, right?

So there's a lot of evidence that suggests that occasionally you want to deplete the glucose in your body and your store glucose and switch over to this fat metabolism state. So the switching is very healthy for the body and is a sign of healthy metabolism. So how do you know if you're burning fat though, right? It's not easy to tell though and the scale is not a great indicator for a bunch of different reasons.

Not least of which is that it can't tell you if you're burning fat at this moment. It can tell you over

the course of, you know, a couple of days or weeks or months if you have been, but it doesn't give you that instant feedback about is your body burning fat or not. And that's really where ketones come in. That's really where measuring ketones comes in. Because any time that your body is metabolizing fat, you're going to be producing ketones.

**Bret:** Yeah, that's a great point. So it's basically the surrogate for a fat burning metabolism. And you mentioned, you know, there's evidence to suggest sometimes we want to deplete the glucose and switch to fat burning, I'd say that maybe more than sometimes, maybe even all the time. But your point is well taken that it is a measurement of fat burning.

So if you want to be burning fat, which we can talk about the benefits of that or we've sort of talked about that a lot on this podcast, but if you want to measure it, what ways can we measure it in the moment? Ketones are definitely one. Are there other ways to measure if you're burning fat in the moment?

**Trey:** There are certain other surrogates that are a slightly less perfect than ketones. So for example, you could measure respiratory quotient, like carbon dioxide to oxygen ratio, right? This is complicated for several reasons. Not least of which is that that measurement is typically a laboratory measurement where you have to, you know, lay on your back for 30 minutes before to kind of let everything equalize to get an accurate measurement there.

And there really haven't been any portable tools that have been able to reproduce the accuracy of those lab tools. So in principle, can you tell, you know, if you're primarily burning carbohydrate or primarily burning fat from respiratory quotient measurement? Yes, absolutely. But you have to, you know, go into a lab and lay down on... and do the metabolic cart measurement and the whole thing.

But that is another way that you could do it aside from measuring ketone. But ketones are a more direct measurement, right? Because they're produced as a direct byproduct of the fat metabolism process.

**Bret:** I think I'm going to have a whole another podcast on metabolic carts and testing like that. But I remember I did one of those exercise tests where they measure your respiratory quotient, where you're breathing and you wear that big mask and then we'd take the mask off, like all your spit drips out of it like... But that's... I digress.

It was kind of cool to learn, but you're right. Like you can't go through that at the moment every day. So that's where the ketone test is really is beneficial. So one of the things that can get confusing for some people though is saying, okay, if I'm going to eat a low-carb diet, I need to test my ketones to make sure I'm getting health benefits. Now, would you say that that is an accurate statement or not?

**Trey:** I think it is to a degree, right? Because people's bodies are different. So everybody's body is going to react differently to a certain stimulus. So you could have a certain lifestyle change. Like you could start exercising in a certain way, or you could start eating a certain macronutrient content, but really the only way to know how that's affecting your individual metabolism is to take a measurement, right?

Because we've seen folks actually go on exactly the same macro content and because they're different age, maybe different gender, different, you know, metabolic history, like health history, they just have wildly different reactions to the same stimulus, right? And that's something that I

think people are starting to appreciate more and more.

And this is the age of personalized medicine, right? When people are getting into genetics and genomics and all this stuff, right? Things being hyper-personalized. And I think that this is a great example of that. This is a great example of how, you know, individual bodies react differently and the best way to know how your specific body and your specific metabolism is reacting to these inputs is to measure.

**Bret:** Yeah. So if you-- But again, I think it's important to differentiate that you can still lose weight, you can still improve your health, you can still lose body fat even if you're not producing ketones. So I guess from that sense, you don't necessarily need to measure it, but if you want to know if your diet is putting you in that fat burning mode and in ketosis, then it makes sense to measure.

And before we get into the level, let's talk about now the different ways to measure it. Let's get into the sort of the details. So what are the main ways people can measure their ketones?

**Trey:** Sure, so as we talked about, there are three different ketone bodies and each of the measuring methods is sensitive to a different ketone. So if we're talking about acetoacetate, that's typically measured in the urine with urinary test strips.

So there's a couple of important things to consider about this. First of all, that's actually the excreted acetoacetate. So I like to think of it as kind of the excess acetoacetate that your body's not using that gets excreted your urine, right? So it's not really a measure of the amount of ketones that's circulating in your body. It's more related to what your body's excreting.

Also because that measurement, due to the nature of that measurement, it's actually semi quantitative. So it gives you ranges essentially. So if you look on the ketone strip, it tells you... I think there's maybe four or five different color ranges, and it can kind of give you a sense approximately of where you're at.

That's going to be sensitive to things like your level of hydration, like how long the urine has been in the bladder, stuff like that. Another effect of urinary ketone tests that people who have experience with testing know is that after a couple of weeks of cutting carbs or doing calorie restriction, actually your urinary ketones drop, right? And that's basically because your body becomes more efficient at using them so it's not dumping them in your urine.

