Zan Fleming (00:00:04):

So we're about nine minutes from Showtime and anybody who is in the audience and joining us now, feel free to listen in and respond by chat. I wish we could put you live by voice, but technically we are not able to do

Ralph DeFronzo (00:00:32):

Then I have to say I'm impressed with the background. It looks like you're in heaven here in Boston. It's freezing and raining and they haven't figured out the is supposed to be here.

Zan Fleming (00:00:45):

We've just gotten through a lot of rain and the river is very high. It was at flood stage earlier this week, but we do have some good weather now still. Cool. Can you hear the train that just went by?

Ralph DeFronzo (00:01:06):

Nope, we're okay. We can hear you though. Okay,

Zan Fleming (00:01:09):

Well that's good. There's a train going by right now.

Ralph DeFronzo (00:01:16):

You truly are outdoors then.

Zan Fleming (00:01:19):

I am outdoors. We do things to look different. We stand on our head or act crazy. So I'm going to get started outside, but I'm going to move in as we get started. Are you all set ready to go?

Speaker 3 (00:01:52):

I think we're ready.

Thomas Seoh (00:02:11):

Saif, are we in the green room and you'll elevate us to the main room or how does that happen?

Ralph DeFronzo (00:02:18):

No, when I lifted the curtain, our attendees have now joined and are listening in with us.

Thomas Seoh (00:02:22):

Oh great. But we are in the main hall. We're on stage, correct.

Zan Fleming (00:02:27):

Yeah, we're just informally ki saying while people watch, gosh,

Jay Skyler (00:02:36):

There's about 22 people who signed in.

Zan Fleming (00:02:40):

Yeah, that's good. Welcome everybody say hello in the chat.

Ralph DeFronzo (00:02:49):

Yeah, I was impressed by the number of pre-registered people in the diversity of the group and the A global audience. The problem with finding the funding for these jro science type programs is that if we're going to follow people on a long-term basis, it's a lot of people for a long time and a lot of money and finding the funding I think is going to be somewhat problematic.

Zan Fleming (00:03:31):

Well Ralph, I'll remind you that we approved many of the early products for diabetes that of course you were involved with metformin with three months trials and why? That's because we had a surrogate endpoint a1c. We didn't have to do an outcome trial to show get a diabetes treatment on the market. So it's the same deal for health span products. We need surrogate markers and that's really what our session today is about.

Ralph DeFronzo (00:04:13):

Yeah, I think that's critical that the FDA understand that these huge long term trials really cost a lot of money and that have the kind endpoint that probably we're going to need are going to be difficult if we need to have people dying or living longer, not so easy to quantitate.

Zan Fleming (00:04:38):

Well, and as you said, it's not just money if you have to do a clinical outcome trial, so survival or prevention of multiple chronic diseases, if that could take a decade. So we got to do some hacks and

Ralph DeFronzo (00:05:07):

I'm sure we'll get questions about the pain study and where that is and what can or cannot be expected.

Jay Skyler (00:05:17):

There were a couple of questions about that study in the chat, the pre-question.

Zan Fleming (00:05:23):

We've gotten a lot of good questions. We'll try to get to as many as possible.

Ralph DeFronzo (00:05:30):

Maybe Dr. Barlow is listening in.

Zan Fleming (00:05:34):

Yeah, he probably will join us.

Thomas Seoh (00:05:42):

Did NIR show up on the registrants list or is it David?

Jay Skyler (00:05:47):

He was not on the pre-registered list.

Zan Fleming (00:05:50):

He didn't see it. Maybe he'll show up,

Jay Skyler (00:05:54):

But I know people, I know some people who I don't see on the list too, so I don't know.

Thomas Seoh (00:06:04):

Well Saif has done this a number of times. Our zoom mista and we'll see whether we can't get the link to the recording later today or certainly over the weekend and we'll distribute it to all registrants.

Speaker 3 (00:06:30):

Go

Ralph DeFronzo (00:06:30):

Ahead. I was saying near started his career, Jerry, I dunno, I think near, was it Yale before Jerry?

Gerald Shulman (00:06:40):

No, no, no, no. I was here. He came after while I was here. We interacted. Yep. Remember him well as a fellow with you? Yep. I was here day one with Luciano when ano

Ralph DeFronzo (00:06:56):

Oh yes. I remember the famous race between you and Luciano and someone fell and broke their wrist and in a cat,

Gerald Shulman (00:07:10):

You

Thomas Seoh (00:07:10):

Remember that sounds like a chariot. It's a fire moment racing on the courtyard or

Ralph DeFronzo (00:07:17):

Something. Well, Jerry's in very good physical shape. Luciano is in probably the worst shape and they just, each one said they could beat the other at a hundred yard dash and it was totally catastrophic. I

Zan Fleming (00:07:36):

Wear one minute before showtime, but keep going.

Ralph DeFronzo (00:07:44):

Yeah, those were the old days.

Thomas Seoh (00:07:49):

Did I understand correctly that Ralph, you'll be there as usual, but the others won't be at a DA this June?

Ralph DeFronzo (00:07:58):

I will be there for sure.

Gerald Shulman (00:08:00):

Yeah, I plan to be there. I don't think I've missed one other than COVID. I've gone every year, I dunno how many, 40, 35, 40 years. Yeah,

Jay Skyler (00:08:13):

I'll be doing it via remote since there's a hybrid option.

Ralph DeFronzo (00:08:21):

That's what the technologically intelligent people,

Jay Skyler (00:08:25):

Hey, it worked.

Ralph DeFronzo (00:08:26):

I don't

Jay Skyler (00:08:26):

Put myself in that category. I don't have to run from one session room to another. I can just press a button.

Zan Fleming (00:08:32):

Yeah, right. We're at top of the hour, so let's get started. Welcome every over to my colleague Thomas sir, who connect some CEO and also executive director of Vitalis Thomas.

Thomas Seoh (00:08:56):

I'll go in just a moment, Sam, but to tell you, I don't know whether you had some wind interfering with your mic. So while I'm going through my little spiel, you might want to see what you can do to stop breaking up a little bit. So thanks Sam. A housekeeping reminder to enter any questions in the zoom webinar q and a function or in the chat, A link to this recording will be circulated to all registrants and made publicly available within the next day or so. The chat function has been enabled for audience interaction. So just for warmup, those of you who are willing, please say hi in the chat, your affiliation if desired and from where you are logged in. So many thanks to those of you who have submitted excellent questions. The panelists will try to get to as many as there is time for turning the mic. Now over to Alexander Z. Fleming, md, founder and executive chairman Conex, a regulatory, clinical and product development strategic advisory firm and founder and president of the not-for-profit CATA Institute, whose mission is to catalyze science into solutions for preventing chronic disease and extending healthy longevity for all San

Zan Fleming (00:10:08):

Well. Thank you Thomas. I hope you can hear me. This getting windy outside, I'm here for a purpose and if I stop to fall apart, let me know and we'll make other arrangements. But we do welcome our friends and experts and collaborators from around the world. I'm thrilled that we're bringing together people from the two worlds in which I live, the worlds of diabetes and geoscience. I'm standing in front of the Potomac River 62 miles up the river from the capitol in Washington. And this backdrop is intended to support a kind of meditation on the key question for us today. How would we know if an intervention, and let me flip these slides if I can.

(00:11:16):

How would we know if the intervention, whether a pill, an injection, a medical device or a dietary supplement could slow the aging process and onset of multiple chronic diseases and even cancer? How could we get to a product with a label like the one in front of you? As it may be, my Jira science world has shown high likelihood that we can bend the aging process and slow the onset of multiple chronic diseases, cancer and disabilities that are age related. A diabetes world provides not only a human model of accelerated aging, but the tools for identifying and managing risk of cardiometabolic diseases measures such as LDL cholesterol and hemoglobin A1C are exactly what we need to answer the question about whether a product increases health span and to do it within a few years, not a few decades. To address that, how would we know?

(00:12:37):

Question. We have a landmark session today and it's open for your participation. We'll be getting to your questions throughout the discussion. Now as an endocrinologist at FDA, I was involved in approving the first drugs on the basis of the surrogate measures LDL cholesterol and A1C. Those approvals included the statins, oral and injected diabetes products and the unique drug metformin. Later I became interested in not just preventing diabetes but in preventing multiple chronic diseases with the conviction that not only can we do it, but we must do it for multiple reasons. This led to our first conference in London in 2017 and after 200 sessions later today's session, the diabetes world and the geoscience worlds do not intermingle as much as they should, but our panelists today have been changing that j Jerry and Ralph are a legendary in the diabetes world, but they are crossing over into the neuroscience world.

(00:14:02):

All have participated in our conferences multiple times, but more recently they've crossed over to healthy longevity audiences like the Peter Atia podcast for example. Ralph and Jerry are preeminent in studying the mechanistic roots of cardiometabolic diseases and Jay is equally accomplished as a prolific clinical trialist in the type one and type two diabetes works. Today we're going to focus on insulin resistance as not just a mechanistic root cause, but as the potential basis for a biomarker or surrogate endpoint that could accelerate the development of healthspan products, just as did LDL cholesterol and A1C for cardiometabolic products including the explosive field. I hasten to add though that insulin resistant of multiple approaches for clinically identifying and managing aging risk and perhaps approving healthspan products. We'll come back to other approaches in future sessions, but we start with insulin resistance because it is further along. In fact, if you are a healthcare provider, you can now order an insulin resistance test. Right now it's early days for insulin resistance, but I have seen early days before and what can happen from there. So you've been in the thick of developing every diabetic therapeutic class, but you always start with mechanisms and that's a good place to start. Over to you.

Ralph DeFronzo (00:15:58):

Okay, I'm going to see if I can get my slides up to start the program. You can stand up ho. Give us just a second to get the slide deck up. We'll get underway. Okay, I think everybody can see this. I hope so. Again, we're here to talk about insulin resistance and I believe, and I think for sure Jerry and I will sort of sing a similar tune, believe that insulin resistance is a foundational defect. Of course it's easy to demonstrate it in people with type two diabetes, but we've also shown it in people with pre-diabetes and the new term that I've called prediabetes. And I think the link between diabetes and aging and general science I think is pretty tight. People with type two diabetes and also for type one diabetes, their lifespan is reduced. They have multiorgan system disease affects the central nervous system, affects the heart.

(00:17:12):

So if we can get insights in how we may prolong things in life and hopefully correct the underlying insulin resistance, maybe this will lead to an extension of life. So this is an old study and it was one of the first studies that we carried out, which I think really highlighted the importance of insulin resistance in this sort of glucose intolerance, diabetes cascade. So in this study which was carried out in San Antonio, it's very easy to find Hispanic parents were both the mom and the dad have type two diabetes. And what we did is we looked at the offspring of the parents, but we had some characteristics that made it a little bit difficult to find the appropriate offspring because they had to be lean and they had to have normal glucose tolerance. And we used the U glycemic insulin clamp, which I developed many, many years ago, and this is really the gold standard for measuring insulin sensitivity.

(00:18:15):

And we infused insulin at two different infusion rates. The basal rate of glucose disposal is the first two bars in the offspring orange in the controls yellow, and then a lower dose at 20 milli unit per meter squared per minute and a higher dose. You can see that in the offspring at both doses of insulin there is quite severe insulin resistance and with the insulin clamp all of this glucose is being taken up and disposed of in muscle. We used treat 80 glucose so that we could quantitate hepatic insulin sensitivity and we didn't really see a defect at the level of the liver. All of this insulin resistance was at the level of the muscle. All of these people had a normal oral glucose tolerance test and we wanted to look at their insulin response. So we used the hyperglycemic clamp and to the left is the plasma insulin response to the right is the plasma C peptide response.

