Transcript

Dr. Jaran Stratford

Hello, I'm Jaran Stratford from the RECOVER Administrative Coordinating Center and the moderator for today's webinar. We'd like to welcome you to the RECOVER Research Review or R3 seminar. The goal of this webinar series is to catalyze a shared understanding of the research within the RECOVER consortium. The topic of today's seminar is metabolism and the gastrointestinal function in PASC.

It is important to note that this seminar series is focused on scientific research and is not intended to provide any clinical guidance. I want to start by thanking everyone who submitted questions in advance. If you do have any additional questions that arise during the discussions today, please feel free to put those into the Q&A in Zoom. After the presentations, we will answer as many of those questions about today's topics and presentations as possible. Some questions may also be answered within the Q&A. A frequently asked questions document for this seminar will be posted with the recording on the seminar on RecoverCOVID.org. It will include answers for questions relevant to the seminar that we weren't able to discuss during the meeting today. Questions about scientific topics will be addressed in future seminars and answers to broader questions about RECOVER will be available within the FAQs.

Today's speakers will discuss what is known about metabolism and gastrointestinal function in PASC, the gaps in our knowledge and how RECOVER will contribute to filling these knowledge gaps. Today, we will hear from a number of seminar speakers, including Dr. Clifford Rosen, physician scientist, and Director of the clinical and translational research at the Main Medical Center Research Institute. Dr. Rosen is a member of the FDA advisory panel on endocrine and metabolic drugs and a former chairperson of that committee who has also overseen numerous phase two and three clinical trials and runs a basic and translational research laboratory focused on understanding the relationship between bone cells and fat cells in the bone marrow.

Dr. Jane Reusch, the Associate Director of the Center for Women's Health Research at the University of Colorado Anschultz Medical Campus will also speak to us today. Her research focuses on understanding the cellular metabolism of diabetes and its complications, including cardiac, vascular and skeletal muscle dysfunction.

Dr. Emily Gallagher is an Associate Professor of endocrinology, diabetes, and bone disease at the Icahn School of Medicine at Mount Sinai. Her research interests focused on how systemic metabolic conditions promote cancer growth and metastasis, and how systematic differences in metabolism may contribute to racial disparities in cancer survival. She runs an onco endocrinology clinical practice treating the endocrine and metabolic complications of cancer and cancer therapies.

We will also be joined today by two discussants, Dr. Phillip Scherer, the Director of the Touchstone Diabetes Center and Interim Chair of the Department of Cell Biology at the University of Texas Southwestern Medical Center.

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Current efforts in his laboratory focus on identification and characterization of novel proteins involved in whole body energy homeostasis, inflammation, cancer, and cardiovascular disease with the aim of identifying novel targets for pharmacological intervention, and to further define the role of adipose tissue as an endocrine organ.

We will also be joined by Dr. Lucio Miele, and he is the head of the Genetics Department at Louisiana State University Health Sciences Center, and serves as Assistant Dean of the School of Medicine for Translational Science. His research interests include developmental therapeutics, cancer genomics, viral genomics, surveillance, and big data COVID-19 research that links socioeconomic, biological and clinical data sets. He's currently serving as the co-chair for the RECOVER Omics Committee. And with that, we'll hand it over to Dr. Rosen and we'll begin.

Dr. Clifford Rosen

Thank you very much, Jaran. And I appreciate the opportunity to speak to you today. This is a group effort. Some of the work we've presented will include some of the other people's name on here. What I'm going to do today is just in 10 minutes, give you a brief overview of metabolic dysfunction and post-acute sequelae of COVID. And I'm going to talk principally about endocrine gland dysfunction because in principle, the five endocrine glands that control our body also control a lot of the symptoms that could relate to PASC and may be important in RECOVER.

I'm going to focus my brief presentation on three of the laboratory studies that we get from participants in RECOVER. And these three laboratory tests are the free thyroid and TSH measurements, the 25 hydroxy vitamin D, and glucose hemoglobin A1C. And these tests will give us just a brief overview of where we think metabolic dysfunction may play a role in some of the symptomatology of PAs, and also may be important in early detection of long COVID.

So just to remind you, there are really five major endocrine glands, and all of them can be affected by infection with a virus or as a post infected. It relates to antibody production that would attack the tissues, the thyroid, the parathyroids in which vitamin D access is important. The adrenal glands and the [inaudible 00:06:12], as well as the pituitary. And each of these glands in case reports have been associated with dysfunction or hyper function during the course of either acute COVID or in the immediate post acute sequelae.

As I said, I'm going to focus principally on thyroid and vitamin D, and briefly give you an overview of some recent data we've required on the characteristics of type 2 diabetes in individuals who have long COVID. So one of the most commonly reported endocrine complication of acute COVID infection is subacute thyroiditis. And we've known about subacute thyroiditis for many years. It occurs post viral infections. It's associated with a fever, usually with neck tenderness, a very high sed rate, and it's characterized by destruction transiently of thyroid follicles with the release of thyroid hormone.

So individuals go through a phase of significant thyroid toxicosis as the thyroid hormone is released, but unlike other kinds of thyroid diseases, particularly Graves' disease, that phase is transient. And it's followed, as you can see in the middle graphic, by a period of hypothyroidism in which the gland has released all of its thyroid. And then the individual becomes hypothyroid, ultimately becoming euthyroid over time. And there are about 10% of individuals will remain persistently hypothyroid.

