Emily Kumler: I'm Emily Kumler and this is Empowered Health. This week on Empowered Health, we're going to be talking about metformin[1]. metformin is a drug that's been around for a long time. It's widely considered to be very safe. It's mostly used in the treatment of type two diabetes and in the last few years it's become more popular for its off-label benefits than ever before.[2] So we're going to sort of look at what those benefits are, why people are really excited about this drug, and then also some reasons to maybe not be so excited if you are healthy. I think this is another one of these things that sort of looks at health on a continuum, which we sometimes talk about and it seems like there's sort of a threshold whereby if you start to become unhealthy, especially if your metabolism is damaged so you're metabolically not functioning properly, which is sort of what we see in type two diabetes, then metformin is a great drug for you and one that you, you know, I think the World Health Organization says[3] is one of the essential medications of modern medicine. However it would seem new research is indicating that if you are healthy, meaning you don't have type two diabetes, you don't have cancer, this drug is maybe not going to help you and in fact it can sort of blunt the effects of exercise. So the positive effects of exercise we know are really important for long-term health[4] and it seems like metformin is having a negative effect on those. We're going to talk to the guy who's the lead researcher and all that. We're also going to look at sex differences with this drug. Something really interesting and sort of serendipitous happened with a study that was conducted out of Canada who's going to be the first source we talked to this week and she's going to explain to us that they looked at this drug in regards to traumatic brain injury and they found nothing. And then a researcher within the lab asked if they could separate out by sex differences, and what they found was pretty amazing. So just to give you a little bit of background, I'm sure some of you have heard of metformin. Maybe some of you are taking metformin, but probably a bunch of you don't know what it is and the mechanisms of action or how this drug works are really not understood. It seemed like people understood them, but now this new research is sort of challenging some of that. A lot of people will say that metformin works sort of like a low carb diet, so it controls the glucose metabolism and some people think that it sort of inhibits the mitochondrial respiration chain complex I.[5] Some people think that it has some impact on gut, the microbiome[6]. But again, it's like the consensus on this seems to be kind of falling apart. It also seems like it reduces gluconeogenesis[7], which is basically like how the liver is processing glucose or sugar. And it also seems like it has some insulin stimulating or sensitivity kind of effects[8], which is great cause that seems to affect most of the organs when

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[1] https://www.mayoclinic.org/drugs-supplements/metformin-oral-route/description/drg-20067074

[2] https://www.healio.com/endocrinology/diabetes/news/print/endocrine-today/%7B3d599445-6a21-46c9-b694-7d91409a503f%7D/beyond-diabetes-metformin-may-prove-to-be-a-wonder-drug?page=1

[3] https://www.who.int/selection_medicines/committees/expert/21/applications/s18_T2D_antidiabetics_rev.pdf?ua=1

[4] https://www.mayoclinic.org/healthy-lifestyle/fitness/in-depth/exercise/art-20048389

[5] https://www.frontiersin.org/articles/10.3389/fendo.2019.00294/full

[6] https://care.diabetesjournals.org/content/40/1/54

[7] https://www.ncbi.nlm.nih.gov/pubmed/24847880

[8] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3398862/

you're taking metformin. But what's really interesting is that a couple of years ago there was a trial that came out[9] that looked at people who were taking metformin and type two diabetes and what they found was that they were less likely to develop cancer. So a lot of people started taking this almost as like a cancer prevention drug. And what we're seeing is that we also know that exercise is a really important benefit in terms of preventing cancer. And this recent study[10] that came out that suggests that people who take metformin are not experiencing the same benefits of the placebo group in terms of exercise. That's not good. So the way that I sort of think about this is that if you're unhealthy and you take metformin, it's probably elevating you to a healthier baseline. But if you are really healthy and you take metformin, it might be lowering you to that same baseline. So again, it's one of these things where we really want there to be some sort of wonder drug, but you have to question like, is this really going to help you from where you are? And you need to know where you are. So we're going to kick this off by talking to the researcher who really looked at the sex difference, and I think in the next 10 years we're going to hear a lot more about this because what they found was truly remarkable.

Cindi Morshead: I'm Cindi Morshead[11]. I'm a professor at the University of Toronto. I consider myself really a neural STEM cell biologist. And in that, part of the role of what we want to learn by studying neural STEM cells is how to repair the injured CNS, central nervous system. So I have a focus on regenerative medicine[12]. So my lab really wants to think about ways to harness the potential of STEM cells so that we can promote neuro recovery from neural diseases and injury. The study[13] really started a few years ago around 2012 when a group of scientists showed that metformin, of course we know it's very, yeah, the prominent role that it has in terms of the clinical setting to treat type two diabetes. But what they were able to show[14] was that if you took STEM cells from the brain of a developing embryo and you actually gave them metformin in a dish, they would make new neurons and new glial cells faster--more of them, I should say, is probably better--than ones that were not given metformin. So metformin seemed to be able to activate genes in these particular precursors or STEM cell like these STEM like cells and make them more neurogenic. So with that in hand, that in and of itself was a phenomenal observation.

Emily Kumler: And that didn't matter whether they were male or female?

Cindi Morshead: So they didn't test that at the early times. So most of the studies are usually done in male mice, but not always. The more and more scientists start using transgenic mice. So these are genetically modified mice. The mice will either express a gene or they'll turn off a gene and you know, we can genetically modify mice to do many things when we breed them ourselves in our own labs, often we want to make sure that the mice are expressing the

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[9] https://www.bmj.com/content/330/7503/1304
[10] https://onlinelibrary.wiley.com/doi/full/10.1111/acel.12880
[11] http://www.neuroscience.utoronto.ca/faculty/list/morshead.htm
[12] https://www.nature.com/subjects/regenerative-medicine
[13] https://advances.sciencemag.org/content/5/9/eaax1912
[14] https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(12)00174-9?innerTabvideo-abstract_mmc2=