(00:19:21):

This may have some relevance to the insulin resistance test that Z just mentioned. And with the hyperglycemic clamp we raised the plasma glucose concentration by a hundred milligram per deciliter and you can see that clearly the offspring or hyperemic. So they're able to read the severity of the insulin resistance and respond appropriately. And I think these studies showed very clearly that long, long before you develop diabetes or pre-diabetes that the insulin resistance is really quite well established and really quite severe. But as I said, this was in Hispanic population. So we wanted to broaden this and look at other populations and these are data from two studies, the San Antonio Metabolism Study and the Veterans Administration genetic epidemiologic study and we again performed insulin clamps. There are a very large number of people in these studies and on the bottom we divided these normal glucose tolerant people into three groups based on their fasting glucose.

(00:20:26):

And you can see that even within the range of what would be considered to be normal glucose tolerance, that there is quite significant insulin resistance. And then if we look at the people who have a fasting glucose a hundred to 126, the impaired fasting glucose, you can see that the insulin resistance progresses and by the time you develop overt diabetes, these people are already severely insulin

resistant. Maybe it gets a little bit worse as the diabetes progresses, the four red bars, but I think what you can see is that you can almost draw a straight line from the people with a fasting glucose less than 90 up to those with the fasting glucose 140. So the insulin resistance is established very, very early. Now over the years we've had the opportunity to do u glycemic insulin clamps and a large number of people who you would probably characterize as having the metabolic syndrome, I prefer to call it the insulin resistance syndrome.

(00:21:28):

The control group is shown at the left and the height of the bar shows you the rates of glucose uptake during the insulin clamp. So if you look at lean type two diabetics, green obese, normal glucose tolerant individuals, people who had essential hypertension, people with hypertriglyceridemia, the last bar, the people with impaired glucose tolerance, they all very severely insulin resistant. And the purple bar was a study that Peter Bressler performed well, we looked at people with established coronary disease, it determined to determine cardiac cath and compare them to people with normal coronary arteries. And you can see these people were also very severely insulin resistant. So insulin resistance is a hallmark feature not only of diabetes but a lot of other disorders including obesity, cardiovascular disease and hypertension, all of which shorten the lifespan. So at the molecular level, and these are all human data carried out with Larry Mandino when he was with us in San Antonio looking at how insulin works.

(00:22:37):

And I'm going to make a point that I think clearly establishes the tie between diabetes, cardiovascular disease and shortened lifespan. So in order for insulin to work, it needs to bind to the insulin receptor. There's a insulin signaling pathway in which IRS one gets tyrosine phosphorylated, you activate PI three kinase A KD glucose enters into the cell. But what's less well appreciated is that you also activate nitric oxide syntase and you increase nitric oxide, which is one of the most powerful vasodilatory agents in the body. It's also a powerful anti atherogenic molecule. So what goes wrong in people with type two diabetes? Well there's a normal ability of insulin to tyrosine phosphorylate the insulin receptor, but an inability to activate the insulin signaling pathway. So what happens, glucose doesn't get into the cell, that's diabetes, you don't generate nitric oxide and that's cardiovascular disease. So it's virtually impossible to dissociate insulin resistance and cardiovascular disease.

(00:23:58):

They go literally hand in hand. And so we then came back to the offspring. So these people, as I showed you before, they're quite severely insulin resistant. They have perfectly normal glucose tolerance and the ability of insulin during the insulin clamp to tyrosine phosphorylate, the insulin receptor actually is increased. And that's because they're hyperinsulinemia. But you can see the ability to activate IRIS one and the PI three kinase a KT system is markedly impaired. So these youngsters basically have the same defect as their overtly diabetic parents. So this insulin resistance starts very, very early. And that means that all of the sort of bad things to go with insulin resistance atherogenesis in particularly have already started at a very early age. So this in a certain way is a phenotype insulin resistance. But we were interested in terms of what at the cellular level might be responsible for this insulin resistance.

(00:25:02):

And so we did muscle biopsies and we measured a TP synthesis. And you can see in the obese, in the type two diabetics that there is a marked decrease in a TP synthesis. And more recently we actually developed an in vivo technique using MRI technology and showed similarly that in obese type twos and not shown in this slide, people with pre-diabetes also have a severe defect in the ability to generate a TP. And if you look, you can see that this defect in a TP synthesis is strongly related to insulin resistance. So we are very, very much along the line here that insulin resistance, in fact may be generated by a

defect at the mitochondria. And I think this will be a good introduction now to turn things over to Jerry who really has done an enormous, enormous amount of work in this area. So I'm going to get rid of the, I'm going to stop sharing my slides and I think I've done that and I don't know whether Z is going to make a few comments about Jerry or Jerry's going to come on directly.

Gerald Shulman (00:26:27):

Z do you want to say anything? Okay, well then I'll start. So thank you Ralph. So go ahead Z.

Zan Fleming (00:26:37):

Sorry Sherry, I apologize I was having a technical issue. I think we will come back to Ralph and our other panelists for questions at the moment, but terrific. Ralph, thank you for a great start. And we continue with another expert in the field, Jerry, who is at Yale and a real powerhouse in the basic research around cardiometabolic risk and the basis for it. So Jerry, take it away.

Gerald Shulman (00:27:11):

Alright, thank you Z, great to be here. And Ralph, that was magnificent as always, introduction and really pleasure to be here and share with you some of our work on this topic. And so again, this is one of my favorite slides. This goes back to our dear colleague Jerry Revan, who in his banty lecture in 1988 first called I think everyone's attention to this clustering of things that with insulin resistance, both of course heart disease, this is what leads to the demise of our patients, high triglycerides, low HDL, hypertension, polycystic ovarian disease, high uric acid. And I think it's fair to say at that time there again these were association, a lot of people might've been skeptical saying these are common things, maybe they're clustering together. And now as we move to current times, we can now add fatty liver to this constellation MAs D mash metabolic syndromes.

(00:28:15):

Now the most common cause of MA LD and mash and end stage liver disease and the requirement for our patients to undergo liver transplantation, obesity associated cancers are skyrocketing. And I'm sure they're related to the hyperinsulinemia, secondary to the insulin resistance. Hyper insulin is a growth factor and certainly through IGF could be promoting. And there's very strong preclinical data from my colleagues Rachel Perry, who's shown in preclinical models insulin resistance is driving breast cancer, colon cancer, and if you fix insulin resistance, you slow down tumor growth and even Alzheimer's, very strong data correlating both not only diabetes but insulin resistance to Alzheimer's. So this is really potentially the thing that is probably to me, one of the greatest threats to humanity in the 21st century. And I'm going to both in this next several minutes, basically give you a molecular basis least how I think what causes insulin resistance.

(00:29:24):

Because you need to understand a molecular basis if we're going to come up with new therapies to treat it. And also share with you causal evidence to show you insulin resistance actually is driving fatty liver disease and mash and atherosclerosis. So again, evidence that again, if we can come up with drugs and fix insulin resistance, we can do a lot of good for our patients. So again, because of Tom, I'm going to just give you a high level overview of what the molecular basis for insulin resistance is. And one of the bottom lines and the key conceptual points I want to make, it's about ectopic lipid fat in the wrong places. And so we developed NMR methods to actually measure fat not only in the muscle but what's inside the muscle cell. That's the intracellular lipid content. That's again with proton NMR, we can

actually see the fat inside the muscle cell and using the clamp method that Ralph introduced to you, this is how much glucose we're infusing during a hyperinsulinemic U glycemic clamp.

(00:30:35):

This is the best predictor of insulin resistance in adults. The more fat you have inside the cell, the more insulin resistance you are. We've done this in young people, we've done this in the elderly, we've done this in children in sedentary individuals. It's the fat in the muscle. This is probably the best marker for insulin resistance, at least in our hands. I'm going to fast forward about 30 years worth of work then trying to understand the molecular basis for how fat inside the cell causes insulin resistance. And again, this gets into the weeds a little bit, it's a little bit of basic biochemistry here, but Z wanted me to discuss basic mechanisms because if we understand basic mechanisms, we can then understand really new ways and approaches to treat it. And so to summarize again, the last three decades we've identified through lipidomics, this is the bad actor d acyl glycerol.

(00:31:36):

It's the penultimate step in triglyceride synthesis. We've gone on to show triglycerides are just a neutral marker. So you measure fat, I showed you the IMCL correlates with insulin resistance, but this is really more of a marker for the bad actor. Dyl glycerol Dyl glycerols are known activators for N pkcs and the two in muscle are epsilon and theta. And they we've shown inhibit the insulin receptor kinase pathway and Ralph gave an ICE introduction for you. And so we've shown epsilon directly binds to the receptor, phosphorylates it and inhibits receptor kinase. And then this other is novel isoform hits the insulin receptor substrate one phosphorylates this and then prevents its binding to PI three kinase. This is a required step for insulin induced glu four translocation to move glucose inside the cell. The key concept I want to leave you with is this imbalance between fatty acid delivery to a cell relative to rates of oxidation by the mitochondria.

(00:32:50):

And we just heard about mitochondria from Ralph versus storage is neutral. Neutral lipid triglycerides. So when you have an imbalance of the fluxes, this accumulates and it only takes a spike in diag glycerol to activate this novel PKC pathway to inhibit receptor kinase activation and the receptor insulin receptor cascade. And again, we've been able to prove this using the power of mouse transgenic mice and knockout mouse and basically showed when we target LPL to the muscle cells, more fatty acid delivered to the muscle cells, dags build up muscle insulin resistance. When we block fat oxidation in the knockout enzymes that block mitochondrial fat oxidation dags build up, you get activation this pathway. And conversely for therapy, we've shown when you promote a mitochondrial inefficiency by over expressing an uncoupling protein three in muscle, we get reduction in DAGS less NPKC activation and protection from lipid induced muscle insulin resistance.

(00:34:07):

This is muscle and we've gone on to show the same thing happens in the liver cell. So his is a cartoon of the liver cell. And we've gone on to actually drill down even more basic where fatty acids are fluxing to the cell and the fatty acids go up these smooth ER and synthesis into the SM one two dags. There's different isoforms of diod glycerols, it's a stereo isomer and it's only the SN one two that will activate the novel pkc. So unless you're measuring these specifically, you're going to miss this. And more importantly, we've shown that it's in the plasma membrane. It's these SN one two dags that accumulate in the plasma membrane. Those are the ones that lead to the NPKC translocation. And for epsilon, we've gone on to show it phosphoryl. It's a critical screening in the insulin receptor catalytic domain, which then blocks the tyrosine auto phosphorylation and blocks downstream insulin signaling.

(00:35:09):

Very important concept. So you read the literature, if you think about insulin resistance, sometimes more often than not lipid inside liver and muscle cells correlate with insulin resistance. But then you always hear someone saying, well look, I have a mouse or even a patient, a lot of fat and liver, no insulin resistance. And we've shown then it's all about compartmentation of these bad acting lipids. The SM one two dags, when they're in a lipid droplet, there is no insulin resistance. So it's almost like putting fat in the subcutaneous fat, that's a very good place to put fat. And when the dags and tags build up in lipid droplets, no insulin resistance. And this explains many models of huge fatty liver, not only in animal models but in humans with A TGL or CGI defects or they can't export the fat MT TP knockout, huge fat in liver, no insulin resistance.

(00:36:06):

And if you biopsy and just measure dax, they may be increased. And we've shown it's because it's in the lipid droplet, not in the plasma membrane, no NPKC translocation, no insulin resistance. And those of you who studied athletes, the athletes' paradox, and again, that was always a question, oh, athletes actually are super insulin sensitive, they have more fat in the muscle. But we've shown actually both in animals, humans that are well-trained, they do have more fat, more dags, but it's all in the lipid droplet, not in the plasma membrane. And that explains the lack of insulin resistance. One other point for those of you who again, drilling down into the weeds, not only does the NPKC especially epsilon hit the receptor dozens of other downstream steps including Essex kinase. And so some of my colleagues say yes, oh yes, there's many downstream defects, not only at the receptor but further downstream.