So you still have the ketones circulating in your body and you're still using them, but you're no longer excreting them in the urine. So when people don't know this, they get very discouraged because like what happened, you know, after a couple of weeks, and it's actually a great sign when that happens. It means your body's actually getting better at using the ketones, right?

**Trey:** But actually you don't know. You don't know if your body getting better at using them or have you completely gone out of ketosis and not producing them anymore. **Trey:** No, that's a great point actually. I should have mentioned that. But assuming that you're, you know, sticking to your diet and you're crushing it, your ketones may still drop after a few weeks.

**Bret:** Yeah. So helpful in the beginning, helpful for beginners to learn if you're doing the right thing, making progress. Not so helpful over the long run as you sort of adapt to it and not so helpful if you want to know your exact level rather than a general range.

**Trey:** Exactly.

**Bret:** That's pretty good summary. So what about blood? Blood is the one people probably are most familiar with. So blood tests are sensitive to that beta-hydroxybutyrate molecule. So this is the BHB molecule. So there are a couple of different - there's a bunch of different meters out there that measure this. And blood tests are generally pretty accurate, right? Of course, they're measuring your blood ketones.

Actually taking a draw from your veins is more accurate. That's like a laboratory ketone test. And there was a paper published... I can't remember if it was a year or two ago, it was pretty recent in the last couple of years... that basically showed quite a discrepancy between those two sites, your venous blood and your capillary blood. But generally speaking, they're pretty accurate measurements. Of course, there's error in all these measurements.

But they work in a similar way to glucose strips where you take out a lancet with a needle and you prick your finger, you get a little drop of blood, put it on a strip and you get your answer right away, right? So blood tests are pretty accurate ways to tell what your ketone levels are. But of course you have to draw blood. There's a lot of supplies involved and it's not the most convenient way.

**Bret:** So just to clarify. So this, when you prick your finger, that's the capillary and when you get the blood test at the lab, that's the venous. So would you say the venous is the gold standard?

**Trey:** Absolutely.

**Bret:** Okay. And then the capillary is generally felt to be equivalent, but you said there is some variation. And is that also prone to... I don't know... hydration or where you prick or how much blood you get, like do those variables matter or are those less important for that?

**Trey:** I think the primary one that matters, and I have to just admit that I'm not an expert on this, but I think the primary difference is where you draw the blood from is really where I think you're going to see the difference. I'm not so sure about the level of hydration and that I haven't heard that as being a major factor.

**Bret:** Yeah. I wouldn't think so.

**Trey:** But certainly where you draw the blood from can definitely make a difference.

**Bret:** Okay. And you were telling me about the... well, we'll get into your study where people were doing finger pricks like 15 times a day for a number of days. Like I can imagine that'd be problematic, but we'll get into that. So the next one then is the breath monitoring. So tell us about that.

**Trey:** Sure. So breath ketone meters are sensitive to acetone. So that's the third ketone body. Now acetone is produced from a degradation of acetoacetate. So the acetoacetate is circulating in your blood along with the beta-hydroxybutyrate. And then there's a decay rate of that into acetone. And then the acetone because of its small size and it's a volatile molecule, it can actually diffuse into your lungs and then you exhale it out, right?

So it's a pretty cool process actually. It's very tricky to measure this accurately. I think that's the key point, right? So you haven't heard a lot about breath acetone in the clinical context because it's very hard to measure accurately. So historically, the way that this has been done is with these big lab tools, mass spectrometer tools, where actually in the old days of clinical research on breath acetone, subjects were breathing into bags and they were like running them off to the lab, right?

That's the way that they were doing it. So you can imagine that didn't produce a whole lot of data.

It's hard to actually get good measurements that were a lot of good measurements that way.

**Bret:** Yeah.

**Trey:** But essentially the way that it works is that the concentration of acetone in your breath increases as your exhale progresses.

So basically, like you can think of it like taking a breath and inhale, and then when you start to exhale, most of what you're exhaling there is just ambient air, right? It's just the same air that you breathe in in the first place. Because it hasn't had the chance to interact with your lung tissue and actually exchange with the blood there, right?

**Bret:** So from an anatomical standpoint, it's the air in your nose, your mouth, your trachea going into the very beginning part of your lungs. It hasn't mixed with your what's called your alveoli sort of deep in your lungs. So, it's a very different type of air.

**Trey:** That's exactly right. So really the trick to doing accurate breath acetone sensing is to do deep - exactly what you said, deep lungs sampling, right? So it's really just selectively pulling from that very last part of your breath. And that's going to make it not only more accurate because the levels that you measure are going to more accurately reflect what's in your blood, right?

Because there is acetone circulating in your blood as well. But also it's going to be more repeatable, right? You're going to be able to blow into the device a couple of times and get a very similar number. So historically, that type of sampling process was not developed. So a lot of the legacy breath acetone tools have simply not been accurate enough to use in a clinical setting.