The reason this is so important is because this can be missed at different phases, post infection. With any viral infection, the post infective phase can be very transient as hyperthyroid or hypothyroid. And in each case, fatigue is a major complaint. So thyroid function tests, both free T4 and TSH are important in screening for this potential abnormality, particularly with a very high sed rate.

Now, the prevalence of subacute thyroiditis post SARS-CoV-2 infection is not known. A recent series from India reported that among over 600 patients that were initially followed with COVID, about 11 developed a subacute thyroiditis for rate of about 6.8%. But one of the unknowns is really how prevalent is subacute thyroiditis following SARS-CoV-2 infection. And is it greater than other viral infections that lead to subacute thyroiditis?

In addition to post infective subacute thyroiditis, there are now several case reports of subacute thyroiditis following vaccination, and it's unclear exactly what the prevalence of this is, but it's also been reported that there is a rate of post vaccination Graves' disease. And again, the difference distinguishing between post vaccination infection, if it's real and post viral infection may be semantics, but actually could be very important.

So I've been collaborating with the group in Italy that have followed the consecutive series of 64 patients referred to St. Rafael's hospital in Milan for Graves' disease. It's a tertiary medical center, and so they accumulate cases of Graves' disease. And as you know, Graves' disease is hyperthyroidism and is associated with very positive thyroid antibodies.

In 20 of the 64 individuals, those that dose 20 had a history of a vaccination within four weeks of the onset of Graves' disease. And they were somewhat different in characteristics to what is considered classic Graves' disease. And in fact, they had lower titer of antibodies, thyroid receptor antibodies, lower free T3, were more male than female and had a faster remission rate.

So unfortunately, and this paper's under review currently, we still don't know if these were individuals that also had a chronic low grade or subacute infection with SARS-CoV-2, since antibodies were not done, but these data are out there along with several other case reports of this post vaccination Graves' disease.

The second thing I'd like to discuss is vitamin D. So vitamin D receptors are present on every tissue in vitro and in some in vivo studies activation of vitamin D receptor can have an impact on the innate immune system, as well as the adaptive immune system. And so many people have considered the USe of supplemental vitamin D as an approach to both treat acute COVID infections and reduce severity as well as individuals taking it who develop long COVID symptoms. And most of our cohorts that we see in RECOVER are taking some form of vitamin D with ranges of supplementation from 1,000 units to as much as 50,000 units a day.

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The evidence that vitamin D may have an impact on COVID is based on a fair amount of cross sectional data, which suggests that low of 25 hydroxy vitamin D levels predict a greater risk of mechanical ventilation or serious COVID infection during the acute phase. However, 25 hydroxy vitamin D is bound to vitamin D binding protein, and it goes down, vitamin D binding protein, with acute illness. So the predictive value of this is mitigated as a serum marker for acute COVID.

We looked at this in N3C, the degree of vitamin D supplementation among hospitalized patients. And we were unable to find a protective effect of vitamin D supplementation on acute CoV-2 patients who were hospitalized. In fact, there was a greater risk of length of stay and mechanical ventilation, even after a controlling for a number of different covariants. Unfortunately though, this could be complicated by the fact that more sick the patients are, the more likely there to get other treatments such as such as vitamin D and attempt to make them better.

But there are two very good randomized control trials. One gave 100,000 units of vitamin D during hospitalization and showed that there was no impact on the prevention of complications. And a second study, which is currently on Med Archive is really a very important study, 6,300 subjects who had low vitamin D levels to begin with were given either no treatment, 800 units or 3,200 units of vitamin D. And as you can see on the left hand side, vitamin D levels increased, but there was no impact on the acute COVID recovery or clinical sequelae. And importantly, for the first time, some evidence that it did not impact at all symptoms of long COVID.

So finally, I'd like to just finish, and you'll hear a lot more about this from the other speakers on the bidirectional relationship between glucose intolerance and CoV-2. We know that diabetic individuals are 30% more likely to develop long COVID symptoms. We're interested in understanding those individuals who did not have diabetes initially. And so we've been using a platform using AI and machine learning of almost a million EHR records from the Mayo clinic through nference, which is a company in Boston that works with Harvard. And they've been able to scan data and look for what the characteristics of diabetic individuals are who do not have diabetes longitudinally prior to infection with SARS-CoV-2, and not surprising in 1,400 individuals that they detected with onset type 2 diabetes, essential hypertension and obesity were major risk factors for development of type 2 diabetes.

We then went ahead and we just did this last week. We compared post influenza type 2 diabetes in 2019 versus post SARS-CoV-2 infection with type 2 diabetes and found that those individuals that had infected with SARS-CoV-2 had significantly greater body mass index, 35 versus 24, and considerably higher blood sugars in hemoglobin A1Cs than those individuals were SARS-CoV that had post influenza type 2 diabetes.

So in conclusion, multiple endocrine glands can be affected by COV-2, both as a direct infection or as a post autoimmune type infection. Sub acute thyroiditis can occur post CoV-2, as can Grave's disease. And the relationship to vaccination still needs to be determined. There's no evidence from randomized control trials that vitamin D has any impact on the clinical course of acute CoV-2 or on long COVID symptoms. Glucose intolerance is

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secondary to immune response, and that glucose intolerance may be more severe post SARS-CoV-2 infection than other type of viral infections.

Dr. Jaran Stratford

Thanks, Dr. Rosen. Now we'll have Dr. Reusch.