(00:37:03):

And these other downstream defects in such as Essex kinase can explain these other downstream defects. So we've now gone on to show the same mechanism of dag activation of the n pkcs is not only in liver, not only in muscle, but also in fat and also in the kidney. The kidney is insulin responsive actually, and the renal cortex and you actually get lipid induced insulin resistance in the kidney. So all these organs are impacted through this mechanism and you almost have to scratch your head. And again, this is, we actually look at this pathway, the PKC epsilon pathway and phosphorylation is conserve from humans all the way down to fruit flies. And that's hundreds of millions of years of evolution. And here we just, I gave the introduction, both Ralph and I talk about how bad insulin resistance is. And here this pathway that causes insulin resistance has been conserved again through hundreds of millions of years of evolution.

(00:38:08):

One has to ask the question, why has nature conserved this? What's now a very detrimental pathway? And the answer which I will propose to you is this. And so we've shown that with starvation, you get increased lipolysis, more fatty acid delivery to these organs and triggering of this insulin resistance pathway. And during starvation and then refeeding, this is important for survival. It basically prevents you from storing glucose as glycogen in liver and muscle and keeps it available for CNS red blood cells in the renal modela. So that to me is the evolutionary basis for lipid induced insulin resistance. And now in our toxic environment of overnutrition, we're triggering this pathway and leading to this pandemic of insulin resistance and cardiometabolic disease. So that was my basic science approach. Again, ECT topic, lipids specifically lipid in the wrong places inside the cell and particularly the di a sub glycerols activating the insulin resistance pathway.

(00:39:20):

I now want to just show you building on what Ralph talked about of young healthy individuals who are insulin resistant. Because I think this is really, I think what I'd like to focus, I'm going to go both start with the young and then just move to the old, the elderly because this topic we were talking about

geosciences here. So this is the demographics of mostly healthy lean young Yale undergraduates, 18 to 21 years of age, you give them a drink of glucose, you measure insulin sensitivity using the METSUDA index that Ralph developed and measuring insulin levels. And to me the real surprise, and these are all sedentary individuals, is the broad distribution of sensitivity. Look at this all the way from two to 10 really bell shape, almost a bell-shaped distribution. And so by definition, these bottom quartile are resistant by the ISI and these folks are sensitive.

(00:40:26):

And we asked the very simple question is when you take in carbohydrate, do you store energy differently if you're in the bottom quartile versus the top quartile? So we gave these resistant and yellow in the sensitive and blue to high carbohydrate mills meals and measure glucose. And not surprisingly, not different. And again, Ralph talked about his experience in the pre-diabetic individuals and the reason, excuse me, their normal glycemic is the beta cells are working overtime, pumping out twice the amount of insulin. And remember the liver cell seen three times this concentration liver cells are seen almost 500 to 600 microunits per mil of insulin. We can measure where this ingested carbohydrate is going with both carbon and MR to measure glycogen changes and proton NMR to measure fat changes inside liver muscle cells. And I didn't have time to get into this, but this is what we've shown previously is when you're insulin resistance, most of that insulin resistance is a defect getting glucose into muscle glycogen.

(00:41:37):

And these young individuals have this same problem. They can't get glucose stored properly as muscle glycogen. And this is due to a defect in transport activity, but no problem getting glucose or carbohydrate ingested into liver glycogen. So just consistent with what Ralph showed you is a problem getting glucose into the muscle and where's that glucose going? It's going to liver fat. So this is proton NMR measurements changes liver fat, it's increased twofold, oops. And we can actually quantify how much of that fat is coming from de novo lipogenesis. That's the conversion of glucose to fat using heavy water which was in the milkshake, tracking it into the backbone of VLDL. And that's increased by twofold. This explains then the increase in liver fat. And when the liver is geared up to make more fat by DNL, it exports more fat. So plasma triglycerides are already increased 80% in the resistant individuals and that leads to reductions in HDL.

(00:42:47):

So conceptually, the key point I want to leave you with is this is where you want to be. This is when you're sensitive. This is the top quartile, this is common one in four individuals. When you ingest your carbohydrate, you want to store it as glycogen. If you're that one in four individual who's insulin resistant, and if you're already overweight or obese, you're probably already here, you have increased IMCL blocking transport activity. The ingested glucose cannot be taken up and stored as glycogen. It's diverted to liver. You have portal vein hyperinsulinemia, you're revving up SRE BP one C, the master regulator of DNL de novo lipogenesis that converts that carbohydrate to triglyceride high triglycerides low HDL. This is your atherogenic dyslipidemia leading to your first heart attack in your fifties if you're not careful. And with time, this is what's driving fatty liver disease, which we talked about now the most common cause of cirrhosis to test this hypothesis.

(00:43:57):

We went on to see can we reverse this? And studies we did again many years ago, we were able to take these resistant offspring and showed with exercise training we could actually normalize insulin stimulated muscle glycogen synthesis. We can get into the molecular mechanisms of how this works. One of the questions related to this A MPK activation and A MPK will bypass that defect I showed you in

insulin activation of pediatric kinase. It kind of short circuits it so causes glute four translocation independent of that defect in lipid induced blocking of insulin signaling. So knowing this, we actually said, we'll exercise reverse this defect. So to test this hypothesis, we took these insulin resistant individuals, we exercise them and we showed that you could normalize then glucose disposal into glycogen lowering DNL lowering liver triglyceride. So the key concept here is if we can fix insulin resistance, first of all, it happens first in muscle.

(00:45:03):

And if we can fix this defect in muscle, we can fix the atherogenic, dyslipidemia and eventual development of fatty liver disease. And so not only the message here is we should all stay active whether or not I think we're sensitive or resistant, but if we could come up with agents to fix insulin resistance, this to me, we should be treating insulin resistance in young healthy people like we treat cholesterol, hypercholesterolemia and hypertension. If we can do it safely and inexpensively, fixed insulin resistance and we can prevent these things from happening. And is the evidence taking this to humans? Again, fatty liver, and this is again one of my favorite studies. This is again, I think how the GLP one incretins are working. I'm sure we'll have questions about that. This is again, we did this 20 years ago before fatty liver was popular. We studied, this is what I would see in my clinic, type twos in the mid fifties, fasting, hyperglycemia, this we and others, and again, studies by Ralph and Lesky.

(00:46:09):

This was again related to the reason patients have fasting hyperglycemia is this increased rates of glucose production. We were able to go on and show this is due to all due to increased gluconeogenesis. And again this after, and this is also hepatic insulin resistance in these individuals. And here with just a 1200 calorie 88 diet, after six to eight weeks, we were able to normalize fasting glucose. This was reduced to reduction in hepatic glucose production. And we showed that this is reduced to reduce gluconeogenesis. And again, we'll talk about metformin. This is what metformin does and we are able to normalize insulin's ability to suppress glucose production. So what's accounting for this? The first key point here, again, this is only required 10% weight loss. This was again 20 years ago. Now everyone talks about that's all it takes is 10% weight loss. And again, this is why the incretins are doing so well.

(00:47:12):

Again, they get 15, 20% loss. But again, it's with this threshold. This is the second point. This is well established. Now again, this is 20 years ago. Every poorly controlled diabetic we put in the magnet has fatty liver, 10 times normal. This was news at that time. Now it's well established. And the third point is just this modest weight reduction gets rid of this relatively small pool of fat and that makes a huge difference. Getting rid of that fat in liver fixes the diabetes key point. They still have muscle insulin resistance, but they're not diabetic anymore. So I think again, the liver fat pool is a great target to fix type two diabetes. A key conceptual point here is what's normal for in terms of liver fat. Most of my hepatology colleagues always talk about the 5.5% threshold. It's actually much, much lower than that.

(00:48:11):

So this is a study in 1500 mostly young individuals that we study. The threshold is actually 2% and it makes a difference. This is a threshold phenomena we all get excited again in the fatty liver world owe 20 30% reduction by drug X or drug Y. To me it's not a relative percent reduction. That's nice. But I think we really need to think about an absolute threshold of less than 2% because here in this paper that kid and I published a few years ago, we showed that even if you're above this threshold of 2% liver fat, actually 1.85%, you still have insulin resistance. You still have hypertriglyceridemia, increased LDLs, high uric acid, increased diastolic blood pressure, and low HDL. So this is a very important point. Maybe we'll

get into this, that we need new drugs to not only just relative reductions, but actually there's going to be a threshold that we really need to achieve.

(00:49:14):

And then finally, just to end up on, because we're talking about geoscience and aging, I'm going to show you the same concepts apply to all of us as we age. So this is the Hanes study and here we are age 65 and 40% of us have either IGT or diabetes. It's really a profound number. Again, we all know as we get older, we put on weight, we become less active. These are all things that will contribute to insulin resistance and diabetes. And we wanted to see are there other factors that contribute to insulin resistance, even if you're the over 70 or 65, but you're lean. So these are lean 70 year olds that we study kid and I studied BMI 25 match for fat, mass body fat, lean body mass, normal glycemic. And we have very simple question, are these healthy lean 70 year olds different?

(00:50:12):

I won't show you the GTT data, but the glucoses are relatively normal, but they're hyperinsulinemic. And this is why again, they have profound muscle insulin resistance. Again, lean, healthy, 70 year olds and we can measure, I showed you liver fat, muscle fat and they're both up healthy lean 70, increased IMCL and increased liver fat. And the question is why is fat accumulating in lean individuals? Is a defect in the fat cell delivering more fatty acid or we heard about the mitochondria, is it a problem there? This is where we burn the fat. So we did microdialysis experiments and really no differences in basal or insulin suppression of lipolysis and turned our attention to the mitochondria. And we developed the first in vivo studies to measure mitochondria activity. And we did this in two independent methods. One with carbon NMR. We developed a method to measure oxidation in vivo.

(00:51:09):

A lot of people do things with muscle biopsies, but I always worry about the environment of what you're measuring in that biopsy when you put it into the seahorse machine. And so this is incy to carbon measurements of oxidation and it's reduced in the elderly and an independent method. Phospho, we developed method to measure a TP synthesis and that's also down by 35%. So conceptually what's happening is as we age, our mitochondria are slowing down 35%, not clinically significant in that you can still walk and do fine and do activity, but it's a predisposing factor. This 30% reduction if we don't change energy intake, this is predisposing us to ectopic fat buildup as we age. Dags more importantly and insulin resistance, we've gone on to show this is happening unfortunately in all of our tissues. This is a study we did with our colleague Doug Rothman.

(00:52:12):

We can do the same measurements of mitochondria activity in the brain and neuronal rates of mitochondrial oxidation are also slowing down in 70 year olds compared to 20 year olds by about 28%. Can this be fixed? This is an interesting provocative study I want to share with you. We've all known about Ross damage to mitochondrial DNA, mitochondrial DNA do not have the repair mechanisms that nuclear DNA. And it's been a hypothesis that's been discussed for many, many years. And studies by Peter Rabinovich has shown that when you overexpress MCAT to the mitochondria, you can actually reduce mitochondrial DNA damage. And so studying these mice, we asked the question, well can these mice, this is mitochondrial catalyst targeted to the catalyst targeted to the mitochondria. And so we studied these mice and we showed that just like humans with aging, the mitochondria slow down with aging.

(00:53:19):

And that when you over express catalyst in the mitochondria, they are protected from this reduction in mitochondrial activity as they age. And again, this is this age associated reduction in insulin sensitivity in old mice by clamp. And when you overexpress and protect the mitochondria, you protect the muscle insulin resistance. So I think to me, this is the strongest evidence that aging is associated with reductions in mitochondria activity. If we can preserve mitochondria activity as we age, we can prevent ectopic lipid buildup and muscle insulin resistance and probably liver insulin resistance. So these are my last slides here is there are multiple ways to get this ectopic lipid buildup, not just one way. And again, ectopic lipid inside the cell is what drives insulin resistance. All of us can get there independent of our genetic background simply over nutrition. We spill over from the ability, oops, ability to store fat in the fat cell.