The other issue historically with breath acetone is that folks have been using basically like repurposed alcohol sensors. So the same type of sensor that you would use if, you know, that law enforcement would use. And so that's like not very sensitive specifically to the acetone in your breath.

**Bret:** Right. So that's a problem. A lot of people, if you've had a drink within so many hours, it's going to give you false positives. Or even if you have like breath mints that might have certain things in them or alcohol or cough medicine or whatever, all these things can give you false positive for breath meters, if it's that type of meter.

**Trey:** Yeah. Exactly. So a couple of things really enable a technology to do this well. One is you want a highly selective acetone sensor over those other compounds that are in your breath. Because there's thousands of compounds in your breath actually that you breathe out. And what we really want to do is just pick out the one. We really just want to know what's going on with acetone and we want to really pick a sensor that doesn't respond well to those other compounds in your breath.

That's the first thing. And secondly, we just want to sample that last part of your breath. It's that deep along sample. So it's those two pieces combined that really allow you to do accurate breath acetone sensing.

**Bret:** Okay. And now when it comes to beta-hydroxybutyrate and acetone, are they prone to the same problem with the acetoacetate? Meaning as you become more adapted and are utilizing your ketones better for fuel, would you see a level drop or decrease despite no change in your diet, despite still doing everything right, that would make you say, wait a second, why are my levels decreasing if I'm doing everything right? Or is it not subject to that?

**Trey:** So this is a great question and actually the answer is a bit involved. And we've been having ongoing conversations with thought leaders in this space, trying to work this out and understand this. Because we do see effects of levels of these different ketones changing as you become more "keto adapted." And trying to understand why is totally fascinating. So happy to talk about that here.

What people see is if you're looking at your breath acetone, first of all, let me just back up one step. Breath acetone is really a proxy for the acetoacetate in your blood, right? Cause we mentioned before that acetone is formed when the acetoacetate degrades. So it degrades into acetone at more or less a fixed rate and so it's kind of a proxy measurement for the acetoacetate in your blood, right? That's the one very important point to keep in mind.

**Bret:** Yeah.

**Trey:** So what we see with folks who have been doing low carb for a while, who have been in ketosis a lot, is that their breath acetone is much higher than their BHB. So they'll be getting like the equivalent of like a 4-millimolar acetoacetate when they're sitting at like a 1.2 BHB. So what they do is they write into us and they're like, "Hey, you know, I just pricked my finger and I'm getting a one and your meter says that I'm a lot higher than that. Why is that?"

And invariably when we asked them how long they've been doing low carb or keto or have been in ketosis, it's always a long time. So there are really interesting reasons why that may be that we can get into, but that ratio of the acetoacetate to BHB in your blood is not a fixed ratio. It's actually controlled by enzymes and your body can turn that on or off. That conversion process between the two is actually regulated by enzymes in your body.

**Bret:** So that's pretty confusing. **Trey:** Yeah. **Bret:** So for the person at home wanting to know how that affects them, I guess as long as you're sticking to one type of monitor and not trying to go between them then for your relative gauge, it probably doesn't matter. But if you're used to doing a blood test and you switch to the breath test or vice versa, then maybe you need to sort of recalibrate what your normal is. Is that about right?

**Trey:** Yeah, I think that's about right. The only thing that I would add to that is that, you know... again, if you've been doing low carb or you've been in ketosis for a while, your blood meter may actually be underestimating your state of ketosis. That's the one part that I would add to that. You might have be in deeper ketosis than your blood meter is telling you.

**Bret:** Yeah. So then let's talk about the values. So generally, you know, 0.5 millimoles is where nutritional ketosis is said to start. And we can argue about whether that is an absolute cutoff or not, but it is probably not an absolute cutoff, but that's what we hear most of the times. And it can go up to 10 millimoles, which is usually, you know, diabetic ketoacidosis.

So in your experience and in the research that you've seen, what do you think the sort of sweet spot, so to speak, is that people would want their ketones to be in when they're following a low-carb diet and trying to get maximum fat burning?

**Trey:** Yeah. Good question. So, as you mentioned, that transition into ketosis occurs at about a 0.5 millimolar if you're talking about a blood BHB meter, right? So if you're really just trying to maintain this metabolic flexibility and switch between this glucose burning state and this fat burning state, as long as you're transitioning through that 0.5 millimolar cutoff, then you're probably accomplishing your goals, right?

If your goal is to just kind of dip into ketosis and come back out and just kind of maintain that flexibility. There is some evidence that higher levels of ketosis are beneficial. So the caveat behind all of this is that these are primarily animal studies so far.

So I'm going to put that disclaimer out before I say anything else, but those studies suggest that levels above 1 millimolar and sometimes as high as 1.5 millimolar can be beneficial for things like anti-inflammatory effects, right? So ketones, BHB in particular has some anti-inflammatory effects.