Dr. Jane Reusch

I really appreciate Dr. Rosen insisting that I talk today, because I want to share a little bit about where we're going with RECOVER in terms of looking at incident diabetes, deterioration of diabetes and diabetes remission, and then also share a small mechanistic RO1 that is driven by many of these factors that cliff has started to discuss, and that others will discuss in more detail. So when you're thinking about the RECOVER cohort and trying to understand what are going to be the long term sequelae of a COVID infection, either severe or mild, we want to look to the early indicators that we had in the pandemic, which is early in the pandemic it became very clear that people with diabetes had worse outcomes than people without diabetes.

And in addition, there appeared to be about a 19% to 20% increase in incidents of new onset hyperglycemia that would meet the diagnostic criteria for diabetes. So that already for diabetologists among us, and me in particular, really said, "We've got to pay a lot of attention to this pandemic in terms of its long term consequences for people living with diabetes."

And so I work with a number of intensivists, who I work with very closely looking at endothelial dysfunction, and so wanted to say, what do we think that we know about sepsis and the intersection between sepsis, obesity and diabetes? And we see a lot of profound increases in insulin requirements in sepsis, and we see increased glucogenesis and decreased muscle insulin sensitivity, but we also see an attempt by the pancreas to increase insulin secretion, mainly all the models without actual physical testing of insulin secretion versus insulin sensitivity suggest that insulin resistance is the predominant factor in a sepsis mediated hyperglycemia. So when we look at the early onset of sepsis, we see increased inflammation, we see decreased anti-inflammation, and then there's a recovery towards a homeostatic inflammatory [inaudible 00:19:03].

But those of us who live in the world of diabetes know that people with diabetes have persistent and constant inflammatory [inaudible 00:19:13]. So when we're thinking about how COVID might interact with diabetes, there's been a number of models put forward in 2020 and 2022. And they indict a few different things. First, that we see that there's a more severe cytokine storm in people with diabetes, and that goes along with marked insulin resistance.

But then there's also been a question and a major debate in the literature of whether or not there is direct SARS-CoV-2 infection of the beta cells, or whether it is indirect. And the model I'm going to present might suggest that it could be both, but that the impact of SARS on the micro vasculature is something very important.

There's also, as Cliff just mentioned, a lot of in interactions between comorbid conditions, including hypertension, obesity, and then there's been a peculiar and interesting effect that looks like this is differentially impacting people by sex.

So when we then move forward to, what do we know about sepsis in the context of diabetes? Is that we're starting with a higher pro-inflammatory and lower anti-inflammatory [inaudible 00:20:36], and then you could expect an exaggerated response, which might in fact be persistent, which is why when I first started hearing about long COVID, I was very concerned that people with diabetes may experience additional burden from long COVID.

So let's take a look at, in a little bit more detail about the acute hyperglycemia that can present in a COVID infection. And this is an Italian study, but really excitingly one of the best studies to actually look at insulin secretion, as well as to, by a HOMA analysis insulin action. And what they showed in these individuals were that in over 500, they had a pretty high proportion of people, higher than that 19% that had new onset hyperglycemia without preexisting diabetes, at least by chart review. That new onset hyperglycemia in a smaller subset that was studied in more detail persisted in some of these people out at two months. So it's important to note that this study is at two months.

And for these people, what we found was that their hospitalization was slightly different. The people with diabetes had higher baseline, poor clinical score, but what was really interesting and very interesting to me in terms of diffuse endothelial dysfunction, was that people who required oxygen support had more likelihood of hyperglycemia. People who had [inaudible 00:22:14] support and people who were in the ICU.

And interestingly, and I just got lucky when I laid out my proposal, I wanted to think of diffuse need for oxygen support in a patient population as a metric of diffuse endothelial injury in that population. In these patients, what was really exciting was that this group used an arginine stimulus to increase insulin secretion. So that's insulin reserve. It's not the same as glucose mediated insulin secretion, but what they showed was that in the setting of acute COVID, there was an increased insulin secretion, an increased beta cell demand.

And there was also insulin resistance by a calculated HOMA-IR measure. But what was really interesting was that there was this hyperemic response to the arginine, very, very acutely suggesting that there may be a high metabolic demand or a high insulin secretion in these people, which is something we have seen in youth at risk for type 2 diabetes and rapid progression in the RISE study.

So the questions that I feel like we, RECOVER as well as my RO1, is attempting to address are what are the implications of diffuse endothelial injury? COVID specifically infects the endothelium. That's not controversial in any way. And when this COVID endothelial infection collides with the existing pre diffuse endothelial injury, we see an even uncomplicated diabetes. So is sepsis related hyperglycemia different with COVID? Will it persist, or will it remit? We've seen some remission already at two months, and will it have implications to the progression?

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Most importantly, to me, of diabetes related cardiovascular and microvascular complication, will it be a new cardiovascular risk factor when we're using cardiovascular risk factor engines? And so let's take a quick lesson from the preeclampsia. So preeclampsia really struck me as a parallel for COVID because it is an acute time limited diffuse endothelial injury, like a COVID infection may be, but it has long-term sequelae. And the long term sequelae that we see are increased outpatient visits. So a lot more outpatient visits. Increased car hazard ratio of cardiovascular disease and increased relationship to hypertension. And does this sound familiar? It sounded very familiar to me with post COVID syndrome.

In an article that I thought that Cliff was going to show earlier, they had shown in 3,700 people, increased incidents of new onset diabetes post COVID, and in a larger us veteran population that has been seen again. So with these earlier studies were not US population, and here is a US population. So in the US, in 2017 or 2018, when I was president of the American Diabetes Association, there were 30.3 million people in the US living with diabetes. Now there are 37.3 million. So already we have a crazy escalating epidemic.