(00:54:26):

And I'm going here and we get spillover and there's a threshold. We didn't talk about this. We will maybe in questions and answers. There's a genetic predisposition, especially on our Asian Indians. They get spillover to ectopic lipid even when they're lean. And this we've shown they are prone even the BMI, they have more ectopic lipid liver and fat certainly when you have no fat, we've shown with lipodystrophy, you get build up of if no can't store the fat and the subcutaneous fat and it builds up. And again, there's partial lipodystrophy with the HIV and HIV medications and I think this is what's happening in our different ethnic subgroups, the inability to store fat properly in the subcutaneous fat and it spills over. And conversely, we've shown this is how the tds are working is they reduce, they promote fat storage in the adipose sites and secondary lower it in liver and muscle.

(00:55:30):

And this is why they are an insulin sensitized and aging, I'm sure Ralph have more to say about TCDs and pioglitazone. And we've also shown, our group has shown that adiponectin actually works in this way by stimulating lipoprotein lipase and fat and lowering fat in liver and muscle. And then finally, the mitochondria, which we just talked about, we've shown with healthy aging mitochondrial slow down. We've shown that in the offspring of parents with diabetes, as Ralph showed you, we've shown independently that mitochondrial both with a TP synthesis and oxidation, slow down predisposed ectopic fat buildup. And now as people are looking carefully, there will be genetic variants that will be identified that will predispose to ectopic fat buildup and insulin resistance. And my prediction is there'll be variants that actually have have increased rates of oxidation. They'll be more subtle. But these individuals, if you're lucky enough to have that, you'll be protected from ectopic fat buildup and insulin resistance.

(00:56:38):

But then this leads me finally is to, this is to me a very nice therapeutic target. If we can promote mitochondrial inefficiency, we might be able to protect against ectopic lipid insulin resistance and all these other bad things associated with it. And so this is now a concept we've been tracking for the last 10 years. We're now, I should say in human studies phase two studies showing safety and efficacy. But the concept is we know about how well the incretins are working through decreased energy intake and we'll talk about that. But here we're promoting increased energy inefficiency through pitton of wars. And by doing that, we lower ectopic lipid and we lower not only DAG tags, but more importantly dags less NPKC translocation we've shown when you burn the fat in the liver, you have less in insulin inflammation. You can reverse fibrosis and you lower acetyl-CoA, you less gluconeogenesis.

(00:57:40):

And most importantly, when you burn the fat in the liver, you export less fat and it's heart healthy. So you have lower triglycerides, lower LDL. And this has now been shown both in animals but non-human primates and most importantly in humans now with independently by multiple different provos and you

export less fat to muscle and this is now then you'll have secondary improvement in muscle sensitivity by L ectopic fat in skeletal muscle. So I think, oh, and this is against this aging. This was an aging mouse study. We've showed this approach actually works in aging mice. This was done by our colleague at the NIH Raffa de Cabo who did the mouse studies and he showed that with aging, this approach promote mitochondrial inefficiency, less hepatic cytosis, less inflammation, less oxidative distress and increase the sensitivity. And in female mice don't die of heart disease, they die of cancer and at least the female mice are protected from hepatocellular carcinoma by reversing insulin resistance through this approach. So that is the end of my talk and I look forward to questions. And if I can just turn off my screen here, stop share. We're back to questions.

Zan Fleming (00:59:05):

Wow, Jerry Bravo. Amazing two to four presentation, elegant and profoundly important and a great progression from Ralph's excellent start. And now we are on to pay Skyler for what will be a more clinical perspective. So thank you Jerry. And take it away. Jay.

Jay Skyler (00:59:30):

Ralph, you wanted to say

Ralph DeFronzo (00:59:31):

Something? Yeah, whatever happened when we transitioned from Jerry, I can hear you all, but they cut off my screen so I don't know what they did. But as I said, I can hear you but I can't see anything on my screen. Maybe you can fix it internally, but go ahead

Thomas Seoh (00:59:51):

Jay, can you look into that while Jay is going through his talk, please?

Zan Fleming (00:59:56):

We do see you, Ralph, even if you can't see us.

Thomas Seoh (01:00:00):

Oh, okay.

Zan Fleming (01:00:01):

Good. Hello, I'm waving to you. You're good. You're with us. And now we're on to Jay. So take it away Jay.

Jay Skyler (01:00:09):

Well, thank you. So the subject really is the health span in 2025 and looking at it, if I can get the slides to advance, what we've seen is that life expectancy at birth in the United States versus other countries has really remained much lower and has even dropped lately. We've bounced back from that. Some of that dip may have been COVID in there for a little bit, but the reasons for that may very well be. The cumulative change in the share of US adults with obesity has risen by 125% since 1990. Diabetes has risen by 75% since 1990. Hypertension is reasonably well controlled and hasn't been rising very much. One of the things that I always go back to when we talk about blood pressure, the National High Blood

Pressure Education program, which was instituted in 1972, we went out to churches to all places all over the country and advocated for getting blood pressure below one 40 over 90.

(01:01:31):

And that was different than the rest of the world at that time. The rest of the world used the WHO definition for blood pressure, which was 1 65 over a hundred that they were aiming for and we were aiming for less and we got blood pressure down more and we reduced our life expectancy more than the rest of the world. Then the rest of the world switched over and caught up with the newer recommendations. And we've continued to actually lower the targets even more for blood pressure today. And I think we've done a good job with hypertension. Part of that was the large scale education program. We have not had as large a scale education program to deal with obesity and diabetes, and that's why they keep rising. I think that's a serious issue. This actually is very recent data was published in the Wall Street Journal just a week or so ago.

(01:02:31):

The other thing that we've seen is that there are people who now are sanitarians, they live to over a hundred and they've been called the welder. And it turns out there's almost no difference between their biologic, makeup, genetics, and that are their peers, but they are more physically active, more social, and typically better educated. We can certainly do something about the physical activity and trying to get people involved socially to try to improve our outcome and to have a healthier lifespan, that health span being better and strategies for doing this. The things that Eric Topel has advocated, and he's got a recent book on this, is take up strength changing, schedule your sleep and be sure to get enough of it. Bolster your mental health, manage stress and improve your mental health more broadly. Use tests and trackers sparingly. Don't go into all these things that are sold online and be wary of these influencers because they're pushing some gimmick most of the time and not scientifically based. And he recommends for food choices that we focus more on fruits, vegetables, whole grains, unsaturated fats, nuts and legumes. And these things will help us age more.

(01:04:03):

Yeah, I'll get that right somehow. And Camilla recording his book on the health span code points out that the pillars of health span and trying to do this are predictive diagnosis years before the first disease symptoms will appear to identify invisible factors that you cannot defeat what you cannot see. Healthy nutrition, we mentioned that a moment ago. Low glycemic index, anti-inflammatory foods, portion control. And considering intermittent fasting, physical activity and exercise, he emphasizes that the chair is our worst enemy. We need to be up and around protective molecules to prevent or reverse silent inflammation and insulin resistance. Vitamin D three, Omega-3, fatty acids, polyphenols and serin, activators and GLP one receptor agonists, brain exercise and mental health. We've got to keep our brain working, have purpose social life, listen to music, be involved, integration with protective molecules that cannot be assumed by diet and that decrease with chronological aging when exercise is no longer enough.

(01:05:20):

And consider the blue zone ecosystem. There's not a single bullet or magic remedy. We need to think about all these kinds of things. Yes, this sedentary chair being the culprit is illustrated by this picture of our change in activity level through evolution that now we sit at the screen all day instead of being out hunter gathering for various food and the like. So what do we need to measure this? Well, Z in the beginning pointed out that Quest diagnostics now has what they call the Cardiac IQ insulin Resistance panel and score. It is a single test, you just take it with a single blood, a blood sample. You've heard from Ralph about the gold standard with the U glycemic clamp. And you've heard from Jerry about looking at

some of these things in depth in detail. But what we need is something at the bedside that people can use to get an idea that insulin resistance is present.

(01:06:29):

I agree with them that insulin resistance is the underlying factor that's responsible for much of this. And this just shows you that quest has compared the IR score, it has greater discrimination than either insulin or eptide alone. It actually puts insulin and eptide levels together by GC mass spec measurement of it. And it does better on the right side than the HOMA ir, which some people have used as a quick way of trying to assess it rather than using the clamp or the MASUKU index, which was mentioned that Ralph developed at one time. But that requires having multiple values and you can't do it just with a single fasting sample. Some have suggested that the triglyceride HDLC ratio may be an index of that, but the IR score does better than that as a greater odd ratio of picking it up. And these were all compared to a large population that was studied by Jerry Revan at Stanford and looked at the detailed measurements of insulin resistance that he used.

(01:07:42):

And so what's the relevance of this? Even in lean people, you're insulin sensitive. If you have a score of one normal insulin sensitivity, you're totally insulin resistant at a hundred by 33 or about a third of way up, you're fourfold more likely to have insulin resistance in a patient with normal insulin sensitivity. And at 66, you're 15 fold more likely to have insulin resistance. So it does help you pick out who may be insulin resistant and you can target that Z asked in the beginning, he wanted to know a measure for health span that would be equivalent to A1C or LDL cholesterol insulin resistance score may be one way of getting to that on a large scale basis. If you're not doing u glycemic hyperglycemic clamps, which in the course of the clinical trials to get drugs approved for insulin sensitivity may be necessary. But in assessing things in clinical practice, this IR score that you can get from Quest right now may be the answer.

(01:08:49):

And then we mentioned, and Jerry mentioned, and I mentioned in showing you the slide earlier, what things you can do. GLP one medications, they're common right now, and everybody talks about them as drugs. They were originally developed to treat diabetes, but they've also been now widely used for lowering weight. But it turns out they decreased cardiovascular risk factors. They decreased cardiovascular outcomes including stroke, heart failure, myocardial infarction. They also decreased the metabolic liver disease that Jerry was talking about, decreased kidney disease, decreased sleep apnea. They have effects on many inflammatory markers and inflammation. And they're being studied now for neurological diseases, Alzheimer's and Parkinson's. They already have been shown to decrease stroke. So they offer neuroprotection. They may actually, and I'm being studied also for looking at substance use disorders, alcoholism and drug use and compulsive behaviors. They also may benefit from GLP ones. And we've already mentioned the myocardial infarction, atherosclerosis, metabolic liver disease and diabetic kidney disease.

(01:10:02):

And so we get a lot of these things from GLP ones. And I think that we ought to be thinking about them as a real way to expand our health span so that it becomes closer to our lifespan. And I'm a big advocate of that. You could argue that some of this may be due to consequence of weight loss. Nothing wrong with that, but some of it is direct effects. And I think that's important to bear in mind. So in the center you see the evidence-based things that it has been shown to decrease diabetes, obesity, cardiorenal disorders, and so established benefits for kidney disease, myocardial infarction, heart failure with preserved ejection fraction and stroke. And it's being investigated further for metabolic liver disease,

Parkinson's, peripheral artery disease, and Alzheimer's. So I would champion as the one thing that we might have at the current time that we could potentially be using for promoting health span, which is what Z was asking about, is GLP one receptor agonists.

(01:11:11):

And he put forward the combination of what he called rap forin, rapamycin and metformin. They've worked well in animal models, but rapamycin has its own potential side effects that can be quite serious. And metformin, if you really want it to be effective, you have to take enough of it. Turns out that the average dose prescribed for metformin, for type two diabetes where it's useful, the United States is somewhere between 1,011 hundred milligrams a day. And if you really want to get the great effects from Metformin, you need to be upwards and above two grams a day in the 2000 to 2,400 milligram dose. And people don't do that. So if we're going to use metformin more, we to be coupling it with the message that they need to be using adequate doses. So I think that what that says is we have three things around at the moment that we can think about that have been mentioned today. One is metformin. I'll leave the rapamycin portion out of your hypothetical there, Z. But metformin, if we advocate for high doses, we need to advocate the same way we did for blood pressure in the 1970s. We need to have a campaign to get it right. Pone that Ralph mentioned and GLP ones. I think we have three things there that we can use already to promote healthy lifespan and those would be the ones that I'd be pushing for.