gene or not expressing the gene of interest. So we'll use males and females because we just want to have more of these. These mice are expensive to breed. These mice are more difficult to come by. Animals have--the mice have litters which have both sexes in them. When you order mice, you often order one sex. So you will say, I want 12 male mice aged, you know, eight to 10 weeks. I'm giving this as an example just in terms of how, how the way we do research is different in that we now have more breeding in our own labs. We breed colonies of mice to use in our experiments. You know, things have changed just in that perspective as well. People don't always think about is this a male or a female mice, they just say these mice are genetically modified. So that's sort of one of the ways that we've kind of come to this, this place where sex can be, or it's important to consider sex as it always has been. But even more now that we're starting to use both sexes in our research, but we need to keep track of it. So that's one of the things that I think the work highlighted. So let me just go back to this idea that we first found out that you could change what a STEM cell would do in the presence of metformin. Again, very exciting. So then we thought, wow, if a STEM cell can really do this in the presence of metformin, what if we gave an injury, where we know we're going to lose STEM cells. Could we stimulate the STEM cells to make more with metformin. So you lose neurons, you lose specific cells in your brain. And if we give the animals metformin after the injury, will that help? And so that was really a very simple question to ask in terms of the simplicity of the question, but a complicated experiment to do. So what we did was we gave a neonatal mice, so newborn mice, which we know have a lot of STEM cells in their brains. And we gave them a stroke and then we gave them metformin and we gave them metformin for just one week. And what we were able to show is that they had better motor recovery. So animals after a stroke, you know, are impaired in their motor abilities. But we could rescue those with just one week of metformin. And that was quite striking. We published that work and then we looked at--a graduate student in the lab, Rebecca Ruddy[15], she said, well wonder if you can improve motor function, I wonder if you could use metformin to improve cognitive behavior. You know, if you have a neonatal stroke, it long-term consequences[16]. A lot of them are cognitive. They last obviously for the lifetime of the patient. And so this was a very important and interesting question. So what she started to do was gave metformin not just for a week, but she gave it five weeks and she gave it every day for five weeks. And then she asked if the mice could do better in cognitive tasks.

Emily Kumler: And so that's like a puzzle box or like a maze kind of a thing.

Cindi Morshead: Yeah, we did a puzzle box. So we asked about, you know, learning, memory and acquiring a new task. How good were they at doing this? And mice that had neonatal stroke did not do well. So they did poorly on acquiring a new task. And when we looked at the metformin treatment, what we first saw was that there was no difference. And we were, you know, sort of thinking, okay, well doesn't seem to be having an effect on cognition. And then Rebecca said she pulled the males and females apart in her study. And then when

[15] https://morsheadlab.technology/rebecca-ruddy/
[16] https://www.birthinjuryguide.org/2018/03/neonatal-stroke-affect-babies-long-term/

she looked, she saw a striking difference between males who did not recover and females who were doing significantly better on the task.

Emily Kumler: So when you had pooled them together, you were looking at the overall statistical significance of the treatment and you didn't see anything, but then she thought enough to separate the two. I mean, that's amazing, right?

Cindi Morshead: Oh yeah. It was phenomenal. And you know, it was rather serendipitous in a way, but you know, we had kept track of males and females. We know that stroke outcomes are sex dependent. Some, you know, females tend to do worse, have worse recovery. And so we always knew it was important, but when we first analyzed the data, what we thought this has no effect. What it brings me to recall is that, you know, in clinical trials that fail, if you were to have done this in a clinical trial, you would have said no effect to metformin. And that's pretty impactful given that all we had to do is separate the sexism. We saw this increase or improvement in females but not males. So of course then we went back because we're STEM cell biologists and we said, does this have anything to do with met's action on STEM cells? And you sort of alluded to this earlier, but met seems to have a lot of different effects. We call it pleiotropic and that it can affect a number of different cell types. And so we went back and said, is this have anything to do with STEM cells? And it turns out that we were able to show that the STEM cells in an adult female brain are still responsive to metformin. They still can expand in number and promote differentiation into neural phenotype, into neural cells in a female brain, but they don't expand a number in a male brain, so they're non-responsive in the male brain. This is adults now. So you know, we were able to then take it one step further and go, maybe this is about the STEM cells and if it's about the STEM cells, why doesn't metformin activate male and female equally? Are the STEM cells different or is the environment of the brain different? And Rebecca was able to show that it's actually the environment of the brain. The hormones in the female are able to modify the environment around a STEM cell to make them responsive to metformin and males, who do not have the female sex hormones obviously, they are non-responsive to the metformin. So the STEM cells themselves at the same in males and females, but the environment due to sex hormones is different and males cannot respond to the drug.

Emily Kumler: I mean, I have so many questions, but I think the first thing that I'm really struck by is that there, you guys also followed up on that, right, and then tested post-menopausal mice to see if the lack of estrogen and post-menopause, is that right?

Cindi Morshead: No. So what we did do was we ovariectomized mice, so we took away their female hormones.

Emily Kumler: So inducing menopause essentially?

Cindi Morshead: Yes, we induced menopause essentially. So in the absence of the sex hormone, they were not responsive. So they behaved like males. They were non-responsive to the drug.

Emily Kumler: So I know this is a leap to make, but if we were to say that the results in mice were the same in humans, which we know often is not the case, but just for the sort of thought experiment. Sure. The idea would be that if somebody had a traumatic brain injury and they were female, metformin might be a great, you know, sort of remedy or ongoing treatment for a female producing estrogen who has a traumatic brain injury. But if a woman had a stroke after menopause, this would no longer see the same benefit.

Cindi Morshead: So that's a difficult question to answer at this point. We would need more studies to do that. And I'll tell you why. Because we think that the environment in the presence of the hormone, it could already be changed. So you've been exposed, your environment in the brain, you've seen the female sex hormones, estrogen for 15, 20, 30 years, then taking it away at that point isn't going to matter because the environment is already changed. Whatever cells are in that environment, maybe they've already been modified. We don't know that it's, we know that it's not about the sex hormone acting on the STEM cells. The sex hormone is acting through the microenvironment in the brain. So you've already changed the micro environment by having the sex hormones around for 30 years, then it may not matter.

Emily Kumler: So it's not the circulating estrogen?

Cindi Morshead: No. So if I just throw estrogen into a dish with cells, just STEM cells. It has no differential effect on males and females, right? Like they're both equally responsive. But if I put all the brain environment in there that came from an animal that had estrogen, then I see the difference.

Emily Kumler: Okay. So help me understand that because I think that's confusing. So it's not the presence of the hormone, like we couldn't give estrogen to men and see them have this impact.

Cindi Morshead: I'll tell you what we know. If you're never exposed to the estrogen, your STEM cells won't be responsive to metformin. So if you don't see it, so you know that when we ovariectomize them before they've had a chance to make it, then you won't be responsive to metformin, the STEM cells. But if we actually keep estrogen in the environment, you could change the microenvironment so that when I give you metformin, you're acting through a different cell in the brain to activate the STEM cells. Does that make sense to you?

Emily Kumler: Yeah. So I mean, I'm just trying to think of an analogy. So it would be like sort of if you...When the mice have their ovaries removed after they have had estrogen circulating for whatever period of time. They still do see an effect of the metformin.

Cindi Morshead: Well that's your menopause question, right? So we haven't done that. So we haven't let, and we haven't taken an adult animal, and ovariectomize an adult mouse. We've done one that's, you know, just entering, just finishing up, just entering puberty. So around 28 days. So before they ever started really to make high levels of the estrogen, we ovariectomize them, so they never had it. And if they never have it, they won't be responsive. But whether having it and then taking it away, you've already changed the environment and they're still responsive. We haven't answered that question.

Emily Kumler: Okay. And so how do you determine that it's the environment?