So if we add anywhere between 0.25 and 0.5 increased likelihood, this could be a major public health problem. So one perspective that was very interesting to me by Peter Libby and Tom Lutcher was that COVID is, in the end an endothelial disease. So if we think of a healthy endothelium, it promotes cardiovascular, pulmonary, brain and renal health. But the minute that you are disrupting endothelial function and activating endothelial cells, what you will see is a cavalcade of effects, all of which more greatly affect people with diabetes.

Now, in my research with Dr. Reagensteiner, and more recently with Dr. Nadeau and pediatric endocrinology, we have been looking at the interaction between type 2 diabetes and decreased functional exercise capacity, seen the impact on cardiac dysfunction and skeletal muscle dysfunction that can be explained a lot by heterogeneous tissue perfusion, which is what people see in sepsis and what we see probably more so in people with a COVID related serious infection.

The RO1 that we put together was looking at COVID and incident diabetes, and was looking at the relationship between systemic endothelial injury and insulin secretion and insulin action, as well as skeletal muscle function. So our overarching hypothesis is that COVID 19 deleteriously impacts carbohydrate metabolism and skeletal muscle function due to systemic perfusion abnormalities, worse in diabetes and hyperglycemia, and post-hospitalization of recovery will be slowed in the context of hyperglycemia mediated, persistent endothelial injury.

So when we're thinking about the beta cell and the eyelet within the beta cell, sometimes we forget that in addition to alpha cells and beta cells, what we have in the eyelet vasculature is a very responsive micro vasculature. So as shown in these slides by Al Powers group, what we see is in hyperglycemia, if you're looking at the perfusion in an eyelet, you will see higher perfusion with hyperglycemia, lower perfusion with hypoglycemia. So you could imagine that if you don't have the ability to regulate perfusion because of diffuse endothelial injury, you might disrupt glucose sensing and, or have a deleterious effect on insulin secretion.

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Aim one of our RO1, which we can be further supported by data generated under the RECOVER study is to look at insulin secretion in action post-hospitalization over 3 to now 12 months to see about the intersection between persistent hyperglycemia and diffuse endothelial injury recovery in line with insulin action by an oral glucose tolerance test, as well as insulin secretion by the oral glucose tolerance test.

There is an interaction that is robust in the pancreas with diffuse endothelial injury that is even more strongly seen in the skeletal muscle. So our second hypothesis is that dysglycemia and diffuse injury will disrupt muscle recovery. And we know that we're seeing a lot of weakness and a lot more weakness in people with diabetes. So we have a bunch of research demonstrating that microvascular perfusion augments the decreased metabolic oxidative flux in people with diabetes. And we wanted to see if post recovery COVID, that those two pathways were interacting.

So when you hit somebody with a severe acute illness, such as a COVID hospitalization, they will lose muscle mass and they may not completely recover. And we think that diabetes would exaggerate that and a COVID infection will exaggerate that. So there have been models put together about even people not getting COVID infection having decreased functional status. So in our work under this aim, what we're going to do is we're going to use a very innovative design, MRI based muscle profusion, blood flow and oxygen extraction developed by Dr. Aaron England, a talented bioengineer at the University of Colorado on skeletal muscle.

And then we will also be using our phos, our MRI phos labeling to study oxidative phosphorylation. So we can do that with, and without oxygen to see if perfusion is limiting oxidative function in vivo, and this is based on data from our group, showing that decreased oxidative function in vivo in people can be restored by simply giving them increased oxygen availability. So is there a simple bedside test for this diffuse endothelial injury? Well, of course I wouldn't be asking that question if it wasn't one. So we'll be using a microscan device of sublingual intravital microscopy to look at microvascular perfusion under the tongue, which is a very similar embryological origin to the gut and the heart and skeletal muscle. And so these indices, plus some serum markers of diffuse endothelial injury may inform our question.

So this work is going to be done by me and Dr. Douglas, [inaudible 00:31:45] and Albert. And so let's come back to what this might mean for RECOVER. Well, the opportunity for RECOVER is for us to understand what is the mechanism underlying incident diabetes. This is not a broad epidemiological study. It can be complemented by N3C, but we really want to have the opportunity to look at what is going on after COVID in terms of deterioration of diabetes and or diabetes remission. So I'm now going to turn this over to Dr. Gallagher.

Dr. Emily Gallagher

Thank you. So I'm going to take up where Dr. Reusch left off and talk a little bit about health disparities and diabetes and how it may be contributing to worse outcomes and long COVID, and also how RECOVER is going

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to address these issues. So these are my conflicts of interests, which are not directly related to COVID or COVID related issues.

So the objectives for what I'm going to talk about are ready to describe the racial and ethnic differences in SARS-CoV-2 outcomes and the potential influence of diabetes in affecting these outcomes. And secondly, to understand the role of RECOVER in examining the links between SARS-CoV-2 and diabetes. So I'm going to focus on two things, the first just being the racial and ethnic differences and the prevalence of diabetes overall, and the associations with SARS-CoV-2. And secondly, evaluating the mechanisms of diabetes. So as Dr. Reusch mentioned, it's important to try and figure out why people are getting diabetes in the setting of COVID.