Zan Fleming (01:12:43):

Well, terrific. Jay, you've given us a lot of food for thought and some things to come back and maybe discuss a bit, but let's now make this a wider discussion. We'll take some questions that we've already received and one of 'em is over to Jerry is Metformin magic.

Gerald Shulman (01:13:08):

It's certainly an enigma. We've been prescribing it in some way or another for over two centuries and we're still arguing how it works. I'll tell you what I think clearly it lowers in poorly controlled diabetes. These are the things I'm pretty sure about. It lowers fasting hyperglycemia and that's through reductions in hepatic glucose production due to reductions in gluconeogenesis and that's in patients. The question is how does it do that most? I think evidence there was an interest in A MPK activation. It does do that, but the reductions in hepatic gluconeogenesis are independent of that.

(01:13:56):

In my view. It basically increases cytosolic redox state through inhibition of this glycerol phosphate shuttle, which is inhibited indirectly by inhibition of complex four. I'm kind of in a there, I think I may be one of the people, the only person on the planet who thinks this. I think the rest of the world thinks it's complex. One. Again, since we want to get into mechanisms Z, you encourage me to get into mechanisms. The reason it's not complex one is you only inhibit complex one at millimolar concentrations. Our patients even at two grams, 2.4 grams, you're at micromolar concentrations and that does inhibit complex four at micromolar but not complex one. Secondly, when you knock down complex one, you don't get in mouse models. You don't get reductions in glucose, but you do when you knock down complex four. And finally, when I told you everyone, I think multiple groups have shown this increase in cytosolic redox state with metformin that happens with complex four inhibition but not with complex one.

(01:15:07):

So having said that, it's really gluconeogenesis. One of the most biggest misconceptions I think when I hear metformin discuss is it or is it not an insulin sensitizer? And I had like to just make it clear at least in my thinking is again, most of it is through reduction in gluconeogenesis, but through reductions in glucose and glucose toxicity, you will have this improvement in peripheral hepatic sensitivity. And these are studies I did with Ralph and Lua Wasti glucose toxicity is a real phenomenon. This is why our type ones are insulin resistant. And again, as Ralph has really I think brilliantly shown, you get rid of glucose toxicity and you can reverse insulin resistance that way. So I think secondarily, metformin will have this sensitized in effect, it's not a IV as glucose toxicity and will only happen when you're hyperglycemic and get down to normal glycemic levels.

(01:16:06):

And the last thing I'll say about last thing, I know Ralph is dying to say something. Well, last thing is we've studied now and we're writing it up now and this is appropriate for now this the use of metformin in aging and we will talk about the tame study maybe, but these are normal glycemic individuals. What effect does it have? Because you have normal rates of hepatic glucose production. When you're normal glycemic, it still has a slight glucose lowering effect. And what does that do to? And the studies we've now just shown in normal glycemic individuals doses of two grams a day actually promote glucose clearance and increase glucose conversion to lactate. And that's perfectly consistent. Again, when you inhibit the mitochondria, whether it's complex one or four like I think or others think either way you knock out the mitochondrial electron transport chain, you decreased oxidation, you take glucose down to glycolysis, more comes out as lactate. So in this way you're promoting increased glucose clearance and that actually is responsible for a little bit of glycemic A1C lowering independent of this reduction in normal hepatic glucose production. So that's I think again, has relevance to use of metformin in the normal glycemic individual Ralph chopping at the bed to say something.

Zan Fleming (01:17:31):

Well, indeed he is, but the simple answer is metformin is somewhat magical.

Gerald Shulman (01:17:39):

Well, in that way, again, I would like to understand, again, I don't like the use of magic and science. It does things and I think clearly it's in the mitochondria. I don't think there's little doubt there and whether it's electron transport chain one or four that will work out. But I think if we understand this basic mechanism, we can actually maybe come up with an even better metformin. But I think that's why I think it's so important to understand mechanistically how these drugs are working.

Zan Fleming (01:18:11):

Yes, indeed. Well, Ralph, over to you. Metformin is your baby, but you are also an advocate of a true insulin. So take it away.

Ralph DeFronzo (01:18:22):

So as you'll know, the entire drug development, Metformin I supervised, and actually when we did that, we actually did insulin clamps in people and we never could show at any dose level that metformin improved insulin sensitivity. Moreover, metformin gets in the muscle cells through the organic cation transporter and that basically doesn't exist in muscle. So there is some small buildup of metformin probably through passive entry, but there's no way because people have done pet studies with labeled metformin and metformin doesn't accumulate in the muscle, so it would virtually be impossible for it to

be an insulin. And in fact, we showed that the thing you have to be careful, and by the way, everything Jerry said about gluconeogenesis is absolutely correct, and we've done very similar studies, but people have to be careful. About 20% of people cannot tolerate metformin. That GI side effects. And I think some of the confusion that's come in the literature is that people lose weight on metformin and when you lose weight, even two, three kilograms, that can improve insulin sensitivity. But I'm pretty convinced that metformin does not improve insulin sensitivity and muscle and all of its effect is in the liver. So if we're talking about insulin resistances, at least in muscle being the driving force, I'm not a strong advocate of that sort of line of reasoning.

Gerald Shulman (01:19:54):

Yeah, no. Again, no disagreement. I should mention, I think one of the best studies that studied this was our colleague Jerry Leski. And so he took type twos and treated them with, I think at that time, troglitazone and metformin, and he showed that both lower glucose, but when he brought in the diabetics and gave them insulin infusions normalized their glycemic level, then Troglitazone continued to have improvement around peripheral sensitivity, yet metformin had no effect. So again, I think we're all in agreement. Metformin is not a sensitizer and it works on the liver and hepatic gluconeogenesis. Yeah,

Zan Fleming (01:20:39):

But Ralph, you like pone and it is a insulin sensitizer. What would you say about using pioglitazone as AAN approach?

Ralph DeFronzo (01:20:53):

As I said, I can't see the screen, but if it's possible, you have my slides. The very first slide after I ended is a pioglitazone slide because I do think as Jay pointed out, we have a number of choices, GLP one receptor agonist, pioglitazone, and then the mitochondrial target. I'll make a couple of comments about the mitochondrial target. I don't know if you can get slide 13 up, but these are

Zan Fleming (01:21:24):

Just speak to it conceptually, the shortness time we've got.

Ralph DeFronzo (01:21:30):

Yeah, so what we showed was, and again these are all human studies that peel glitazone activates that insulin signaling pathway. It markedly increases glucose transport into the cell. It markedly increases nitric oxide generation. It is a true insulin sensitizing drug. And we know from the IRIS study, remember those were people who had strokes with a mean hemoglobin, A1C of 5.8. In the IRIS study, those people were treated with POG on a placebo. Even the people with A1C less than 5.8, there was a 30% reduction in recurrent cardiovascular events and he marked reduction in the conversion to type two diabetes. So we actually have a study and to get into the Irish study based on the Homa ir, you had to be insulin resistant. So we actually have a study in insulin resistant people who have an A1C that's less than 5.8 saying the tisone works.

(01:22:39):

And we've published the data. In terms of the heart major misconceptions, if you look at tisone, what it does in normal, in people who have diabetes with without H HFpEF or mild HFpEF, there's a 75% improvement in insulin sensitivity. In the myocardial, there's a major increase in myocardial blood flow.

There's a significant increase in ejection fraction. If you look at every measure of diastolic dysfunction, E over a E over E prime, every single thing gets better. So people get confused with the peripheral edema. The edema is all because you vasodilate the blood pressure goes down, and when you under perfuse the kidney, you hang on to salt and water. And if pioglitazone were named amlodipine, this drug would be approved for heart failure because people use amlodipine. Cardiologists do in the incidences of edema is about 20 or 25%. And pioglitazone and amlodipine are basically doing the same thing, but people get upset with pioglitazone but not with amlodipine.

(01:23:49):

So we're working with a company called Sirius to develop an insulin sensitizer that would do what pioglitazone does maybe by working on the powder of eight transporter without activating PPAR gamma. And that may be a way of getting around the fat weight gain and the fluid retention by having an insulin sensitizer. And then Roger, she and I are working on an LCAP one inhibitor that really works on the mitochondria. So I think that there are other approaches and we clearly need new approaches to improve insulin sensitivity in addition to the three that are out there. I would

Zan Fleming (01:24:39):

Thank you, Jay. I just wanted to come back to before I come over to you to thank Ralph for the really great summary about pone. And by the way, we'll have Roger on another session along with Jerry Cola, who's got to be glad that you mentioned his efforts with CS and yet another approach. But Jay, over to you.

Jay Skyler (01:25:08):

Yeah, I was going to say the side effects of pioglitazone can be avoided in most people by keeping the dose down, trying to stay at 15 or at most 30 milligrams and avoiding the 45 milligram dose, you will minimize those side effects. If you stay at 15, you practically don't get them at all, but you might want to be up to 30 to get the full effects on insulin sensitivity.

Ralph DeFronzo (01:25:32):

What Jay says is correct. When we analyzed with Sylvia at Yale, we looked at the dose response curve in the iris. The cardiovascular protection in the IRIS study was equally apparent at 15 and 30 milligrams as it was with 45 milligrams. The other thing you can do is you can put the pill, and this is all published, you can put the PO glitazone, we did this with liraglutide, and you actually get all of the weight loss that goes with liraglutide in node fluid retention. And we've also done the PO glitazone SGLT two inhibitor combination, and that also attenuates the weight gain and the fluid retention. So maybe today the best two drugs that are out there are PO tisone with one of the newer GLP one.

Zan Fleming (01:26:20):

Well, that's the Ralph. But let's stay with Jay a moment and we're going to queue up Thomas to take some questions off the chat. But Jay, you are an advocate of GLP one agonist perhaps for health span purposes, but let's also keep in mind that there is some adversity associated with GLP one agonist and it may not make them suitable for people who are younger who don't yet have disease and for whom the benefit risk may not be positive. So just to make that distinction that we've got abundant evidence that GLP one agonists help people who are overweight or have diabetes, but we don't have data yet for people who are pre disease, at least not much data.

Jay Skyler (01:27:16):

It's accumulating though. And my argument is that the issues with GLP one receptor agonists in terms of adverse effects are not serious adverse effects. Mostly they're usually just

Zan Fleming (01:27:35):

Muscle loss, GI, osteoporosis.

Jay Skyler (01:27:39):

We're

Zan Fleming (01:27:40):

Talking about decades of treatment now.

Jay Skyler (01:27:42):

Yeah,

(01:27:45):

I've been on GLP ones for two decades myself, and you avoid the osteoporosis and muscle issues by maintaining good physical activity. I'm in the gym three mornings a week to do that, and you can totally overcome those things. And there's not really, if you look at risk benefit compared to other drugs and serious things that are not preventable, there's very few of them. And I think that I would argue that they are like the statins that you mentioned earlier are something that we ought to be using for a wide scale basis to try to improve health span.

Zan Fleming (01:28:32):

But just to point out, statins are not a health span agent or category. As you know, they reduce cardiovascular disease, but they actually increase the risk of diabetes. So we have to take that into account.

Jay Skyler (01:28:50):

That's arguable too, but we won't get into the details of that. Okay.

Zan Fleming (01:28:53):

Alright, fair enough. Thomas, throw some questions out.

Thomas Seoh (01:28:58):

Well, I want to exercise privilege here and ask the question I just put in the chat back to the general question, is insulin resistance as a number, a candidate for a basic health metric like A1C or blood pressure, et cetera? How about as an aging metric? What more do we need to know to decide? And what are some other candidates?