It's a signaling molecule and it can basically turn down some of the inflammatory pathways in your body, right? So it's not just a proxy for whether you're burning fat; it also has its own benefits for your health. Yeah. And that's a great point. I think that's important to make that there are sort of two ways to look at ketones.

One, which we know a lot about, I think the science has very well evolved, is the marker for burning fat, the marker for low carb, low insulin as well. And I think that's another important point we didn't bring up. That it's a marker of your insulin being low because you're accessing your fat stores.

But sort of a very exciting area where the science is not as well developed, but certainly developing on an almost daily basis, is the ketones themselves can be active molecules, signaling molecules, anti-inflammatory molecules.

And that's where the use of a ketogenic diet for epilepsy, for cancer, for traumatic brain injury, for Alzheimer's, all these sort of emerging areas where-- well, aside from epilepsy, but these other areas where we don't have so much data, but there's a lot of excitement, a lot of promise that might be where we really want to push the levels higher. Can you think of other areas where you might want to really push the levels higher?

**Trey:** Yeah. The only other one that's related to what you mentioned is the downregulation of certain oxidative stress, which has implications for longevity. So some folks in the longevity space are really interested in that higher ketone levels. So you know, ketone levels around like the 1.5 millimolar.

And again, animal studies and there's some proxy measurements for longevity. But that data suggests that indeed levels of 1.5, 1.7 millimolar can be beneficial for longevity as well.

**Bret:** So we've already sort of defaulted back to just talking about blood because that's where probably the most experience is and the most evidence is. But you ran a study looking at the breath, to see how that correlates and to better quantify that. So give us a little bit of the details about this study and how - tell us why it's important, the things you learned about the breath monitoring.

**Trey:** Yeah, absolutely. So we wanted to run this study because as I mentioned there wasn't a lot of data on this topic primarily because of the breath acetone tools were all lab tools. So because we are able to do this with a portable breath acetone meter, we're able to gather a lot more data. So what we did - this trial was conducted in the fall of 2019. We had 20 people.

We gave them a breath meter and we gave a portable breath acetone meter and we gave them an Abbott precision extra blood meter, right? So they took, as you mentioned, quite a few measurements per day for two weeks. -So we had them--

**Bret:** How many was it?

**Trey:** It was only five. It was not 15.

**Bret:** Five.

**Trey:** We're not that brutal with them.

**Bret:** That'd be pretty harsh.

**Trey:** It was already pretty bad. They were kind of begging for the end of the trial by the end of it. I had to rotate fingers a lot as you can imagine. So we had them - they were all trying to follow a low-carb ketogenic diet for the most part. And then we just have them take five measurements a day, you know.

They would sit down, and they would take a blood measurement and a breath measurement, and they would record the values and they would do that five times a day for two weeks. So what that produced is about 1300 data points pairwise, blood and breath data points. And historically to date, there were only about 540 up until that point with all the literature combined.

So that produced about two and a half times the existing amount of data on that topic. And not only that, but previous studies had not looked at the daily variability of ketones, which is really interesting and really important. And that's one of the most interesting things that we found in the study is that ketone levels vary a lot during the day. Just during a single day, right?

**Bret:** Yeah. And right. So how much did you see them vary?

**Trey:** So the average was about 50% actually, right? So if you're sitting there at one millimolar, then you could have a fluctuation of 0.5. Like in fact, that's the most common fluctuation for somebody at that level. So 50% is quite a bit of variability and, you know, we're just starting to appreciate the sources and the causes of that variability because again, we haven't been measuring this before.

But you know, waking up in the morning and just taking, you know, sticking your finger or taking a breath measurement is really not capturing the full picture of the ketone exposure that your body's getting during the day for the vast majority of people. So you said you're still sort of figuring out what some of these details are that caused that variation, but so far, what have you learned so far? What are your theories?

Because I think this would be interesting for people to know because if they test and they're at 1.0 and then they test again and they're at 0.5 or 0.6 and they're scratching their head, trying to figure out what they did, what this means, what are some of the things on their checklist that they should see? Did I do this, this or this that could explain the difference?

**Trey:** Yeah. Great question. So the most one is probably your diet, right? So something like a hidden carbohydrate in something that you're eating is a big one. So if you're, you know, sitting there in ketosis and then you eat something, and a couple hours later, you're totally kicked out, then I think it's a fair assumption that there was something in there that was a hidden source of carbohydrate that kicked you out.

It could of course be something else, but that's awfully suspicious, right? And we've had people write into us as well, talking about that, where it's like, "Oh, I had no idea there was sugar in this

or that," right?

**Bret:** It's amazing where they can hide it.

**Trey:** It's amazing, isn't it? And so this is a very common experience is a hidden source of carbohydrates. Exercise certainly can affect it. So typically exercise will increase your ketones over the course of, you know, several hours after, but interestingly, they can actually dip immediately after your exercise.

**Bret:** Yeah. So is that part of the usage? Like you're using them up more, so they dip, but then your body is producing more to make up for that? And is that the presumed physiology? I would assume we don't know for sure, but what's the level of evidence?