Cindi Morshead: We determine it's the environment. Because if we take cells from the brain, obviously there, when we first take them out there in their environment and we put metformin on them, they will respond to the metformin if they're in their own environment. If I take a female STEM cell and I put it in an overwhelming male environment, they won't respond to the drug. If I take a male cell in a dish and I put it in an overwhelming female environment, it will respond. So we know that it's about the environment and not about the actual STEM cell itself.

Emily Kumler: So when you hear something like that, what does it make you think?

Cindi Morshead: In terms of the responsiveness?

Emily Kumler: Yeah. Well, and just in terms of the overall like way we treat stroke now that this idea that there is such a difference in the environment in the male versus the female brain. Right. I mean even just something that basic I guess.

Cindi Morshead: Yeah. I mean it's, it's remarkable to be honest. This is really about one drug's actions on one population of cells, right? So one drug and one population of STEM cells. Can only imagine how other cell types in the brain would be responsive. You know, people have done things like with neuroprotective drugs trying to protect cells from dying. And it wouldn't be surprising at all that you would have some neuroprotective drugs that tried to stop the damage that's induced after a stroke. Like, you know, rescuing cells would be different in males and females because there are differences in hormones. The environment of the brain is completely different. So I wouldn't be surprised that with anyone who was to say that, oh, we better try this in both males and females because I could see absolutely you'd have differential effects.

Emily Kumler: Yeah. Or just just even as simple as like prescribing different things. Right.

Cindi Morshead: Absolutely.

Emily Kumler: Because yeah, I mean it's so interesting to me too because I feel like so much of this research has always historically been done on men and then women are just supposed to assume that they'll respond the same way.

Cindi Morshead: Yes. Especially true, I think--I think it's true overall as a rule--but in the brain, you know, it's been always thought that, you know, female brains are just more complicated, so everything we need to know, we can learn from a male brain and then we'll just apply it to the female. You know, it was, well, hormones are thought to be, you know, there's so many differences in hormones, socialization, females. AndI'm quoting sort of old rationale for why we didn't look in both, you know, 50% of the population essentially we didn't look at. I'm really all about this idea to get very emotional. This is going to change the response. Their socialization is different. And so there's a slew of reasons why people thought it would be more complicated to look in a female. And I just think that's not good enough reason not to look obviously.

Emily Kumler: Well, yeah. And I think there was even an old thing that like women weren't as smart because we had smaller brains and then it turned out that like, we actually have the same number of neurons or cells or whatnot, but they're just more tightly wrapped together. And I think that was in that book, "The Female Brain"[17], which was an interesting read.

Cindi Morshead: Yeah. There are sexually, sex-based differences in, you know, anatomy. There are some bundles of fibers in your brain that are a bit thicker or thinner in males and females[18]. Certainly like, but I'm not sure, you know, from a structural perspective there are differences and not sure why we would have ever thought they would be identical. But we treated them as identical. And that was really the really, you know, the step backwards if you will, in trying to learn about how to treat people as a rule.

Emily Kumler: Well, and it's interesting too because we know that when estrogen drops in women during menopause that they do suffer, you know, sort of cognitive or they like brain fog[19]. You know, there's a lot of that kind of complaint that comes up, you know, and then it's even just curious to think of like two thirds of all Alzheimer's patients are female[20], right? So in some ways I wonder whether the application of something like, you know, metformin, this is just a, I feel like it's such an interesting thing that you guys have found, but I also feel like it's really, it seems like the tip of the iceberg, right? In terms of like, not just how different we are, but also like what is the role of estrogen and brain health? And what happens as a woman ages when she's no longer producing that estrogen and this idea that you just, you know, sort of brought up for the first time for me of the environment having been sort of saturated or whatever, soaked in estrogen for years does have a lasting benefit, right? That like even if you're not producing the estrogen anymore, it sounds like the environmental factors benefit from having had that. I mean this is all just amazing stuff.

Cindi Morshead: Yeah, it's very exciting. It really opens up, you know, a number of different avenues for trying to find new targets, right? So, you know, if new targets for therapies that we

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[17] https://www.penguinrandomhouse.com/books/18520/the-female-brain-by-louann-brizendine-md/
[18] https://www.ncbi.nlm.nih.gov/pubmed/16124013
[19] https://www.ncbi.nlm.nih.gov/pubmed/19470968
[20] https://www.alz.org/blog/alz/february_2016/why_does_alzheimer_s_disease_affect_more_women_tha

might want to use, you know, if really, if we think that this cognitive recovery, that this, you know, this benefit in cognition is really due to STEM cells, then you know, you have a new target for what we can look at it. If we think it's about estrogen receptors on different cell types in the brain that make the environment better, then we have a different target. And so, you know, I've been asked based on this work, so is there any hope for men? You know, this is kind of this idea that like it doesn't work in men, but you know, really we're not, maybe it would, if you were to be able to find the target cell that's changing the environment and change that in men, maybe you don't need estrogen to do that. You need to target those cells to activate cells to be responsive to metformin. You know, it's a cascade and we really need to think about that. Like not these necessarily direct effects, but this cascade and how we would activate this whole cascade of responsiveness.

Emily Kumler: Yeah, I feel like the feminist in me is like, imagine trying to tell a bunch of men that were going to change their brains so that they're more female than it'll be protective of them. I mean, I feel like I can only imagine the people who are gonna stand up and walk out of the room at that point.

Cindi Morshead: Yes.

Emily Kumler: And so, a lot of us started because of research that was happening at a children's hospital in Toronto, which, you know, I feel like, can you just talk a little bit about how that, you know, working with kids who have traumatic brain injury, is anybody trying any of this? Like is that going to be the next step? I mean, I feel like metformin is, I mean, despite this most recent research, which I feel like has to really be vetted pretty carefully about the impact of metformin on muscle, which, you know, obviously we know that like, high impact exercise and weight training is really important in terms of longevity. So I think you gotta kind of weigh those things, but I think if you're talking about something as serious as a brain injury, obviously metformin has been around for a long time and is a pretty safe medication for people to take. Is that something that anybody's trying, I mean, I feel like if--I have two children and if some, if either of them had a brain injury, that seems like a really noninvasive, pretty easy thing to try.