Ralph DeFronzo (01:29:23):

Let me start to answer that. My very first, NIH grant 1975 was from the Gerontology Institute and it was basically to look at insulin resistance as a function of age. I know 1975 people that's like in the archives and if it's more than five or 10 years old, people

Thomas Seoh (01:29:44):

Forgot last century.

Ralph DeFronzo (01:29:46):

Last century. But what we showed very clearly is a dramatic age-related decline independent of changes in body weight and insulin sensitivity. So I would say that they're pretty good data. And we also have data from the gerontology center, Ruben Andres and Jordan Tobin, that as people get older and these are non-diabetic individuals, that insulin resistance becomes more predominant. So I think there's a lot of data out there linking aging with insulin resistance. Now, can we overcome this? Well, there are drugs. Jay mentioned exercise. And when Ricardo Bonadona was a fellow as part of these aging studies, what he showed is as the people got older, and Jerry Schulman mentioned this earlier, that what happens is that even though they have the same quote BMI, there's a marked increase in body fat and a decrease in muscle mass. So these are age related changes for which we actually have things that already could potentially be used.

(01:30:56):

Now in terms of the GLP one receptor agonist, I think you have to be careful in aging people because there is a decrease in muscle mass of using these drugs. But in the average diabetic person, if you lose 30 kilos, you should be losing some muscle mass. And I think whether that you are losing muscle mass disproportionately to the decrease in body weight, I would say this is a very controversial topic at this point. But again, in the aging population, that would be the population that I would be most concerned about using the GLP one. Although I think as Jay said, if you have to pick one drug to treat diabetes, that's probably the drug I would choose along with Jay

Gerald Shulman (01:31:40):

Jerry.

(01:31:43):

Yeah, no disagreements. I mean it works. I think, again, I'd like to know more mechanistically. I think a lot of it is through ectopic lipid. Again, we certainly know it lowers liver fat, which is ectopic lipid, but its effects on the periphery I think of it is again, even before major weight losses through the mechanism we described. Again, to me the issues are really compliance. I mean, why is it that jay's may be an exception being on it for two decades, but whatever, one or two decades. But most people, I think the data says half the people stopped taking it for some reason or another after one year. And I think that's a concern. And then the pricing, hopefully that will change, but as we know, only a small percentage of individuals who could be on it, even again by definition are on it. So again, these are other issues and again, things are evolving.

(01:32:38):

Hopefully we'll get into oral small molecule GLP one analogs. Prices will come down. But again, is compliance an issue in terms of these side effects? Which are there? Is that a reason people or the fact that people's weight levels off? It's hard to get back to everyone's what they were in high school, whatever, you lose weight, substantial amounts, but people say, oh, I've plateaued. And maybe that's the reason they stopped taking it. So I think that that's a wonderful drug not arguing. It is transformed

the lives of millions of peoples. But I think we need additional drugs that again, if we understand molecular mechanism, we can make even better drugs. And certainly combinations. Again, I'm most excited about, again, mitochondrial inefficiency combination where you have energy and reduce with a GLP one analog, you have increased energy inefficiency. And we've already shown in preclinical studies that gives additive weight loss. And the other thing is when you promote mitochondrial inefficiency, you do not lose lean body mass. So that's a nice thing and it is really well tolerated. They're not any GI toxicity. So one could have a combination, get down to target weight, get rid of the insulin resistance, and then back off on the incretin and maintain on a proton four or something like that to promote mitochondrial efficiency. So that's on my thinking of the future.

Zan Fleming (01:34:06):

On that point, Jerry, what about the thyroid receptor agonist?

Gerald Shulman (01:34:10):

Yeah, so the THR beta agonist, they again, first FDA approved drug to treat MA LD and mash because the first drug to show actually can reverse both the inflammation and more importantly fibrosis that really leads to the demise of our patients with liver disease. But it's not a hundred percent, it's about 30%. So again, not all of individuals do benefit from 'em, but I'm encouraged by the fact that it's a metabolic approach that will fix inflammation and fibrosis. And again, we've shown at least in preclinical studies, again, it's consistent with you get rid of the fat, inflammation goes away and the fibrosis goes away. So here again, we have a metabolic approach, RevUp mitochondrial fat oxidation, and we can make a difference in the patient with fatty liver disease and insulin resistance. I will say one thing though is again, we're activating the thyroid receptor in the liver with this thyroid has many, it's a transcriptional regulation, thyroid hormone.

(01:35:18):

And so we're affecting many genes in the liver. And we've shown in multiple preclinical studies that you actually, besides revving up fat oxidation, you stimulate gluconeogenesis. And so again, for someone with metabolic disease prone to metabolic syndrome diabetes, I've shown you how gluconeogenesis is not a good thing. You don't want to have that revved up in your pre-diabetic or certainly your diabetic individuals already revved up and I think this will negate the beneficial effect of lowering ectopic fat. So you have two things, which one's good? You're lowering liver fat and that whole pathway gets better. You get less inflammation fibrosis. But at the same time, you're actually potentially at least, and we've shown this in preclinical studies, revving up gluconeogenesis, which is the wrong direction. And I think this needs to be tested sooner or later in humans with these new agents. And that's where again, other agents don't have that stimulation of gup neurogenesis.

Zan Fleming (01:36:23):

Let's see if we can squeeze one, maybe two questions, Thomas right quick.

Thomas Seoh (01:36:29):

I really ought to raise some questions from the audience, but I just wanted to come back to my first question. Is IR a metric that we should adopt? Yes or no? Like a C or so? Jay's saying, yes,

Zan Fleming (01:36:46):

Raise your hands.

Gerald Shulman (01:36:48):

I want to treat insulin resistance in everyone. Everyone, we should just hypercholesterolemia and just like hypertension, I would advocate. And then I think, Tom, to your question, I think you want us to be a little bit more commitment. Is this index a good surrogate for insulin resistance? And it's not bad. I mean, again, if you're resistant, we have a marker to treat it. Again, it's better than fasting insulin or eptide. It's a start. So

Thomas Seoh (01:37:18):

As a lay person, I hear about useful topics like insulin resistance and metabolic syndrome, and what's the problem, what's the obstacle to a general adoption? I'm assuming that this information can help biohackers, it can help medical practitioners someday it may make regulatory decisions, but there has to be some sequence of getting it out into practice.

Gerald Shulman (01:37:42):

Well, I'll go first. I'll go first and I know Jay and Ralph will want to wait, but so we have a marker. And the issue is we need then things, new therapies to treat it. So exercise, diet and exercise. Yes, again, it all tell our patients, please get out there, be active, lose weight. There's no pill for that. Now maybe having just said that, maybe Jay will sweat. There's not a pill, but there's an injection. GLP one is getting us there and certainly PO is in sensitizer. So we have drugs again. So you could have a marker and then the physician can say, okay, I want you to stay active, get out of the chair and lose weight. And then potentially these other agents and use this as a marker like we do. Cholesterol to me again, it's again in the young individuals, again, the question is whether you'd want to treat like our 20 year olds who I showed you already have muscle insulin resistance, one in four, they're prone to hypertriglyceridemia and low HDL and fatty liver.

(01:38:48):

And I don't think I'd want to treat them as much as, again, PO is a sensitizer or GLP one does this for the rest of their life on this. So this is where, again, we may have a marker, but we need better agents that are going to be really safe and expensive, well tolerated to actually go and with confidence like we do with statins, say, all right, you're in your twenties or thirties, you have hypercholesterolemia and we're going to keep you on the statin probably for the rest of your life. So I think this is kind of where in my view, the issues are, again, especially making the decision in the young individual

Jay Skyler (01:39:23):

Second half. I think the dilemma with this is that if the goal is to increase health span, we need long-term longitudinal studies that show that these things are making a difference. And the issue then becomes what kind of control group one has. Is it ethical to randomize people to a control group? If you're trying to increase longevity and you have things that actually are touching on markers that we think are important, and would regulators accept the insulin resistance score from Quest or would they insist that you do a clamp to really demonstrate that insulin resistance is gone? And I think those are real questions that we need to ponder there. On the other hand, you talk about somebody in their twenties, I would have no qualms in putting them on pioglitazone for the rest of their life. At 15 milligrams, you can get 15 milligrams of pioglitazone a month's supply for $5.

(01:40:28):

It's a generic out there easily. And so it's not expensive. If you leave it at 15 milligrams, you're not going to get the side effects that we were talking about earlier. And I don't see any problem with using that for

a lifetime basis. I also think GLP ones would be good for that. But before I put people on it in their twenties, if they don't have other disease things, I'd wait for, as Jerry was saying, some of the pills that could be used. I don't object to a weekly injection, but the cost of making a drug and getting it into an injectable form is huge. Whereas the cost of making a pill is very, very inexpensive. And I think we could hopefully get to the pill stage at a very low cost that we could afford to give it to populations at large that may be a few years away. They need to earn back the innovation effort put into making the pills. So the initial cost will be a bit higher, not as high as the injectable, but I think soon it could drop to the same kind of cost that pone has.

Zan Fleming (01:41:45):

Jay, that's a great summary for us to end on, at least for our official period of time. The FC requires the F can

Ralph DeFronzo (01:41:54):

Make comment about the Quest study because I don't want people to leave thinking that that Quest test is an end all. If you'll read the paper, Jerry rein's name is not on the paper, and they use the insulin suppression test to get the correlation. And remember the insulin suppression test that involves infusion of glucose, insulin, epinephrine, and propranolol. So I would say even though I'm a big believer of insulin resistance and finding a marker, I'm not sure that that Quest test is really not ready for prime.

Zan Fleming (01:42:34):

Okay, fair enough. Fair enough. Now we're going to end officially. Now, Thomas is going to bring us to a conclusion the FCC requires that we read a statement at the end. He's going to do that, but some of our panelists may stick around for an informal discussion. I hope we can keep going, but Thomas do bring us to an end. Here's the with my great thanks.

Thomas Seoh (01:43:00):

Here's the boiler plate. All registrants will receive the link to a recording within a day or two as well as announcements of future targeting healthy longevity 2025 sessions. Session three will be a regulatory primer for longevity, biotech companies applying for the XPRIZE health span and ARPA H Prosper programs. We're going to target July for that. And we have future sessions planned on sarcopenia and frailty and other programs. With that, the formal portion of this event will close with thanks to the panelists and to you the audience. However, as Z mentioned, it is our practice. We like to leave this Zoom webinar open for some minutes for those speakers and audience who are available to Terry and chat. So many thanks. Have a great weekend. And now we're in the after party.

Zan Fleming (01:43:52):

Wow, what a great session. We can't thank you enough. Jay, Jerry and Ralph, I don't know if you're still hearing this, Ralph, but you're at least real great. That was just magnificent and we got the ball rolling. Conceptually, we understand that insulin resistance is an important consideration for identifying people at risk and managing it as an age-related indicator, age-related disease indicator. And we have abundant evidence that Jerry and Jay and Ralph wanted to support it.

Thomas Seoh (01:44:42):

We had a terrific number of questions and we just couldn't get to them.

(01:44:47):

But Ralph Abraham asked a very practical question here, is IR ready for prime time? He uses different approaches or formulas and gets very different results. So even if concept, so one question is conceptually, do we think that IR is a good number for cardiometabolic wellness? Do we think that it's generalizable to aging as a score metric for aging? But even if that's a good thing, what remains between here and there in order to have a reliable sensitive specific test, that's enough for us to be, we know blood pressure, we know A1C, we have confidence in them. Is this something that technical details still need to be worked out over a period of time? So any response to,

Jay Skyler (01:45:35):

I would ask that Ralph has done all these clamps on all the kinds of people who showed you them all in the beginning, and hopefully he still has a fasting sample from those subjects before they started. I think that he ought to get together with Michael McPhail at Quest and ask Michael to run the IR test on his various samples and see whether or not it correlates with his measure of insulin resistance, which is the gold thin to the hyperglycemic clamp.