**Trey:** Yeah, that's right. So I think that that's one effect. The other is cortisol that is a result of exercise is actually going to cause your body to release glucose into your blood, right?

**Bret:** Yeah. Right, right.

**Trey:** So when that happens, then your ketone production drops because your body basically detects that there's glucose in your blood. So they can turn down your ketone production a little bit.

**Bret:** So even if glucose goes up without insulin necessarily going up as much, you're still going to shut down or lower your ketones a little bit.

**Trey:** Oh, good question. I would imagine that the insulin would probably have to go up too, right?

**Bret:** Because the insulin would keep the glucose from just going too high, so the insulin does go up a little bit.

**Trey:** Right,and the insulin is also going to regulate the ketone production. Like insulin glucagon, regulation of ketones, which we don't need to get into, but I'm sure that there's also insulin involved in that as well that's turning your ketones down.

**Bret:** Okay. So we talked about carbs. We talked about exercise. What else is on that list that you can think of?

**Trey:** Circadian patterns, right? So folks see that when they wake up in the morning, their ketones are a lot of times lower. Now this is not the case for everybody. And actually this is a fascinating topic because some folks have lower ketone levels in the morning, and some have higher ketone levels in the morning. Just as a general pattern. And we certainly don't understand that difference all the way.

But one thing that could be causing low ketones in the morning is, again, the release of cortisol as your body wakes up. And the intended increase in blood glucose due to that. Since we're talking about cortisol, stress, right? So some people who are like I've kept my diet, the exact same, and you know, I've done everything the same and my ketones are dropping.

If you start to probe that sometimes, have you had any stressful events in your life lately? And oh yeah. I just lost my job. Okay. Well, that may be it, right? For the exact same reason, like cortisol levels causing a spike in your blood glucose. So hormonal, exercise, circadian patterns, food. Those are probably the first four that I would think about when trying to interpret patterns.

**Bret:** That was an interesting finding from that study that hadn't really been shown very well in detailed science. So you guys showed this with your study. And what else did you see about the correlation between the acetone measurements and the blood BHB levels?

**Trey:** So the first thing to point out about this is since you can actually graph the two right alongside each other, you can watch, you know, your blood ketones change right alongside your breath ketone, right? So it's very cool to look at some of these plots and they're in the paper that we publish. A couple of examples of that.

So the first thing you see is that they don't always change in lockstep, right? So sometimes there's a little bit of a time delay between the way that the two change. So I'm talking a matter of like an hour or so, hour or two. So if your blood ketones go up, a lot of times your breath ketones will follow behind that by like an hour or two, right?

**Bret:** Okay. **Trey:** So if you're doing just bare correlations between the two, that time delay between the way that they're changing is going to affect the correlation that you get, right? Because your blood could have gone up, but your breath is maybe still low and hasn't caught up to it yet, right?

So the bare correlation for blood and breath ketones is around 0.6, like R-squared, which is like a moderate correlation. So they've seen that in the past literature; we saw that in our trial. But if you actually look at the cumulative ketone exposure over the entire day, so now we're looking at a daily metric, not an individual point in time, the correlation is about 0.83, right? So this is an excellent correlation.

So what this means is we can kind of boil this down into plain language is that if you were to take five blood measurements a day and five breath measurements per day, they're going to tell you almost exactly the same thing. They're going to indicate almost the exact same level of ketone exposure for that day.

**Bret:** So that's interesting. So then it comes down to, what are you really trying to learn? Are you trying to learn about what you did for your entire day and how that affected things? Or if you want to know specific things, this one meal, this one exercise?

Then based on what you said, it seems like if you're using a blood meter, you could test within, you know, 30 minutes of that activity, or even maybe like 15 minutes or five minutes of that activity, to see what effect it had on ketones. But if you're using a breath meter, would you recommend delaying an hour based on what you said to see what that effect was?

**Trey:** So actually both ketones are going to take some time to respond to anything that you do, right? So the first thing to mention here is that glucose responds-- or excuse me, ketones respond a bit more slowly than glucose. My mind went to glucose first. So you know, you see these CGM traces where like you eat a cookie and your glucose spikes like immediately, right?

Ketones take a little bit longer to show up, for those changes to show up. And the other thing is breath does not always lag behind blood. Sometimes it actually leads blood. So there are different situations where-- and again, we're assessing all of this out, right? Because this is brand new science. So we're not totally sure why that is, but it's not consistent that one goes before the other.

But you bring up a really interesting point, which is that if you're looking at cumulative exposure, if I want to know generally how I'm doing, I want to know how many ketones my body is seeing

each day over the course of a week or a couple of weeks, or I want to use that to track my weight loss, then that cumulative exposure is a great metric.

If you're doing, if you're testing certain individual lifestyle choices that you're making, then at those individual points kind of before and after testing, for example, like I'll test my ketones before and then after a meal, those are great, like spot checks, right?