Cindi Morshead: I agree completely. So if I just go back to this idea of, you know, using it in human clinical trials. So we work with someone at the hospital for six years old, Don Mabbot[21] and Eric Bouffet[22] and they actually started a pilot clinical trial[23] really based on the mice work. So, you know, that's such an exciting thing for us. Fundamental scientists like myself, of course, everything that we do, we hope to be able to translate human health. I mean that is the goal. But you know, these are very, these are challenging things to actually do. But because metformin was, had already been used in children, it had already been shown to be safe. Millions of people literally take it. It was actually very exciting to be able to get this treatment metformin administration into a clinical setting for children. And it came about because the drug was used

[21] http://www.sickkids.ca/AboutSickKids/Directory/People/M/Donald-Mabbott-staff-profile.html
[22] http://www.sickkids.ca/AboutSickKids/Directory/People/B/Eric-Bouffet-Staff-Profile.html
[23] https://academic.oup.com/neuro-oncology/article/20/suppl_2/i168/5000969

in children who had medulloblastoma[24]. And so these children--a resection of the tumor, so the tumors removed--they have chemotherapy and they have radiation therapy. And the outcomes in terms of survival are exceptionally, I mean most the vast majority will survive[25], but they do have these long-term deficits[26] in cognition, socialization, learning, socialization. These things are very challenging for them throughout the rest of their life. Based on the fact that we had motor improvement in our very first set of studies that we could improve motor function. We actually were able to get a clinical trial started. That was a pilot clinical trial. So not that many children. There were like I think 25, 22 to 25, they were hoping for 30 but it's hard to enroll children in these studies. And these were children who had the cranial radiation, the chemotherapy, and they improved their cognitive function improved the patients that were treated with metformin. Quite striking, so exciting and promising. But the pilot, the study was too small to be able to segregate males and females and we didn't actually know that there was a differential effect at that time. So keeping in mind that neonatal or newborn pups, so in the pre-pubescent state, males and females respond identically to metformin. It's only in the adult state that the neural STEM cells are differentially regulated. So you know, we had given this to children and maybe it won't make a difference. The sex difference because they're equally responsive. These, the population was prepubescent.

Emily Kumler: Is that at all because there's still, there is some estrogen that the baby takes from the mom?

Cindi Morshead: I'm not an endocrinologist, but there is...yes, some estrogen does pass from the mom through the mother's milk, but we don't think that that's necessarily what's driving this. The niche, the STEM cell niche, the environment, the microenvironment is very different in a newborn than it would be in an adult for many reasons. Just even through maturation, like newborns have less of one cell type oligodendrocytes myelinating cells in the brain. So there's, there's huge differences in the environment and given that we know it's about the environment, metformin acting through the environment, we think that that could be, it could be for a number of other reasons, but we do know that estrogen in the later times is sufficient. I'm going to make the story more complicated now. I'm a bit hesitant to do this, but if you take a male, a mouse and you give it, you can reduce the animal's responsiveness to metformin. Estrogen is sufficient to make you responsive. So you know, if you have it, you can change the milieu and you'll be responsive to the drug. But if you give testosterone, you actually lose your responsiveness. So it's actually inhibiting the response.

Emily Kumler: That's fascinating too. Right?

Cindi Morshead: Yes, it does complicate the story a little bit.

Emily Kumler: Well, but that also explains a little bit more about the children part, right? Because little boys aren't producing as much testosterone as they would when they're older. So the inhibitory effect, I would imagine would also be somewhat stunted.

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[24] https://www.cancer.gov/rare-brain-spine-tumor/tumors/medulloblastoma
[25] https://www.stjude.org/disease/medulloblastoma.html
[26] https://academic.oup.com/jpepsy/article/32/9/1040/910727

Cindi Morshead: Exactly. That's why I was kind of introducing it because we think the neonates are, you know, all neonates, male or female or responsive to the drug. Their STEM cells are responsive to metformin even though they don't have the, the, the hormone circulating. So again, without testosterone as well.

Emily Kumler: Theoretically it could be less about the production of estrogen and more about the production of testosterone. Have you been able to separate those two?

Cindi Morshead: So we know giving, if we take an animal that is not responsive, has no circulating estrogen and we administer estrogen, we can make them responsive. So what we know is it's sufficient, right? So we can take someone who doesn't respond, give them estrogen and they will respond. So we know we can do that. We know it's sufficient for the response, but we don't know that that's the only thing that's happening.

Emily Kumler: It's so fascinating. And the only other thing I wanted to make sure I sort of asked you about, which, you know, again, I'm, this might be slightly controversial, but I feel like, you know, metformin in its most simplest way of explaining what we know that it does is that it does sort of control glucose metabolism, right? Which is why diabetics benefit from it the way that they do. And so now with the popularity of the ketogenic diet[27], which we know has been used to treat kids who have epilepsy[28] for a long time with really phenomenal results. Is there some connection for you between like sort of the carbohydrate metabolism that we have today and brain health versus like something like metformin working off of controlling glucose production and that deleterious effects of that on the brain?

Cindi Morshead: That's just an excellent question and I honestly don't know how to address that. So people are looking at mitochondrial function in these cells. So the energy stores of these cells, the metformin acts through different pathways in liver cells versus brain cells. And so one of the questions we used to always get is if you're giving metformin to these mice, are they becoming, you know, glucose deprived? Like have you messed up the gluconeogenesis? And now you know, it's not really about the metformin, it's about some metabolite that's released in response to the lack of glucose we don't see in the mice that have, are not diabetic, giving them metformin does not change the blood glucose levels. So it works in a diabetic model to change the glucose levels, but it does not seem to have an effect on glucose level. That's really an important question for us too. Right? So, the targets are a little bit different, so I'm not, I wouldn't be surprised if this, I can't imagine, I think all of this is going to come is going to end up being very circular. You know, you affect one thing and you recheck, you affect metabolism in the cells and metabolize their release can have differential effects as well. So I don't think you can separate those so easily, but it really, those are just excellent questions.

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[27] https://www.webmd.com/diet/ss/slideshow-ketogenic-diet
[28] https://ci.nii.ac.jp/naid/10019167655/

Emily Kumler: And then I think my last question for you is like, and this is doesn't mean to be so pointedly personal, but you know, a lot of people are taking metformin now as like a sort of preventative measure for cancer and all kinds of other things. Is it the kind of thing that you take or you've thought about taking or do people in the lab take it and now that they know this or I guess specifically female scientists that you know?

Cindi Morshead: So I get that question a lot and I always say that I think we should all be on metformin to be honest. It sounds like it's just, there's no reason not to be from what I can see so far. But no, nobody, like certainly there's no one taking metformin just because, you know, one of the interesting studies we had originally thought about doing was would we be able to go to a stroke registry and see if patients who were taking metformin for obviously for co-morbidities, for their diabetes, did they recover better from their stroke injury and there are registries in Canada that, you know, keep track of all the patients and outcome measures and their treatment regiments. But it was a, there's so many comorbidities that it was actually not feasible to pull out anything that was going to help us understand cause we made the strong prediction that females would have had better outcomes than males.

Emily Kumler: Or maybe be less likely to have a stroke.

Cindi Morshead: Yeah. I mean that's, we have not tested that, but I'm not sure that that is necessarily any conclusion we can draw because, and we didn't look at vasculature thrombus formation or anything like that, so we not sure that it would prevent stroke, but it may result in better, more effective recovery or even just a faster rate of recovery. All of those would be potential.