Ralph DeFronzo (01:46:10):

It's interesting you should say that, Jay, because when Richard Kahn was the medical director or the research director, we did all of these insulin clamps and we measured the fasting insulin. And the idea behind this is if we could show him that the insulin level all done by one radio immune assay in our lab reflected insulin resistance, he would make an argument. He would go to the biochemistry leaders of the world, the standardized the insulin assay, and we did all of this on a gazillion million people, and it maybe I can assume that data, the problem was, even though we showed it, Richard never followed up by standardizing the insulin assay, but just measuring the insulin level or the eptide are great measures, but there's a lot of variability in them. And I'm not convinced, as I said, the insulin suppression test is, remember you give propanolol epinephrine to wipe out the liver and then you give a glucose infusion in insulin. And so now you have all of these effects of maybe propanolol and epinephrine that are not blocked. And in addition, you're not looking at insulin sensitivity, you're looking at hyperglycemia mediated glucose uptake as well as insulin mediated glucose uptake. So the insulin suppression test would definitely not be the way I would do to justify that the assay worked. So I'm sorry I interrupted Z, but I think it's important that people,

Jay Skyler (01:47:48):

Oh, it's very important, Ralph, you've been arguing against the insulin suppression test for 40 years and in favor of the clamp. And I fully appreciate, that's why I said the clamp is the gold standard, not the insulin suppression test, but this was done in correlation with the insulin suppression test. We need to do it in correlation with the clamp, and you've got all those samples from all those disease states and everything that could be done to make it to see whether or not it really does work.

Zan Fleming (01:48:15):

Yeah. Well, it's a great suggestion, Jay, to Ralph, and I hope Ralph will follow through. And sort of going back to Jerry's point about the could be a general concern is that there is variability day to day and insulin resistance, however you measure it. Does there need to be something that is analogous to A1C and integrating insulin resistance over time? Sort of analogous to fasting glucose is a measure, but a better measure is A1C to give you an average's more robust

Thomas Seoh (01:48:58):

Or a derivative measure like a delta rate of change or something that gets more specific and reliable.

Zan Fleming (01:49:05):

What could you do to address that concern, Jerry?

Gerald Shulman (01:49:08):

So yeah, no great questions. And again, we found at least using Ralph's matsuda index, the extremes. If you're resistant, you typically stay there. If you're sensitive, you typically stay there. Again, unless we've shown with exercise, even a single boat someone was on the questions is sufficient to reverse that. So again, you can imagine how variable just that is the he is basic, he or she's running to the doctor's clinic and you can actually alter you cause that A MPK activation, glute four, and then all of a sudden insulin is a little bit lower and you say, oh, you're sensitive when most of the time you're not. To me, the most best predictors. My third slide was ectopic lipid. That doesn't change that quickly. And you measure ectopic. How do you measure that, the IMCL in muscle and or liver? And that is insulin resistance through the mechanisms we described. The problem is that's not a simple blood test. That's a sophisticated measurement. I don't see that happening in the clinic in the near future, but that is your chronic index because even with exercise, that's not going to change quickly. So I don't have an answer. I can't think of a blood test that's going to give you the A1C, a good index of sensitivity over the preceding several weeks.

Thomas Seoh (01:50:30):

And we talked about this in the planning call that someone was asking about mitochondrial inefficiency and other measures, other candidates for some kind of metric for aging. Any comments for the remaining folks in the audience here?

Ralph DeFronzo (01:50:46):

Well, if you had a simple measure that really that's something you can measure in the bloodstream that reflected mitochondrial function, I think that would be actually a good marker. The problem is I'm not aware of such a measure, and I do believe that mitochondrial dysfunction is playing a critical role here, but a simple measure of it. I'm not so sure we have that. Jerry, are you working on that, Jerry?

Gerald Shulman (01:51:17):

Again, this is why I'm spending a lot of money and time on doing NMR studies. They're very expensive, but that's the only way I know to actually measure activity in vivo. Again, liver muscle brain are going to get ready to do this in the heart, but it is not a trivial measure. And again, many people do exvivo measurements of mitochondrial function, and that to me is really assessing capacity of the mitochondria, but not telling you what's happening in situ to. And that to me is really what I care most about is situ to mitochondria activity. And the only way I know how to do that is with NMR.

Zan Fleming (01:51:57):

Well, could it be a kind of imaging test? You go in and you get an NMR,

Gerald Shulman (01:52:03):

As I say, not in the near future. This is, again, there's only a few sites on the planet that can do these sophisticated measurements and quite expensive. It's not something that a general practitioner's going to want to order on check NMR measurement of mitochondrial activity.

(01:52:20):

And again, to me, I am not so sure if I would put on my physician's cap again, I necessarily would want that to me, I care more about than the implication. It's a predisposing factor. I'd care more about if I could order a test ectopic fat. That to me is really what I, as a clinician, that's what I want to fix. Ectopic fat, even in the lean individual, that's what I'd want. A marker of mitochondria can be tribune. But to say in most cases, again, especially in younger people who are not have a genetic predisposition, this, this gets into this, we didn't talk about, there are South Asian Indians. Again, these are individuals prone to ectopic lipid liver and muscle. Even with A BMI of 24 25, again, the good news is a mild white caloric restriction reduces the ectopic lipid and the diabetes insulin resistance reverses. So again, consistent with this concept, and I don't think it's a mitochondrial defect or something else that's leading to this alter distribution of fat inside liver muscle cells. So we're interested in

Zan Fleming (01:53:31):

Understanding, could there be an imaging test for fat? I mean for

Gerald Shulman (01:53:41):

They're currently are people, this is my hepatology colleagues have taken, we do proton NMR, and you can do DEXA imaging. This is what the, but they're very expensive tests, not something I would recommend hundreds of dollars per test. And the HEPA

Speaker 3 (01:54:00):

Is

Gerald Shulman (01:54:00):

Doing this in liver, but not necessarily muscle, but it's just too expensive to think about routine.

Thomas Seoh (01:54:07):

Well for routine screening for the public today. But in long bio, there are healthy longevity clinics springing up all around the globe and sort of concierge medicine approaches. So if you're talking about some imaging or other tests that are in the three zeros, hundreds, even thousands, I suppose that there'll be folks at the tip of the sphere, maybe not Brian Johnson, the millionaire who's trying to live forever, but there'll be people, executives and so forth who actually would take those tests and will get some validating or correlating data.

Gerald Shulman (01:54:42):

If price is not an object, that to me is your best marker for insulin resistance.

Zan Fleming (01:54:48):

Okay, maybe a regulatory marker.

Gerald Shulman (01:54:52):

Again, you guys are more of experts on these things than I am. You served on the FDA regulatory means. When you say regulatory, not something to be, how are you using that word, Z? Regulatory?

Zan Fleming (01:55:05):

Well, as a primary efficacy endpoint, that would,

Gerald Shulman (01:55:08):

Yeah, well, certainly. I see. So to consider whether something a drug is approved, certainly, I mean, well, it's being used of course for, well, again, we don't have indications for nash. So again, as you know, the indications for NASH are not just liver fat, it's actually inflammation, more importantly, fibrosis. So right now there are no regulatory endpoints to, in my view, it should be actually. Yeah, I think that's a very good point, Sam, that in my view, we know this threshold gets below 2% or a threshold in skeletal muscle, and that could be a very good regulatory endpoint potentially.

Zan Fleming (01:55:48):

Perfect. Great to hear.

Gerald Shulman (01:55:51):

I need to go. It's been talking to everyone. Really always fun getting together with you guys. You always learn from everyone here. My colleagues, Ralph and Jay

Jay Skyler (01:56:01):

And I too need to go. Thank you.

Gerald Shulman (01:56:05):

Take care guys.

Jay Skyler (01:56:06):

Alright, Jerry, sign off. Thomas, thank you for organizing this. Ralph. Jerry, good to see you. Ciao. Thanks everyone. I'm

Ralph DeFronzo (01:56:15):

Still here. Z

Zan Fleming (01:56:16):

Okay, good. Well, we'll focus on the rest. Yeah, there's so many questions we did not get to, but go ahead if you had some thoughts, Ralph.

Ralph DeFronzo (01:56:28):

Yeah. Yeah. So again, I come back to the PO Glitazone story. So that basically everything that Jerry said, and of course a big believer, he and I think very similarly, but pioglitazone it to me is probably the best drug that's out there for getting fat out of the liver, in my opinion. If you go back and look at the data that we published, it's as good if not better than the thyroid drug that's out there. It gets fat out of the liver markedly. In fact, Jerry Schulman and I, our names on some of these papers together, it gets fat out

of the muscle. And what we've shown more recently, the fat that's around the heart, the epicardial pericardial fat, it markedly decreases the pericardial fat. And now we've got preliminary data that it also mobilizes the fat out of the myocardium itself using the clamp. It's a great insulin.

(01:57:34):

It has all of the attributes of a drug that's truly an insulin sensitizer. We know from Iris that it worked in insulin resistant normal glucose tolerant individuals and preventing recurrent strokes. So it seems to me that we have an avenue, we have a drug that actually will work. People have misconceptions about the fat weight gain and the fluid retention. Those are big issues. And maybe what Sirius is doing will get around the stigma of the fat weight gain and the fluid, and that will be a bypass. So if we had a good measure of insulin resistance, and I actually agree with Jay, if I had someone who's say 35 40 and their mother died of a stroke and the father of my car infarction, whatever the genes are accelerating the atherogenesis, to me, I would treat that person with glt. And you'd have to explain to them why you're doing it and that it's not approved for this intervention. But the fact is, if your mom died and your dad died at a very early age, you're probably carrying some of the same genes. It might be worthwhile focusing on a population that's high risk in doing such a study.

Thomas Seoh (01:59:02):

Ralph Art Santoro was asking why was PO never developed as a drug for hepatic C ptosis? His guess is that it was off patent, but there

Zan Fleming (01:59:14):

Was actually it. There were some studies towards developing it, but I'm sure the lack of IP to put the kibosh on a serious effort

Ralph DeFronzo (01:59:27):

In the serious drug, which you'll hear more about it, it turns out that the weight gain is more related to activation to PPAR gamma in the brain, and that stimulates your appetite. So the serious drug, which is unfortunately a Thiola dine down, I told 'em they should never mention the word TCD. They should come up with a name for the drug. They not poison people's mind. The other thing that this class of drugs do is it activates the pyruvate transporter and doing so markedly enhances mitochondrial function and you get all of the insulin sensitizing effect without the appetite stimulating effect. So that may have some promise. And remember that drug also, they started the N nafl study and the data looked very, very good. So that drug also works as does po tisone or did rosiglitazone or did Troglitazone, although those other drugs had serious side effects.

(02:00:36):

So maybe this is a way around it. And then this dag gly tapin that Roger she and I are working on, if we just could get the funding, we're ready to do the human study, which would show that a drug that works on the mitochondria and it would get rid of ectopic fat everywhere. That would be, I think a good choice that would improve the insulin resistance, improve mitochondrial function. And who knows, the animal data that Roger has shows that the longevity in the mice is markedly extended. So there is this potential insulin sensitizer out there if we just could give us enough money. And when you think of these big companies, they spend millions and millions and they spend billions of dollars. A secretary error hitting the wrong button would produce the $5 million that we need to get through the FDA and start the human study.

Zan Fleming (02:01:48):

Well, we are going to bring Roger on because I am excited about that approach. It's really quite spectacular, and we want to feature him at a couple of other novel approaches that are very promising for targeting healthy longevity. Yeah.