And you know, in order to capture, remember, in order to capture the variability in your ketones over the course of a day, you have to take somewhere in the 3 to 5 measurement range to really capture it.

**Bret:** So that gets us back to sort of the pros and cons of these last two measurements, the blood and the breath. So with the blood, you get accuracy, you get relatively immediate feedback. Although like you said, it's going to lag behind glucose. But if you want multiple tests, it's multiple sticks.

And with the cost of the lancets and the strips. Can you give us an idea of sort of what that cost is now? I know it's probably pretty variable, but are you up to date on the cost of some of the blood measuring devices?

**Trey:** Yeah, I think so. I think really, as you mentioned, the primary cost is the variable costs associated with the strip. I think the meters themselves are like what, 30 bucks or something like that. And then each strip is about a dollar, right? So each time you use a strip, it's about a dollar. So if you figure a buck a day and you're doing three measurements a day, that's going to add up pretty fast, right?

**Bret:** So the downside, if you don't like blood, the downside of the cost, the downside of your fingers being sore. So the breath meter gets away from that. Because you don't need any blood, you don't need to prick your fingers, which is great. You can test as much as you want and there's no additional costs. But the upfront cost tends to be more. So what's the upfront costs or the range for some of these higher quality breath meters?

**Trey:** In the hundreds of dollars. So you're looking at somewhere in the, you know, $200 to $300 range typically for the high end breath meters. And if you think about it, like I said, if you do the math on, you know, three measurement per day with a blood strip, you can figure out for yourself how long that takes to pay for itself relative to blood strips. And it's not too terribly long.

**Bret:** All right. So those are the benefits. You can test as much as you want. You get feedback many different times a day. No muss, no mess, which is kind of nice. But one of the downsides has been, one concern about accuracy, and two, not being specific.

Again, sort of giving a range. So I guess there are a number of different specific devices on the market now. Some that can give a specific level and some that give a range. Tell us what you know about some of the differences among the way devices report the measurement and what their accuracy might be.

**Trey:** Yeah. So I do think you're onto something really important about the ranges. So typically when you see devices that offer ranges, most devices wouldn't offer a range if they could offer something more specific, right? So usually it's a matter of, like, this is kind of what the resolution of the devices.

So typically devices are going to report down to their best resolution, right? So if you can resolve,

you know, four different levels of breath acetone, you're going to report four different levels. If you can resolve 40, you're going to do that, right? Because people would always want something that's more specific provided that you can put that number into context.

So the way that you get specific with these numbers, we had mentioned a couple of them before, these advanced sampling methods to really pull from your deep lung, these highly selective sensors actually isolating the sensor from the surrounding air.

Because something that you'll notice in some of these devices is you can actually see the sensors, which means that as the acetone from your breath is passing over them, it's mixing with the outside air in a way that is not controlled, right? So, you know, if you get a draft from your AC vent or something that blows in there at one time, it might totally change your reading.

So that's the other thing that I didn't mention before in addition to the sampling and the selective acetone sensor is actually having a sealed and housed sensor environment where you're only looking at the acetone and you're locking out all the outside stuff.

**Bret:** Yeah. That's a good point. So now that we've sort of gone through the three different types of testing and the pros and cons, what do you think the future holds for ketone testing? What do you think is like on the horizon that would be the next great monitor or the next great advancement? Or are we sort of like it's good as it's going to get? What do you think?

**Trey:** Yeah. I think something that's going to become really interesting is the data itself, right? So if you can start to gather this high-frequency ketone data, and we basically start to build a data set about people's fasted state metabolism, I think a whole world opens up for us, right?

A whole world involving different treatments and nutritional interventions for different conditions, where we can basically say, you know, look, we'll help you keep your ketones to a certain level, or we know that if you keep your ketones to a certain level, that you're going to see outcome XYZ improve, right?

And we'll actually be able to be a little bit more prescriptive with folks and actually help them achieve those levels. And kind of guide them on that journey. And so I think what's really exciting about the prospect of high-frequency, high-density ketone data is that is really being able to build out some of these nutritional interventions to be real interventions.

Because the first line treatment for things like type 2 diabetes are always lifestyle changes, right? But it's hard to actually do that. It's hard to achieve and sustain lifestyle changes without feedback about how your body is doing. So I think there's this big psychological effect here of getting the feedback about, hey, I did something and I'm moving in the right direction right now an hour later, two hours later.

This isn't something you have to wait a week for to see the results on the scale. You actually get a result an hour or two after you make a decision. And I think the reinforcement of that is really going to drive some of these nutritional interventions in areas like you mentioned, like diabetes, like Alzheimer's, other neurodegenerative diseases, cancer now is a really interesting topic as well.

So all these different areas that you use nutritional interventions, being able to provide that feedback in order to drive adherence to nutritional protocols and actually achieve better outcomes as a result.