So to begin with, you all probably remember, and at least I distinctly remember the first wave of COVID here in New York, in March and April of 2020. This paper was from the group who examined the US statistics, national statistics, and looked at different phases over the course of the first two years of COVID. And what you can notice here is two things. I mean, the first, I think we all recognized immediately when COVID started and when patients started coming into the hospital was that the mortality was greatly increased with age. And so this year on the Y axis you can see is a logarithmic axis. And so really there was an exponential increase in the mortality as people got older. What you can also see here is differences between racial and ethnic groups across the US. So the top here is men and the first column is Black men, Hispanic men in the middle, and then white men on the right hand side and women on the bottom.

And so if you just look for example, at 50 year old Hispanic and Black men, you can see here where the line hits the Y axis of their mortality, which was much higher than if you look at the equivalent 50 year old white men during the first phase of the pandemic. And so there was an increase that we saw in mortality, both with age, and there was an obvious increase in different racial and ethnic groups.

And obviously we know that there are a lot of social and access to healthcare issues that contribute to this. But one question was whether diabetes might also be contributing. So when you look across the US, generally, you can see that the mortality, this is compared to non-Hispanic white patients, and this is from the CDC data that I downloaded yesterday, and so you can see that American Indian and Alaska natives had increased number of cases, hospitalizations and mortality compared to non-Hispanic white, and the same with African American or Black individuals, and the same with Hispanic individuals.

And so we know previously from before COVID that there are differences in the prevalence of diabetes in the US. So here on the right hand side is non-Hispanic white men and women. And you can see that Hispanic, Black, and American Indian and Alaskan natives have much higher prevalences of diabetes. And this was before COVID. And then if you just superimposed the table that I previously showed you, you can see that those who have the highest prevalence of diabetes also had the highest risks of hospitalization and death with COVID. And so the question was, is there an association between the higher prevalence of diabetes in these groups and their higher mortality?

So this is a very simplistic view of what Dr. Reusch showed you already. And so that we know that preexisting diabetes in individuals who developed SARS-CoV-2 was associated with an increased risk mortality. What we still don't know is whether this is associated with an increased risk of long COVID. And we also know that people who had SARS-CoV-2 had an increased incidence of newly diagnosed diabetes, but was this associated with also long COVID, was diabetes persistent until they developed long term diabetes? And we do know that it was associated with an increased risk of mortality.

So the references here in the bottom are not from this. This is just a simplified figure of what's in other papers, but this review in diabetes care is an excellent review of this interaction between preexisting diabetes, new onset diabetes and mortality outcomes. And then the second paper is just from Mount Sinai here, where we looked at the new onset hyperglycemia and people who came in with a first wave and how it increased the ICU associated mortality.

So there aren't that many studies looking at really how this interaction maybe playing at across different racial and ethnic groups. So this is a study from NGH, where they looked at the prevalence of newly diagnosed diabetes in individuals who are hospitalized with SARS-CoV-2. So here are the people with preexisting diabetes are the blue columns, and then the gray columns are people who developed new hyperglycemia or newly diagnosed diabetes when they enter the hospital. And so you can see if the gray column here is highest in the Hispanic group. And so these people had the highest rates of new onset hyperglycemia after they were hospitalized.

Just notably in this study, the Hispanic and non-Hispanic white populations were the two largest populations. And the distribution here is just the distribution across races of people who developed new diabetes or people who had preexisting diabetes. But you can see that Hispanic groups seem to have the largest risk of onset of diabetes. This has been associated with an increased risk of mortality in other studies, but it wasn't examined in this one.

So then this is also the same study that Dr. Reusch showed you, but just a different figure from it. So this is the one from the VA study here in the US, and this looked at something different. So this wasn't nuanced diabetes. This was people who had a risk factor for prolonged diabetes at 12 months. So people who developed diabetes and have persisted. So here, you can see that they did not look at all across all racial and ethnic groups. They just looked at Black or African American individuals versus white. And they saw that Black individuals had a higher risk of developing diabetes 12 months after the diagnosis of diabetes. So this seemed to be a risk factor for persistence of hyperglycemia.

So what about other types of PASC? So people who developed hyperglycemia or had preexisting diabetes, is it a risk factor for long COVID? So this study came out of UCLA and what they actually were looking at was not persistent diabetes, but they were looking at other symptoms of long COVID such as fatigue and shortness of breath. And what they found was that actually there wasn't an association between an increased risk with different racial or ethnic groups, but diabetes itself did increase the risk of long COVID. So it's possible that long

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COVID is not specifically related to different racial or ethnic groups, but it could be that the diabetes is actually increasing the risk. So what do we know, or what do we think we know about SARS-CoV-2 and diabetes? Well, so far we do know that SARS-CoV-2 is associated with new onset hyperglycemia or newly diagnosed diabetes.

And there was a little bit of a question on this. And some people, it may be spontaneously new hyperglycemia and other people that maybe people who did not see the doctor for a while, or did not realize they had diabetes. And therefore they came in with this inflammatory infection and it just brought out the diabetes diagnosis. Preexisting diabetes and or new onset hyperglycemia, we do know is associated with an increased risk of hospitalization, intensive care unit admission, and mortality. And then there may be racial or ethnic differences in the new onset of hyperglycemia or diabetes as suggested by some of these studies, although there's very little data on this. And then it seems, at least from some of the studies that diabetes might be associated with an increased risk of long COVID.