Emily Kumler: The other thing about metformin that I find fascinating is that it's basically like an off-patent drug, right? So it's like a dollar a month or something ridiculously inexpensive. Yeah. So when you're doing this kind of research, I mean in Canada, are you getting the funding from the government? Because I often find that I am very frustrated with how much money goes to drug companies in the United States that are looking to develop some new drug to treat some chronic illness that we could probably fix if we had more interest in preventative medicine. Yup. Yeah. But you know, I think you guys have a different healthcare model, so it's sort of interesting to talk to you about that as well.

Cindi Morshead: You know, drug companies aren't obviously aren't interested in metformin, we haven't modified it at all. We haven't done anything to it that would make it interesting. There's no money in it for a drug company. The most positive outcome is that we got quickly into a clinical trial. You know, those are repurpose drugs hold so much promise for the idea that we'll be able to get them into a clinical setting faster. And that's probably the most exciting part. We are only, we are only funded by, you know, federal and provincial agencies for this work, for the most part. And we had some private funding from foundations, from a cerebral palsy foundation

Three to be[29], and you know, they supported this as well. Very excited about this idea that, you know, treating childhood, you know, brain injury with, with a drug that is available, has been used in children before to treat metabolic disorders. It's just all very holds a lot of promise in that regard.

Emily Kumler: Okay. So that's a lot to think about and I think really exciting because it certainly goes to the idea that sex differences are important, right? And like think about how many drug trials have happened, where the sexes have been commingled and results have been found. And imagine if we separated out males and females, we might find a whole different range of effects, but that doesn't happen and I really hope that it will. So next we're going to go to the researcher who is looking at the impact of metformin on exercise.

Adam Konopka: Hello, my name is Adam Konopka[30]. I'm an assistant professor at the University of Illinois. I've been here for three years and I direct the Musculoskeletal and Aging Metabolism laboratory. So we focus on the biological and metabolic characteristics that promote aging and how we can design different interventions to help extend healthy lifespan. We recently completed a study[31] and we had 56 individuals, which actually the majority of them were women. So it's actually fitting that we're on this podcast. Half of them were randomized to consume placebo and half are randomized to consume metformin. The metformin dose was about 1500 to 2000 milligrams per day, which is very consistent with the clinical dose you would see given to patients with type two diabetes while they were taking placebo or metformin. They did 12 weeks of aerobic exercise training. So thinking about that, that would be the treadmill, elliptical or stationary bicycle.

Emily Kumler: So a typical kind of cardio workout.

Adam Konopka: Exactly, exactly. So very practical to, to real world scenarios. And then we did a variety of tests before and after the intervention and we did what we call kind of whole body or physiological outcomes regarding cardiorespiratory fitness or VO2 max. We also measured folks insulin sensitivity, which has a key kind of predictor in the development of type two diabetes, As well as a variety of other kinds of measurements. Fasting glucose, fasting plasma, insulin.

Emily Kumler: Did you guys do a glucose tolerance test[32] for somebody like drinks this stuff and then they wait a few hours and they do it again?

Adam Konopka: Exactly. Yeah. So the goal of the study was really to be, well we want it to be mechanistic and we can get to that later, but we also wanted it to be very clinically relevant. And so we did perform an oral glucose tolerance test. So many folks may have done this before

[29] https://threetobe.org/
[30] https://ahs.illinois.edu/konopka
[31] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6351883/
[32] https://www.mayoclinic.org/tests-procedures/glucose-tolerance-test/about/pac-20394296

that you drank the sugary drink, which really doesn't taste very good. And then we measure the circulating glucose and insulin values throughout your body for the next two hours.

Emily Kumler: So I think most women have to do that when they're pregnant.

Adam Konopka: That's correct.

Emily Kumler: If you don't have, you know, if you're not at risk for diabetes,

Adam Konopka: Yes.

Emily Kumler: Okay. So you've run the battery of tests before the subjects start the intervention.

Adam Konopka: Yeah, that's right. And so some of these tests were also designed to do a little bit of screening because our goal was to recruit and enroll participants who were at risk for diabetes but didn't have any sort of chronic disease. So I think that's really important to emphasize as we kind of go through the interview. These individuals were overall, they were healthy, but they had to have at least one risk factor for type two diabetes, meaning either a family history of type two diabetes, a higher than normal blood sugar, fasting blood sugar or an impaired glucose tolerance, which we measured with the OGTT. But overall, if you look at these people, right, they were all relatively healthy.

Emily Kumler: And so does that mean that you sort of excluded people who might have cancer or other chronic diseases as well? Or were you mostly just focused on the diabetes?

Adam Konopka: We did. So, yeah. So if you could be enrolled in the study, if you were five years in remission from cancer, and then we also did blood panels to evaluate kidney and liver health and make sure that no kidney or liver disease, and variety of other factors. So while we were interested in people at risk for diabetes, we also screened out any sort of other potential factors that might be related to different disease states.

Emily Kumler: So before we move on, will you talk a little bit about that decision? Cause I think that's really interesting. I mean in some ways I feel like that's probably very representative of the population at some stage of life, right? Like we know you know that some of the numbers are so crazy about like 50 percent of Americans are pre-diabetic or diabetic[33] and this is like such an true epidemic in that it's impacting so many people. But this idea of sort of looking at health overall with a couple of risk factors, I actually think is brilliant. I mean I think it's really interesting because you're looking at somebody who's maybe on the cusp of going from healthy to becoming unhealthy. Right?

[33] https://www.unitedhealthgroup.com/content/dam/UHG/PDF/2010/UNH-Working-Paper-5.pdf

Adam Konopka: Right. I think you bring up a really good point. So like you mentioned, there's about three times as many folks that are out there that are at risk for diabetes versus those who already have it. So obviously that population that that's a huge population and so that's extremely relevant and important. The other point is that there is epidemiological data to suggest that metformin works very well in folks with type two diabetes, meaning there's data to suggest that it improves survival and decreases the risk of cancer, neurological and cognitive decline. But no one has really done studies in folks that don't already have over chronic disease.

Emily Kumler: Right. And we know that there is a growing cohort of people who are taking metformin for these presupposed off-label benefits.

Adam Konopka: Yeah, that's, I think that is really another good, really good point because there's already 150 million people that take metformin[34], I believe worldwide and now we're having this increasing interest in metformin due to its proposed healthy aging benefits. And so we're only going to see the number of people take metformin increase and that population is primarily going to be in folks that probably are not diabetic.

Emily Kumler: Fascinating. Okay. So you are sort of, I mean I think that's such an interesting way of looking at like the pre-intervention qualifications.

Adam Konopka: Right. And that's something that we've really tried to stress now is that we are really interested in this kind of term health span, which health span is the period of life free of chronic disease and disability. And so if we're interested in testing and intervention to extend health span, then we need to start the intervention before people are diagnosed with over chronic disease. Right? I mean if they already have chronic disease then their health span is already mitigated. So we need to start it before they have these disease states. But also at the same time we want to investigate people who are at a high risk of developing these diseases to make sure that we're able to understand if we can delay health span or at least different biological or metabolic indices of health span.