Thomas Seoh (02:02:07):

Z, just a comment from Alan, our collaborator from Health Span Action Coalition. The topic here is not directly on our Thrive Act, ital proposed legislation for a regulatory pathway for health span products, but certainly a marker, a diagnostic that measured insulin resistance would be able to take advantage of the proposed tier one pathway that would provide an earlier access to market. And for people who are still on the call who are interested, please go to our kates.org website for our web. Actually, our session one for this conference in February was on the Thrive Act. So for those who are interested in policy, just direct your attention to that. Sorry, go ahead.

Zan Fleming (02:02:58):

Well, that's right. The Thrive Act is very important for catalyzing development of these products, not just therapeutic interventions, but diagnostics and getting those available to people with what we could call a health span communication. So folks, please do look at the Thrive Act. It's a complicated discussion and a lot of jargon involved, but we hope that conceptually will make sense to anybody who looks at it, and we'd love to get feedback as we perfect the Thrive Act

Thomas Seoh (02:03:36):

And Zen, you mentioned that the Thrive Act covers not only medical medicines but diagnostics, but it also covers supplements. So Ralph, I'm wondering whether on the topic of insulin resistance, I do see a lot of supplements out there that talk about having, I shouldn't say lot. There are very few supplements that have clinical data, and in a subset of them, there are some that claim with varying degrees of credence or robustness that they address insulin sensitivity. Do you have any comments to make about things that people can do today? Because developing new drugs is going to take years. What's out there in terms of supplements?

Ralph DeFronzo (02:04:17):

Quite frankly, I have been through all of this literature and there really are no, I would say studies out there that have taken any of these supplements and quantitatively shown that you improve insulin resistance, that there's some animal data with some of the supplements. But the fact is mice in men have one thing in common. They both start with the letter N, and the metabolic profile in the mouse is very different than the metabolic profile in a human. So simply, the basal rate of hepatic glucose production, and this can be translated to energy expenditure, is 16 milligram per kilogram body weight per minute. In a human, it's two milligram per kilogram body weight per minute. So the whole metabolic milieu in the mouse is so tremendously different from humans that even if you were to show a benefit of some of these supplements in mice without really going to humans, I think you have to be very skeptical. Well,

Zan Fleming (02:05:25):

We definitely are, and yet there are some unicorn examples of where there has been a big investment at doing, for example, an outcome trial. The CocoVia flavonol extract from Mars was the subject of the

COSMOS trial, which did show very encouraging duction and CV events. And they've actually shown the product does reduce blood pressure, does reduce insulin resistance. And so you could make a case for that particular supplement on the basis of a variety of evidence, both clinical and in vitro evidence.

Thomas Seoh (02:06:06):

And we're not hawking anything here, but just sharing information has commercialized lyan A for mitochondrial biogenesis, there are different, I can't remember the name of another supplement that mimics exercise from a hormone based perspective. But the idea is there may be ways to address mitochondrial dysfunction, insulin resistance, inflammation. Those are all things that are very near and dear to the longevity crowd. People who are looking at ways to extend health span and not have to wait until FDA approval to try to do things. Obviously that comes with its own set of risks and benefits calculations, but I think people are curious about that.

Ralph DeFronzo (02:06:53):

The flavonoid study that you just referred to, if they have cardiovascular outcome data and they have measurement of insulin resistance, why haven't they gone to the FDA with this? Well, that's

Zan Fleming (02:07:04):

A complicated

Ralph DeFronzo (02:07:06):

Answer.

Zan Fleming (02:07:09):

It is in part the way dietary supplements are set up. You can't make disease claims for a dietary supplement, but you can take a dietary supplement and make it a drug just by doing that kind of study. Now, that's your question then. Why did Mars make it a drug?

Thomas Seoh (02:07:30):

Mars, the candy company and the animal food company and the so forth, but not drug company.

Zan Fleming (02:07:36):

Yeah, so we don't speak for Mars. I'm not sure what the answer is to that, but at least they certainly could pursue a drug indication. It's

Thomas Seoh (02:07:50):

Just another plug for the Thrive Act that if we had it in place today, there is a pathway for them to do that.

Zan Fleming (02:07:56):

Yeah, that's exactly right. So the Thrive Act does just to emphasize, include both drugs, biologics, medical devices and dietary supplements. And the important thing, when we say medical devices, that also includes lab tests, diagnostics, that would be potential clinical measures to manage health span risk or actually surrogates by which interventions could be approved or health span

Ralph DeFronzo (02:08:33):

The MAR study. If they have these data, why haven't they made it more available or at least tried to sort of publicize it more to the site?

Thomas Seoh (02:08:46):

Well, that's one of the ironies. Our current laws forbid them from talking about the results of their study. Z you want to elaborate on that?

Zan Fleming (02:08:55):

Yeah. Well, forbid might be a strong word, but there is a gray area about crossing over and to marketing the disease claim without having an approved new drug application for doing.

Thomas Seoh (02:09:14):

They publish articles, but they can't talk to them for the general public or they determine it's a matter of policy. Their legal department or someone has advised them not to do that. Just for people listening, canis has done a specific session on the Cosmos trial. I believe it's in the fall November of 2023 that we did this. So people can look at the articles and the people who ran the study. We had a great panel that talked to the results. Sorry, Ralph. Go ahead, Roseanne.

Ralph DeFronzo (02:09:48):

Yeah, I mean, it seems to me that if you publish, I mean, it's past tense now, but if you published an article saying that Journal of Clinical Investigation or Cell or Metabolism or wherever that would gotten the information out to the scientific community reviewed,

Zan Fleming (02:10:10):

You don't have to make any claims to be absolutely clear, they did publish the data and it was in a less than top tier journal because they technically missed their primary endpoint by protocol. They made the endpoint, but there was clear lack of adherence in taking the product over the period of time of the trial. So that unfortunately dinged the eyes of journal reviewers as well as if they had gone to FA and said, we've got the data, FDA would've said, well, you missed your primary endpoint,

Thomas Seoh (02:10:58):

But it's a huge trial, different segments, but 22,000 or so subjects were studied. So from a natural science perspective, you're looking at and going, there's, there's something physiological happening here

Zan Fleming (02:11:10):

Happen. Yeah. But we exco the virtue of companies like Mars investing in those kind of trials because as you say, Ralph, we just don't have the evidence for dietary supplements. Typically. There's no commercial pace to do that. It costs too much to get data, so you just sell them on a hope and a prayer.

Ralph DeFronzo (02:11:37):

It's also the problem with the same study is where do you find who's going to support such a study?

Zan Fleming (02:11:47):

Yeah, well, near has been looking for support and has come close, but it just hasn't happened, and it would be good to have such a trial done. Some people say there are other therapies that might move the needle more. In fact, near himself says that he's gotten Lily interested in doing a tame like trial of tirzepatide. And so maybe that will happen. It won't be a tame, it will be

Thomas Seoh (02:12:28):

Targeting aging with T trial

Ralph DeFronzo (02:12:34):

Appetite. That's a real double-edged sword because as I understand, he wants to do the study in people who are elderly, not necessarily over the hill. And that's where you might get into trouble with these powerful GLP ones in terms of muscle wasting, because there's very clearly, we showed, I said 1975, there's age related decline in muscle mass, in fat mass goes up. And those are the people where I think the real controversial should be about, should be using GLP one drugs and people in their seventies and eighties where they may start with a mild sarcopenia, so to speak. That's related to age.

Zan Fleming (02:13:20):

Yeah, all two points there. Number one, and this goes to Jay's point about using it for preventing chronic diseases, what the target population is really young people, we want data in young people that they have very low risk. Their event rates will be very low, and it will take years to see clinical benefits in that population. And as you say, older people start with a major muscle mass deficit. And you might say that that in itself is a contraindication for taking these agents, but muscle mass is important to young people too. And this is why I argue with Jay that I'm not sure I would put my daughters on the GLP one agonist for the rest of their lives, certainly for their currently approved indications. I would, but the big question is, would it be safe and effective? Put people on GLP one agonist when they're 30 years old and don't have any major risk factors, don't have diabetes, aren't overweight.

Ralph DeFronzo (02:14:39):

But I would make the argument, you're willing to treat people well, the exercise, let's put that aside for a second, but you're willing to treat people with dietary restriction. And I would argue if you lose weight by dietary restriction, that you would have the same decrease in muscle mass as if I treated you with a GLP one receptor agonist. You argue, well, is that good for the muscle? But the counter argument is that, hey, look, if you have less fat and total body weight to carry around, I need less muscle. So isn't the decrease in appropriate? And we actually about Absolutely. Right. It's a controversy and we don't have an answer.

Zan Fleming (02:15:28):

You need the data to answer the question. And dietary or caloric restriction is a proven way of increasing not just health span, but extending lifespan and mice. That's right. Yeah. It's proven, but it's not preventing people. And in fact, there are a number of reasons to believe that it won't happen in people even though it works in smaller.

Ralph DeFronzo (02:16:02):

Yeah, I think again, all of these studies where you're looking, the smaller the animal, the bigger difference there is in the whole metabolic profile of the animal. Exactly.

Speaker 3 (02:16:14):

Yeah.

Ralph DeFronzo (02:16:15):

So you have to extrapolating may not.

Thomas Seoh (02:16:24):

Ralph, can I just ask a question? I know we're getting down on time here, but I've wondered, as a lay person, the intersection between mainstream diabetologist, endocrinology and cardiometabolic practice of medicine research and medical practice and the Jira science or health span extension, healthy longevity crowd, what is your current thinking about the intersection between those two disciplines or fields? Is my question clear?

Ralph DeFronzo (02:17:04):

Yeah, I got it. So I think there's a huge gap, to be honest with you. So first, just between the endocrine sort of metabolic group and the cardiology group, it's only recently we've sort of come together, but I can tell you, even though we have meetings together, the cardiologist are not really thinking metabolically. They're more sort of hemodynamically oriented, less metabolic, molecularly oriented, but we're coming closer together. A bigger gap now is between the aging gerontology people and both the cardiology group and the endocrine group, although diabetes people have said is advanced aging, you die 10 years earlier. The cardiologist understand, as we get older, we're now seeing heart failure go up dramatically and atherosclerotic cardiovascular disease. So despite the clear cut need for us to interact, we don't really interact now in San Antonio because in large part of Nick Musey, the bar shop, I think is pretty well integrated with the endocrine, metabolic, and cardiology group. But that's kind of, I would say a unique situation. And there clearly needs to be a lot more integration of people working together. And as I said, we actually have done a number of Asian studies, but only because, as I said, the Bar Shop Institute is part of ut University of Texas. We see these

Zan Fleming (02:18:41):

People, well, I could not agree more. We need to be working together these two different worlds. Currently,

Thomas Seoh (02:18:51):

Alan is making the point that it's not just endocrine, but CNS and immunology and so forth. That's the point with neuroscience is that it seems to be an upstream, aging is the biggest factor for a range of these chronic diseases. And so you want to see some sort of integration between the specialists.

Zan Fleming (02:19:15):

Well, it's our quest to break down these silence, and we try to do that by bringing together our conferences. We pull from across the scientific world, and indeed, even outside that world, ethicist and economists, policy makers and so on. So that is one of our main styles to break down these barriers and to facilitate creative thinking together problem solving. Ralph, Ralph, we can't thank you enough for

hanging on this late and No problem for changing your travel reservations, and I hope you'll have a good trip tomorrow.

Ralph DeFronzo (02:20:02):

All right. It was great. It was a great meeting. I think all of the presenters did a great job. You did a great job of all organizing it. So I look forward to the next one, particularly with Roger and Jerry, because I think that will be equally as exciting.

Zan Fleming (02:20:21):

Yeah, well, we're with you and we'll see you in Chicago.

Ralph DeFronzo (02:20:26):

Yes, we will for

Zan Fleming (02:20:27):

Sure. Okay. Alright.

Thomas Seoh (02:20:29):

Thank you everyone for staying with us.

Zan Fleming (02:20:30):

Thank you all. We sure appreciate it.

Thomas Seoh (02:20:33):

Have a great weekend. Bye-bye.