So what we still don't know is what percentage of people develop this new onset diabetes. Is that people, as I said, who have preexisting diabetes to some extent, or who gets this worsening hyperglycemia, and what are the risk factors for developing this new onset of diabetes? Are there gender differences or racial or ethnic differences? As I said, there's some data supporting differences in racial ethnicity contributing to this worsening of hyperglycemia, but there are very few studies looking at it. And then the question that Dr. Reusch brought up, which was what are the mechanisms behind the development of diabetes and SARS-CoV-2? Why do people with diabetes potentially have a higher risk of long COVID? And does the acute hyperglycemia persist 12 months on, or does it generally tend to resolve?

So how are we going to evaluate the mechanisms of diabetes development with RECOVER? So this is a simplistic view of how we think of diabetes generally, and it's simplistic just because it breaks it down into two things, either insulin deficiency or insulin resistance on hyper insulinemia. So oftentimes it's not this straightforward and often there's a spectrum of some insulin resistance, some partial insulin deficiency, but this is just for the concept of trying to figure out mostly what's happening with SARS-CoV-2. Is it an effect on the pancreas or is it more of a systemic effect on other metabolic tissues?

With RECOVER, the plan will be to do the glucose tolerance tests, and the glucose tolerance tests are, we think of them as a way to diagnose diabetes where you give somebody a glucose drink, and then you measure their glucose levels over the course of 120 minutes. But what we can also do with this is look at insulin secretion over the initial phase. And then we can look at in glucose disposal or insulin sensitivity over the latter part.

So in addition to measuring the glucose levels, what we do is we also measure the insulin and C peptide. And so what people will do when they come for Recover, if they meet the criteria of hyperglycemia or new onset diabetes or worsening diabetes in people with preexisting diabetes, then what they will do is come in for the glucose tolerance test and we'll be measuring the insulin levels and the C peptide levels, as well as their glucose levels.

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Basically based on these levels, I'm not going to go through all the calculations, but you can distinguish between beta cell dysfunction or insulin resistance. And so there's this insulinogenic index, which you can calculate over the first 30 minutes, which looks at insulin secretion. You can look at the C peptide index, which is another measure of insulin secretion. And then this Matsuda–DeFronzo index of insulin sensitivity can be calculated over the entire 120 minutes of the glucose tolerance test.

So once we have more information about why people are developing diabetes and whether it's more related to pancreatic insulin efficiency, or whether it's more related to changes in insulin sensitivity, the next question will be what mechanisms potentially could be driving one or other of these. Our next speakers are going to actually probably address more of these factors, so I'm not going to get into them, but there are a number of factors that could potentially be contributing to either the defect in insulin secretion or the insulin sensitivity changes.

So to summarize, diabetes may be a contributing factor to worse outcomes in SARS-CoV-2 and potentially contribute to the differences in racial and ethnic groups. And there are different outcomes with COVID. The risk factors for new onset hyperglycemia in individuals with SARS-CoV-2 are not well understood. And the prognosis for those who develop new onset hyperglycemia is currently unknown, but through RECOVER, hopefully we can help to answer some of these questions regarding the mechanisms of diabetes and new onset hyperglycemia. And thank you. So I think I'm handing over to Dr. Scherer.

Dr. Philipp Scherer

Thank you very much. So we have already fairly far advanced into the hour. So allow me to just give a five minute summary from a basic perspective of what we've just heard from the various speakers. Just starting out here with Dr. Reusch's slide about the fact that we have diabetes, obesity predisposing individuals to a much worse prognosis overall. And the question is, of course, why is that?

She has shown you rightfully a lot of data on endothelial dysfunction, which might be one of the keys. Our perspective to compliment that might be more related to the adipose tissue and the lipocytes specifically as a target for infection as well. And as a contributing factor to the systemic cytokine storm that individuals with diabetes and obesity actually have to undergo. We know the fat cell mostly in the context of its contribution to diabetes, to tumors as well, but then it plays an important role in infectious disease at multiple different levels as a target for various parasitic infections, but also as a target for a host of viral infections as well.

And that actually, since adipose tissue is the biggest endocrine gland that we have. And in some individuals makes up to 50% of total body weight, this has to be taken of course, very seriously. So very early on, actually back in 2020, we had a thought piece on adipocytes and adipocyte like cells and their contribution to pulmonary fibrosis, which was one of the key issues. And we emphasized at the time the relatively recent discovery of the fact that fat cells can actually not only shrink or increase in size or apoptosis and necrosis, they can

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also de differentiate. And in the process of de differentiation, going over to a precursor state, these precursor cells can actually morph into what we refer myofibroblasts. And these myofibroblasts have very potent pro fibrotic characteristics. So in the long, for instance, we have lipofibroblasts, which are adipocyte like cells, and they can actually de differentiate to myofibroblasts.

And these myofibroblasts are a significant source of the fibrosis that individuals experience within the lung. And of course, that significantly impairs the oxygen exchange. So in that context, the adipocyte and adipocyte like cells are potentially major targets basically to alleviate some of the symptoms. An old fashioned way, which it still hasn't really been tested clinically in a systematic way, is the antidiabetic drug class of thiazolidinediones these are activators of the transcription factor PPAR gamma and PPAR gamma exerts pro adipogenic effects. But more importantly, in this context, it also exerts potent antifibrotic effects, potent anti-inflammatory effects, something we take advantage already in the context of fibrosis in the liver, but which hasn't really been systematically tested in the context of the cytokine storm in the acute phase, as well as the fibrotic sequelae that follow up on the infection in that particular context.