Emily Kumler: And what percentage would you say of the participants were female?

Adam Konopka: I can't recall off the top of my head, but the majority. Let's see here. So we have 53 participants and there were only 11 men.

Emily Kumler: So you end up, you develop this cohort, you divide them into two groups and one gets the sort of normal dose of metformin, the other gets a placebo. And then what?

Adam Konopka: Yeah, so then they exercise for 12 weeks. This is a supervised exercise training program. And so everyone exercises.

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34 https://www.mayoclinic.org/medical-professionals/endocrinology/news/metformin-revisited/mac-20430448

Emily Kumler: Meaning they like show up and there's a trainer or like was it self-done..

Adam Konopka: That's right.

Emily Kumler: Self-reported?

Adam Konopka: Yeah. No. So it's all supervised. So meaning they come to basically our gym that was on campus and we had exercise physiologists supervise their training make sure that they hit their heart rate goals. The exercise prescription was designed to be progressive in nature. So it started off a little bit on the easier side and then as the time and the weeks went on, they would get a little bit more challenging.

Emily Kumler: And are they told to not exercise outside of that time period every week?

Adam Konopka: That's correct. Yeah. So we really tried to emphasize that this study was done at Colorado State University and Colorado is inherently, has very active people. So the people may have been walking or hiking or something outside of this study, but there is no structured exercise that other people were that people were doing outside of our intervention. So they did that for 12 weeks and then they basically they came back at the end of the study and repeated all the tests that we did at the onset of the study. A couple of important data points that we found where that we saw the expected improvements and cardiorespiratory fitness and insulin sensitivity in the placebo group. Right. So that's good. That suggests that our exercise intervention was effective. Now we did what all the data suggested we should do. We improve VO2 max and we improved insulin sensitivity. But what was, I guess surprising to some, some folks, but there is precedent in the literature, we saw that the metformin group basically attenuated these improvements in cardiorespiratory fitness and insulin sensitivity. And so that is a bit concerning.

Emily Kumler: Meaning that they did not improve as much?

Adam Konopka: So the VO2 max, they did not improve as much and the insulin sensitivity, they did not improve at all. Yeah. And so these two factors are key in predicting mortality and morbidity. And so if metformin is preventing or attenuating the improvements in these physiological function, these physiological outcomes, that kind of raises some concerns if metformin should be prescribed to everyone for extending health span.

Emily Kumler: Can you explain that a little bit more?

Adam Konopka: If we look at cardiorespiratory fitness, the higher values are associated with lower mortality and morbidity. And so if we are preventing exercise from improving cardiorespiratory fitness, we are essentially preventing some of these health benefits of exercise with insulin sensitivity. We know that it's a risk factor for not only diabetes, but it's also involved

with cardiovascular disease and metabolic syndrome. We are literally preventing the improvement in insulin sensitivity. And when we give metformin to individuals who are exercising,

Emily Kumler: That in particular seems so counter what we had all thought before your study, right?

Adam Konopka: Yeah. So you would think, so the way exercise works is it has whole body effects, don't get me wrong, but there's a strong adaptation at the level of the skeletal muscle. And so you would expect a lot of improvements in different metabolic adaptations. At the level of the skeletal muscle where metformin's primary tissue target is the liver. So you would think if you combine those two together, you would see adaptations at the level of skeletal muscle with exercise and then you get even better benefit with metformin by it's targeting the liver. Both are involved with glucose regulation and insulin sensitivity. However, we didn't see that. We actually saw that metformin completely blunted and prevented the improvement in insulin sensitivity, as measured by the oral glucose tolerance test. Although this is, I think this has grabbed a lot of people's attention, there is precedent in the literature that other people have found this phenomenon as well. So there's a group that was previously at UMass Amherst and they did middle-aged prediabetic individuals and they also showed that metformin prevented the improvement in insulin sensitivity after an acute exercise bout[35] as well as a, I believe 16-week exercise intervention.[36] ***(Correction: 12-week)***

Emily Kumler: And so how, you know, just from a very like sort of lay person's perspective, I think the thing that's confusing to me is how come this is such a great drug for people who are type two diabetic, that sort of insulin regulation is everything, right? Why does it have a benefit for them if it doesn't have a benefit for the general population? Or is it just that their metabolic system is so damaged or deranged or whatever we want to call it to begin with that it helps them slightly, but if you're not damaged, it actually causes more harm than good. Is that accurate to even say that or is that…

Adam Konopka: Yeah, I mean in a simplified version, I think you're on the right track. There are some nuances there. So why is it beneficial for folks with type two diabetes? That very well could be because they have just such high and impaired glucose values and insulin values to begin with. Now the folks that are trying to recommend, that are suggesting that metformin would be this healthy aging drug. They're suggesting that it has off-target effects independent of its glucose lowering effects. However, that hasn't really been fully vetted yet. And I think that's an area for future research certainly. And then to answer your question, even in the folks that we evaluated, so people who are at risk but free of diabetes, we actually had a very highly variable response. Meaning although we saw that metformin prevented the

[35] https://care.diabetesjournals.org/content/35/1/131.figures-only
[36] Correction: 12-week

improvement in insulin sensitivity, when combined with exercise, we actually saw half of our people improve insulin sensitivity and the other half actually got worse.

Emily Kumler: Based on who was placebo and who was metformin?

Adam Konopka: We're looking just at the metformin group, half our participants got better and half of them got worse. And so on average there's no change.

Emily Kumler: And is there any other breakdown that you can come up with as to what the difference was between those two.

Adam Konopka: We have. And so we've done some secondary analysis that's not published and it was some preliminary data for our grant application that we just recently earned funding for. And so what it shows is that the folks that had the lowest glucose, the lowest insulin and the highest skeletal muscle mitochondrial function, and we can get into that later. If you have low glucose, low insulin and high mitochondria function for a lack of a better term, you're the healthiest of our population. Those are the ones who actually saw their insulin sensitivity decrease. So it got worse. So the healthier people at the baseline of the study, were the ones who had the detrimental effects of metformin when combined with exercise.

Emily Kumler: Yeah. mean like do you know, again this is it big generalization that has not been tested, but most people in the population who are really healthy are also exercising. Right? So , that's of specific importance I think to mention.

Adam Konopka: Absolutely. Yeah, exactly. So I think that's a very important question. And then so even in strengthen that argument, those who had the highest plasma glucose, plasma insulin and the lowest mitochondrial function. So those who are at least healthy, those were the ones that saw the greatest benefit or greatest improvement in insulin sensitivity.

Emily Kumler: I mean, I feel like this is just begging for some sort of graphic, right? It's like if you start here you'll improve to here, but everybody is like sort of coming to the same middle baseline or something.