**Bret:** Yeah. That's really interesting. And there are two important points there that I want to re-

hash. And, you know, I frequently say that we don't have evidence to say for, you know, just general health, metabolic health or weight loss that a level of 2 is better than a level of 0.5, and like, it's probably all the same based on the evidence we have.

But the evidence we have is usually one finger stick per day. So what you're saying is getting these high frequency measurements may change that entire thing. We don't know. We actually don't know that. So that would be really interesting to know if the higher levels are better and measuring the higher levels with more accuracy and consistency.

I think that would be really interesting to see some of those studies. But the second point is the feedback. And that's one of the things I think about CGMs. You know, CGMs are great to learn how food affects your body. But then once you learn that, then it's sort of like your accountability partner.

Because you know you're going to see the response if you eat something you're not supposed to, or you know, that this is going to affect your blood sugar. You're going to see that response. And it could be the same with the ketones. If you know if you eat this and your ketones are going to drop, now it's your feedback mechanism, your accountability partner. So that's really interesting.

Do you think one day we might have a CKM, a Continuous Ketone Monitor to go along with it? We have CGM on one side or CKM on the other side and like they'll duel it out. Like, is that coming, do you think?

**Trey:** It's not clear. So there are definitely people who are working on this. It's tricky to do that for a variety of reasons that we probably don't have time to talk about today, but certainly it could happen. I think the important thing to keep in mind with the CGM versus like a CKM, or like a pseudo continuous ketone monitor, like a breath meter, it's that they're kind of complimentary. So let's say that you ate a bunch of glucose and then you started fasting.

So you start off with a high blood glucose level and then you just stop eating. So what you're going to see on your CGM is you get the big spike because you just ate a bunch of carbohydrate and then that's going to slowly drop as your body uses that glucose. Eventually your glucose is going to flat-line, you know, typically this happens down in the 80, below 80 range.

At that point, your body then starts burning through your glycogen. And when it gets through that, then your ketones start increasing. So it's just important to recognize that these are kind of complimentary tools that are looking at different parts of your metabolism. So CGM is looking at your fed state metabolism and ketone monitors are looking at your fasted state metabolism.

And if we're talking about switching between the two, they kind of do this little handshake around when your glycogen is depleted when your CGM -- now I'm getting confused, CGM flatlines and then your ketones start going up.

**Bret:** Right. So you mentioned fasting. So, you know, the ketones obviously go up with a low-carb diet or with fasting. So it seems like the higher levels of ketones come from fasting. So are you aware of any data or experiments on that showing like sort of what the general ranges for nutritional ketosis and how that's different from fasting ketosis?

You know, I've seen graphs that show what the general areas are, but is there any data really to sort of support what the averages are?

**Trey:** I'm not really sure about that. I do think that people - I mean, folks that we see, their numbers are typically highest when they're fasting, as you say. So the highest numbers come from people who are generally eating a ketogenic diet and then they start fasting. Because their numbers are already elevated. And then when they start fasting, they really become elevated. So I think you're right. I think you essentially nailed it.

**Bret:** Yeah. So do you see many levels like above 5? I mean, is it pretty uncommon for you to see levels above 5 even with fasting?

**Trey:** Yeah, I think so. I think so. I think, you know, a 4 is kind of the maximum that we see typically. Five, I think one of the blood meters might go up to six something. That's like very rare. You know, we haven't seen that. We didn't see that at all in our trial. But yeah, we were definitely up in the low fours in our trial, for example.

**Bret:** And actually, let's talk about accuracy at the different ends, sort of at the bookends. Because like the history of these devices was probably geared more towards making sure you don't go too high, you know, making sure you're not in diabetic ketoacidosis. And they've sort of been refined now to say, let's see if you're in the lower end, you know, if you're just getting into ketosis.

Is there any difference in blood versus breath in like the different bookends, whether they're better at the 0.3 to 0.5 or better between the 3.5 and 4? Does that makes sense?

**Trey:** Yeah, it does. So with the blood, I'm not positive, but I think there are typically percent errors on that. So what you'll see if you're up in the 2 range is the absolute error is going to be bigger. It might be 0.4 or something. So you might be at a 2 when you're reading a 2.4, for example. And then at the low end with those same percentages, you might be 0.1, 0.2 off depending.

The big thing there with the blood meters is actually the strips. So we have done some QA on some of the different blood meters and what we found is that the strips are really what make the difference there. Because that's where the chemical reaction happens. So strips that are sealed like individually packaged perform much better. And it's just cause they stay cleaner.

They're just cleaner. It's a cleaner surface to have a chemical reaction on. So that's just something to look out for if you're considering blood meters. As far as the breath goes, you can really design them to be sensitive at either end, depending on what your use case is. So at least the breath meters that we've seen and the ones that we've had experienced with, for example, the one in our trial, that's really designed to be highly sensitive at the low end.

It was designed to assess with a type 2 diabetes reversal, for low-carb diets for type 2 diabetes. And what's really interesting about that low end sensitivity is that you can resolve very small steps at the low end. So you can tell folks if they're moving in the right direction even if they're not quite in ketosis yet, which is a very beneficial, psychological effect. Because I think if you just see like 0, 0, 0, and then all of a sudden you're in ketosis.