So the thiazolidinediones remain an attractive possibility for the future, both for the acute, as well as for the long term alleviation of some of these symptoms. In addition, we also heard from Dr. Reusch the potential of sepsis as a contributing factor. This is preexisting enhanced levels of endotoxin in the system. And we do appreciate that diabetics, obese individuals have slower gastric motility, increased gastric permeability for bacterial debris. So we have a higher baseline level of endotoxin in the system. And when you combine that with the massive TLR mediated antiviral response, we have several systems on at the same time, and they actually combined between the endo toxin and the viral response. We have probably an excellent explanation for the massive immune response, with respect to the cytokine storm that we experience. And presumably much of that is long lasting in the context of PASC as well.

So this endotoxemia is appreciated as being elevated in type 2 diabetics. We've known that for many years, but what we don't yet fully appreciate potentially is the contributions of that endotoxemia to the potent inflammatory response in the context of viral infection.

Now, just to make the point here towards the end of what tissues are majorly involved, the fat tissue is clearly involved. We have an overabundance of papers that for instance, compare gastric bypass surgery before and after the COVID pandemic clearly indicating that mortality is significantly reduced in patients that underwent the surgery prior to COVID 19, just further emphasizing that the fat mass and it's associated dysfunction plays a critical role in this context. This has also been highlighted by a host of papers that actually show that the virus can directly infect fat cells, lipocytes and turn their pro-inflammatory response on, along with all the other important cells within adipose tissue, that include a lot of macrophages and endothelial cells, as well as pre adipocytes that contribute to the cytokine storm in an acute setting as well.

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Some of the critical factors that fat cells produce are essential regulators of the immune system, particularly leptin is actually something that plays a major role in the inflammatory response as well. I'm going to think about leptin based interventions in this context as well. We heard about the beta cells and various other components in the eyelets that can also be direct targets for viral infection and change their fate as well as their ability to actually produce and release insulin.

And again, together with Dr. Rosen [inaudible 00:51:07] here, we summed a lot of that up in this particular perspective here in eLife that we recently published and mused about the consequences of all of that for long COVID and how that will be affecting the metabolic dysfunctions that are fairly characteristic of people long term post COVID exposure. And with that, I want to let Dr. Miele pop in with his summary.

Dr. Lucio Miele

This has been a fascinating discussion so far, and I'm going to bring you the perspective of how the Omics group has been thinking about these things. We have discussed metabolic dysfunction as both a risk factor, as well as a consequence of both acute SARS-CoV-2 as well as long COVID. How do we measure that in addition to, and do we even need additional measurements in addition to oral glucose tolerance test, insulin, C-peptide? We can do targeted metabolomics to look more in depth at glucose and amino acid and fatty acid metabolize in past patients. And targeted metabolomics, at least in the opinion of the experts in our group may actually decrease our sensitivity in terms of being able to detect pathogenetically relevant metabolites.

So our consensus would be to use targeted metabolomics that are guided by the pathophysiological hypothesis that we've heard about during the discussion today. Now, one thing that we haven't talked about yet is the role of the microbiome. Now there is going to be a collection of intestinal microbiome samples.

As you know, the microbiome affects a number of key physiological processes that are involved, or potentially involved in both acute COVID 19 and PASC. It affects immunity. It affects the sense of appetite. It affects metabolism, and it produces short chain fatty acids that can modulate phenotypic plasticity of cells. We just heard from the Dr. Scherer about the phenotypic plasticity of adipocytes and that adipocyte line cells.

So we're going to do two things in the context of RECOVER. The 16 S characterization, which is essentially one of the ribosomal RNA genes, tells us about taxonomy, of what bacterial species are present. And what is the relationship between the various species? There is a lot of literature on this. The problem with the literature on this is that it is inconsistent. There are well known alterations in the ratio between firmicutes and bacteroides in the intestine in individuals with obesity and diabetes. But again, there is inconsistency in the literature.

We're going to do something a little more in depth than that, which is made metagenomics, essentially looking at what metabolic pathways the bacterial species as individual species, and as a community are going to have active in the intestine of individuals with PASC. And I want to remind you that the intestine is an active side of viral replication. So the viral replication itself might interfere with the microbiome.

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That's going to tell us a little bit more, hopefully about bacterial metabolites that may enter the circulation and affect the processes that we've heard about during the presentations before this. Another thing that we've heard a lot about is immune dysfunction in chronic inflammation. Now, this can well be characterized through Omics, specifically with high throughput proteomics, it is possible to do two things. To measure virtually all cytokines in the adipokines present in a sample of plasma, and also to measure auto antibodies that may be involved in consequences, such as post COVID Graves' disease that Dr. Rosen described.

This should be complemented by high throughput immune phenotyping, at least in a subset of patients through things like [inaudible 00:56:44] that are going to tell us exactly what immune populations are present in individuals with different clinical manifestations of PASC. Additionally, endothelial damage. Now, there are other ways to measure endothelial damage, but VEGF 1, 2 and 3 are involved in a number of processes, including response to endothelial damage. And this is one of the things that should probably be tracked. The important issue with some of these measures is that they should be done longitudinally in time, a single time point isn't really going to tell us very much.

Now, there's something also that we haven't talked about that's obviously dear to my heart, which is what is the role of individual genetics? Comorbidities of course contribute as risk factors to the variety of consequences of acute COVID, but is there a polygenic risk score for PASC? And is there a polygenic risk score for gastrointestinal and or metabolic manifestations of PASC? These are questions that could be asked using GWAS approaches.