Adam Konopka: Yeah. Well I think it shows too that even though we're looking at a population who is free of chronic disease, even in that population, there is a very wide spectrum of health. And so I think what's getting lost in some of the media coverage of metformin and it's proposed healthy aging effects are that it likely is not for everyone and that there are going to be certain people that it should be recommended for and they might have very positive outcomes. But there's going to be a group of people where we may not want to recommend metformin for because it could actually have detrimental outcomes that would not be consistent with healthy aging.

Emily Kumler: So talk to me a little bit about the mitochondrial function, because I think, you know, the metabolic theory of cancer[37], which is something that I'm really interested in. Really looks at the health of the mitochondria in cells. Right? And so this idea that there is some benefit from taking metformin, I think is what was attributed, at least in some of the studies that I've seen where, again, to oversimplify things, but for the sake of time, people who are taking metformin for type two diabetes end up being less likely to develop cancer and people don't, didn't really know why. Right. But it does seem to me that interview action with the metformin as a helper in some way to the mitochondria was generally what people thought until your study came out. Or maybe this UMass study that we're less familiar with. Can you just help me understand that a little bit better?

Adam Konopka: Yeah, so I think our study is the first one to look at the mitochondrial function. So we're the first to kind of try to examine what's going on at the level of the cell that may help explain some of these physiological changes. So insulin sensitivity and cardio-respiratory fitness. And so when we think about the mitochondria, the mitochondria are the powerhouse of our body, of our cells, right? So the primary role of mitochondria is basically to convert all the food we eat into usable energy called ATP. We're able to measure that by taking skeletal muscle biopsies from people, and we take their tissue and we are able to examine how well the mitochondria function.

Emily Kumler: Within the muscle?

Adam Konopka: Within muscle fibers.

Emily Kumler: Okay.

Adam Konopka: Yep. So we take a biopsy…

Emily Kumler: Would that somehow be different than if you took it took it from like fat or an organ or something else?

Adam Konopka: Yeah, I mean each, I think they're going to be tissue specific effects.

Emily Kumler: Okay.

Adam Konopka: Yes. So what you see in the skeletal muscle, maybe slightly different than what you would see in adipose tissue, or even perhaps the liver. Now, the thought process is that metformin has, at least in cell culture and animals, has been shown to actually lower mitochondrial function. It actually inhibits complex one, which is the first complex of the electron transport chain in the mitochondria. And so the thought is that it actually creates almost this kind of energetic stress. So if we're inhibiting the mitochondria, we can't produce maybe as much

[37] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4493566/

ATP or energy for our body to use. And by doing so we're actually stimulating glucose uptake into the muscle because the muscle is almost, I don't want to say starving, but it's craving more fuel because we're not producing as much ATP. And so that could be a good thing when you're talking about a diabetic. But when we're talking about exercise adaptations, if we're inhibiting the mitochondria, our data would suggest that is actually why we are likely preventing some of these whole body adaptations. Our data show that at baseline mitochondrial function is highly correlated to insulin sensitivity. And then we also show after exercise training that there is a correlation with the change in mitochondrial function to the change in whole body insulin sensitivity.

Emily Kumler: Like I feel like diet must be a part of this. Did you track anything about what people were eating or like any changes in things that they were eating?

Adam Konopka: We instructed participants to not change their diet.

Emily Kumler: Okay.

Adam Konopka: There's a subset of individuals that wore continuous glucose monitors[38]. And when when we did that, we also had dietary logs and then from there we were able to understand that most of these people, actually, all of these people did not change their diet. They actually listened to our instructions. Okay. But as far as any sort of other dietary control, we did not, this is a free living trial and they ate what they normally ate.

Emily Kumler: You know, it's interesting because I think there is, if we sort of believe that like the health of the mitochondria is really maybe the regulatory system of overall health in a lot of ways, right? Like how quickly your cells can run over and all that sort of fairly newer research that's coming out looking at, I mean this is part of the reason that people fast for a long time, right? I feel like everybody's becoming more aware of the health of their cells and specifically looking at the mitochondria function. So does this study in some way make you feel like we've been looking at this correctly because you've seen that you sort of see the decline of health and healthy people when the mitochondrial function is suppressed In a natural way? Does that make sense? I don't know if I'm asking the question.

Adam Konopka: Yeah, I think we are going to examine that a little bit more closely in a followup study cause right now we got to take into consideration that all these people were exercising. So we don't know necessarily what is going on with metformin alone independent of the effects of exercise. So our study looked at how metformin was basically preventing the exercise adaptations at the level of the skeletal muscle mitochondria as well as these whole body outcomes we talked about before. And so with our data it does suggest that metformin is preventing these positive exercise adaptations at the level of the skeletal muscle mitochondria. And I think our future study is going to be able to look at how metformin is altering the protein

[38] https://www.dexcom.com/continuous-glucose-monitoring

turnover, the damage and the function of the mitochondria just with metformin alone and not with the compounding factor of exercise.

Emily Kumler: But with the exercise factor. I mean, I feel like, again, to go back to that idea of like the healthy user bias or like what, I mean, most people who are going to be in the cohort of healthy people are going to be people who are regularly getting some sort of cardiovascular exercise?

Adam Konopka: Yeah. Agreed.

Emily Kumler: And I think most people who are going to take metformin for some sort of longevity thing are already ahead of the curve of healthy people. Right? Because they're reading up on this stuff or their in the field in some way.

Adam Konopka: And perhaps those are the people that shouldn't take metformin.

Emily Kumler: Right. Well, and so I think that's one of the other things that I wanted to sort of talk to you about in a more philosophical way is this idea that we have such--I mean, a lot of this podcast honestly is really sort of trying to give within evidence-based information and talking to researchers like yourself who doing really good work to try to sort of self-educate ourselves, right? Because like doctors don't have time to go through all this stuff. And even since I started this project, I've been shocked at how bad the information sharing seems to be between institutions and I don't fault doctors for any of that. I think there is really like we have created a medical system that is not conducive to good science and to good sharing and to, you know, sort of patient attention. But I also think it's equally dangerous for patients, like myself, who are not doctors to be kind of experimenting and stuff. You know what I mean?

Adam Konopka: Right.

Emily Kumler: And I mean, I'll throw myself under the bus because I feel like I definitely feel like, you know, you go to the dermatologist and then if you're a woman you go to the gynecologist, you have a primary care doctor who maybe you see once a year for 10 minutes. Like there is nobody who's charting your health except you.

Adam Konopka: Right.