The whole time you're getting 0, it's frustrating. You feel like you're not making any progress. Whereas if you could see that kind of creep up slowly, again, even though you're not "in ketosis" yet, but you can still see it increasing, that's very beneficial for people who are starting off. So that low end sensitivity is important for beginners especially.

**Bret:** That's great. That's interesting to know. Well, I think we've really unpacked a lot about ketone monitoring from the basics to some of the more complex issues. Was there other things

about the monitoring that you think are important to discuss? And also sort of, how would you sum up advice if someone's looking for, you know, different ketone monitors, what they should be looking for? So sort of two questions there. Sorry to overwhelm you with two questions at once.

**Trey:** Sure. So I think it really depends on your goal. So if you are interested in getting personalized feedback about the decisions that you're making to really try to understand, and kind of take this to the next level as it were, and kind of peer inside your body and kind of understand what's going on, I do think monitoring is very important and very insightful. And for all the reasons that we've discussed.

The fact that your body may not respond in the same way to others. So I do think it's kind of a way to just get more insight into what's happening to kind of target your activities. So that you're no longer kind of grasping at straws. Because I think there's so much frustration about, you know, dieting. That has like such this bad rep, is like, do I want to try this diet or that? And I think the really important thing about ketone monitoring to understand is it is diet agnostic.

I think people think about ketones as being part of a ketogenic diet and they need not be restricted to a ketogenic diet. As we talked about before, anytime your body's burning fat, no matter how it gets there, no matter how you put your body in that state, you're going to get ketones. So maybe a ketogenic diet works for you.

Maybe another diet works better than that. But the way to actually tell is to monitor yourself, is to actually do this testing to understand what's working for you. So I do think that's probably is - I'm trying to answer both questions at once actually. I would just want to point out that ketone monitoring is not specific to the ketogenic diet. It tells you if you're burning fat.

**Bret:** Yeah. So that could be another thing too. I mean, just its role in fasting. So, you know, a lot of times people have questions. How long do I have to fast to really get a benefit? And so if you're not on a ketogenic diet and you want to try intermittent fasting, that could be a great tool just to say, all right, at what level of fasting, what duration of fasting have you now gone into ketosis and started fat burning? That could be really useful, too, for people who aren't following the ketogenic diet.

**Trey:** That's a great point, Bret. I'm glad you brought that up because we actually conducted a study a couple of months ago about this because we were curious how long it would take folks to hit a certain level of ketosis. So we set this target of 15 on the breath meter that we were using. That's about 1.5 in the blood. So how long is it going to take people once they start fasting, start the clock and see how long it takes people to hit that 1.5 level.

And we saw this enormous range of times. We got everywhere from six hours to 60 hours.

**Bret:** Wow.

**Trey:** And when you started to kind of dig into the data a little bit, there's some demographic effects there. Probably not enough data to be able to say for sure. But we also had people logged their meals before they started fasting and there's such a correlation between what people were eating before they started fasting and the time it actually takes them to get the benefits of fasting.

**Bret:** So the higher carb their diet, the longer it took, I'm guessing.

**Trey:** Yeah. The 60-hour person, I think, had like ice cream right before they started or some-

thing. So I do think like fasting is great because it's simple and people can kind of understand, hey, there's just this window of time when I'm not allowed to eat and it's easy to follow, but you know, that time window might not be appropriate to you based on what you're doing, based on your own body, and then also what you're doing outside of that window.

So I think it kind of ties it all together that, you know, fasting is not necessarily a silver bullet if you're eating a bunch of ice cream outside of that period. You may never be depleting your glycogen at all when you're fasting if you're not eating reasonably well outside of that window. So this idea of time-based fasting versus like ketone level based fasting is something that we're really interested in.

**Bret:** Yeah. So are there more studies coming? Like where can we, so where can we hear more about you, learn more about what you're doing and access these studies? Because I think this is such interesting science that really isn't so well known or talked about.

**Trey:** Yeah, so our study, I suppose we could link to it somewhere and when we post the podcast, but our studies published in PeerJ so we can link to that. And there's a lot of reference studies about breath acetone and ketone levels. Also our website, mybiosense.com, has a lot of this information in it. And then, you know, just keep an eye out.

Because we have a lot of clinical research collaborations and the meters and a lot of different clinical studies around the country at leading academic institutions. And we're just starting to uncover the science and the implications and what it can mean for new treatments for these different conditions. So it's a very exciting time. So definitely keep your eyes peeled.

**Bret:** Well, I look forward to seeing a lot more from you and I always get excited about new science and new applications of science. So I think this is going to be pretty cool coming down in the future. So thanks for taking the time and thanks for going through all this with us. And appreciate all you're doing.

**Trey:** Thanks so much, Bret. Appreciate it.