Emily Kumler: One of the things that I was really, your study made me think about is you know everything from like drug interactions, right? So like somebody starts taking a supplement and we have a big episode coming up on all these sort of unregulated supplements and how the FTC is now expecting consumers--patients I guess--to like call in and report them when they've had an adverse reaction because they literally cannot keep track of how many supplements are on market now. Which is terrifying, right. So you know, this sort of buyer beware environment has certainly extended itself to the medical world. And so, you know, I sort of, I feel like one of

the things that's come up for me in looking at your work is this idea of like, Whoa, wait a minute, like we all got really excited when it seems like there is some great benefits, but it takes a very specific kind of study to find out that that benefit is not for everybody.

Adam Konopka: Yeah. I think that's super important to emphasize. So two things too. There is, I mean we studied 53 people, so it would be great to have a larger, you know, study to kind of confirm and validate these findings. Because, you know, obviously that there's more impact with a larger clinical trial. But then also, yeah, you know, perhaps this is, metformin is great for those who are type two diabetic or at a greater risk for becoming diabetic or having some other chronic disease. But for those who are generally healthy, you know, I'd really, I would caution the use of metformin at least when you are combining with a physically active lifestyle.

Emily Kumler: And so for you personally, if you had somebody in your family who was interested in taking something like this, would you say like, nope, there's just not enough research?

Adam Konopka: Yeah, I would think so. I would be cautious. Obviously I'm a PhD so I've been very well trained on that to not make too much medical recommendations cause that's outside my expertise.

Emily Kumler: Right, of course.

Adam Konopka: So, I would be cautious, if they're physically active of adding metformin to their regimen. Now if they're not then and they're not for some reason able to become motivated to exercise, then perhaps that's something to consider. But again, I would highly recommend conversing with your physician on any of these kinds of decisions that are made.

Emily Kumler: Was there anything that you were personally really surprised by when you got the results back from the study?

Adam Konopka: Um, surprised, hmmm…

Emily Kumler: I mean, had you had a hunch that this is what it was going to be?

Adam Konopka: Yes, we had hypothesized this. Now I think two surprises that come to the top of my mind here. One is that we measured a variety of different glucose parameters and we found that metformin inhibited the improvement of insulin sensitivity after exercise, but we also looked at a variety of other variables related to glucose and glucose control. And those were not negatively affected. So kind of within a variable of insulin sensitivity we talked about earlier that we had some positive and negative responders. But even if you look at different variables of glucose regulation and in metabolic health, we didn't necessarily see that metformin inhibited all

of these variables. So, you know, I think that it's important to stress is that we did see that metformin inhibited some critical measures and outcomes, but not necessarily all of them.

Emily Kumler: So what does that mean?

Adam Konopka: You know, that's a really good question. For example, fasting glucose, there's a lot of variability in measuring fasting glucose. It's dependent on how much activity you do the day before and what you ate in the days leading up to the measurement. And so there had been previous studies where some exercise studies show improvements in fasting glucose and some don't. And I think that's probably why we didn't pick up any changes there. But it is something important to stress is that metformin didn't inhibit everything, just some critical factors that we measured. And that was surprising to some degree. The other surprise was the variability within the change in whole body insulin sensitivity when people were taking metformin during exercise. The fact that we had some folks, you know, half of the people improve insulin sensitivity and half actually got worse. I think the getting worse was actually really shocking to us. We thought that there might be an attenuation or you know, inhibit, but to see that half the people actually got worse when you use metformin in combination with exercise was very shocking to us.

Emily Kumler: And it was, I mean, obviously it was statistically significant, but how significant was their decline?

Adam Konopka: What do you mean?

Emily Kumler: Well, I mean we say they got worse, right? So is there a way to measure how were, how much worse they were after taking the metformin than they were before they started taking it?

Adam Konopka: Sure. Yeah. So statistically, statistically, yes, there were statistical differences. So what we did is we took the, we split them up into the 50% and 50%. So those who improved and those who did not improve. And then we just compare their differences. And the p-value is less than 0.05. So statistically suggesting that based on their metabolic health going into this study, it was likely dictating their outcomes related to metformin and exercise.

Emily Kumler: I mean I feel like it's also so interesting because if somebody were going to try and either replicate what you have done or take the information to apply to their own lives, it sounds like there is a sort of continuum where you could chart where you are in your own health based on the starting tests and then see are you in the you know group where the metformin was beneficial or are you in the group was detrimental?

Adam Konopka: Yeah, I think, you know, I think that's really, I think that's, that would be the next step. And so we have a study that we're going to start this year and we are going to recruit folks that are either insulin sensitive or insulin resistant. So they don't have type two diabetes,

but we're going to try to address that question. So we're going to see based on where you start going into the study, do you benefit, do you not benefit or do you even have a detrimental effect? Can we kind of, like what you're saying, is there a metric? So we know based on your baseline values, do we predict that you would see benefits or not?

Emily Kumler: Yeah. Cause the other thing that just comes to mind, and again, you know, this may not be relevant specifically, but when I was pregnant with my first child, I was really conscientious not to eat any sugar. And I know when I went in for my glucose tolerance test, my husband was sure that I was going to fail because of the fact that I was eating so low carb. Like I was, you know, really, really not keto in that the way everybody's crazy about keto today, but like really mindful to not eat any process or sugary foods and he was like, you're going to fail because your body is going to have such a strong reaction because it's not conditioned to eat kind of food. And I feel like taking all those variables into account from the perspective of trying to study this stuff makes it so complicated.

Adam Konopka: Yeah, it does. And I think we'll be able to address some of these one thing at a time. Some will have to be an animal studies and then some will be in very much translation what we call translational or applied clinical studies, where you hopefully recruit enough people to account for any of these variables regarding, you know, diet and activity and things of that nature and how we can make sure we can control as much as we can for those variables. But then at the same time, that's real life. And so we have to make sure we design studies that account for that.

Emily Kumler: Yeah. And I mean, I would also just like sort of put in a plug for menstruating women because I think glucose changes dramatically throughout that cycle.[39]

Adam Konopka: Yeah, it does. Absolutely. And so, yeah, then the future study that we have will, it will include some people who, some women who are probably peri and maybe some premenopausal but certainly in post-menopausal. So we have an age group of about 40, 45 until 75. And so it will take into consideration those changes. The other thing that's interesting about metformin are the potential differences and the effectiveness of metformin regarding age. And so if you look at the diabetes prevention study that was done here in the United States, it wasn't designed to specifically examine the effects of age and metformin's ability to prevent the onset of type two diabetes. But when you looked at the individuals who are over 60, there was a trend basically for them to not have positive responses or not have, for metformin not to be as effective in those who are younger. And so if we're thinking about metformin and being this healthy aging drug, it also raises some concerns that perhaps older adults don't respond to metformin as well as younger individuals.

Emily Kumler: I'm Emily Kumler and that was Empowered Health. Thanks for joining us. Don't forget to check out our website at empoweredhealthshow.com for all the show notes, links to

[39] https://care.diabetesjournals.org/content/36/5/e70

everything that was mentioned in the episode as well as a chance to sign up for our newsletter and get some extra fun tidbits. See you next week.