Now we've heard from Dr. Scherer about the role of adipose tissue and its phenotypic plasticity. That calls in my mind for potentially single cell RNA C and proteomics/transcriptomics, not only on plasma, but possibly even on adipocytes. Now I want to remind everyone also, as I said earlier, that adipocytes are a major source of VEGF. Now, VEGF is a key stimulus to the production of myeloid-derived suppressor cells in the bone marrow. Now these cells, as many of you know, or all of you know, are essentially immature myeloid cells that migrate to sites of injury and chronic inflammation and release mediators that are primarily immune suppressors.

The production of these is stimulated by VEGF, which is produced by both damaged endothelial cells and adipocytes. We actually years ago published that at least in an obese mouse model, the production of VEGF is higher. And it does in fact, stimulate production of MDSCs. What is the rule of endothelial damage and adipose tissue derived VEGF in the chronic inflammation that results in end organ damage, including potentially damage to the eyelids, damage to muscles and damage to endocrine organs? And these are all questions that I would love to discuss with the group, and that could result in follow up studies. And I have additional slides, but they simply summarize what we've talked about so far, and I believe they're redundant.

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Dr. Jaran Stratford

So I'd like to thank our discussants and our panelists. And we can also take a second to, Dr. Miele, if you can pull up your slide really quick, some of the points that you had on that last slide, I'd like to open that up to the panelists to discuss some of additional of those questions that you had posed there.

Dr. Lucio Miele

This one?

Dr. Jaran Stratford

Yes. That would be great. If any of the panelists would like to chime in on some of these questions posed here, this would be a good time for that.

Dr. Philipp Scherer

Well, maybe just a very quick comment since I'm the fat person here in charge. I think adipose issue obviously offers a lot of possibilities for further study. It really needs to be defined. We were hoping that we might be able to present today some new data, we weren't quite ready, but there is a new factor that we've all been dealing with that is ... we've referred to as endotrophin, which is a potent fibro inflammatory marker. And we just are looking now at the impact of infection on the circulating levels of this marker and will hope to be able to report that.

But of course, I've mentioned leptin, I've mentioned adiponectin as also a factor that's critically affected. Adiponectin goes down during an infection. And all of these will have a pretty profound impact on long term outcomes and the relative local micro environment of adipose issue with its impact on systemic insulin sensitivity as well.

Dr. Lucio Miele

Is endotrophin a protein?

Dr. Philipp Scherer

That is a protein, indeed. And it's a cleavage product of collagen VI alpha-3 that we have great hopes for as a marker and as a contributing profibroic factor.

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Dr. Lucio Miele

So that could be revealed by proteomic approaches?

Dr. Philipp Scherer

It could only be revealed by proteomic approaches and less so by RNA-seq, because it's a post-translational cleavage product.

Dr. Jane Reusch

And just to weigh in, so general whether you're looking at it from the lens of diffuse endothelial injury or systemic inflammation, and the role of the adipocyte, a couple of comments. Wherever you have that diffuse endothelial injury or inflammation, you're going to have some endothelial fibrosis that is then going to interact with circulatory dynamics of tissue function. So maybe the brain fog, the cardiac function, all of these things can interplay.

And, Phil, I'd love to follow up on the quick side glance you gave to thiazolidinedione. So I'm really intrigued because one of the things that you unique about COVID is that obesity is a factor for premature mortality in a COVID infection. But in some of the other sepsis literature, obesity, it doesn't have an increased impact on mortality. And so I'm really intrigued by the thiazolidinedione. And are you looking at them as a tool to improve adipose health, even in the situation of chronic infection?

Dr. Philipp Scherer

Yes. I mean, improvement of adipose tissue health is one key issue. The thiazolidinedione are unfortunately very old fashioned by now, and everybody's trying to run away from them, but we have to bear in mind that they do an awful of lot of things that will be beneficial in this context. We think of the insulin sensitizing aspect of thiazolidinediones first and foremost, but we have to bear in mind, they're potent antifibrotic and also antiinflammatory actions due to PPAR gamma.

So I think it really combines in many areas, everything we want in this context, in a very broad sense. Unfortunately, they're not very ... given now that we all gather around the latest generation of dual agonists in the GLP-1 GIP area, who wants to go back to thiazolidinediones after what they've been through on the cardiac side effects, which turned out to be not as relevant as we thought? So I think these are very viable, potent interventions still that have not been explored to a sufficient extent. And just for declaration of conflict, I have no conflicts. I'm not working with anybody who is in the market for PPAR gamma agonists. This is strictly from a basic science perspective, going down the list of what we want to happen in adipose issue.

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Dr. Lucio Miele

I mean, drug repurposing is always a viable idea if it's safe. So about the brain fog, we, and by we, I mean our pathology group have a long series of autopsies from victims of acute COVID 19. And I've looked at those slides. What I can tell you is that there is very diffuse and very evident and endothelial damage throughout the brain. I mean, I'm not a pathologist and I couldn't miss it in the slides. So if anything like that happens in non-lethal cases of acute COVID, we really do need to look into endothelial injury as one of the central mechanisms of this, that could essentially cause many of the consequences we talked about so far.

Dr. Jane Reusch

Yeah. And Joel Trinity at the Utah part of our RECOVER site has done a lot of noninvasive assessment of diffuse endothelial injury, including brain perfusion, showing decreased brain perfusion, as well as lower extremity perfusion and just regular old [inaudible 01:07:26] vasodilatation in PASC survivors versus non PASC COVID survivors.

Dr. Lucio Miele

There are seven questions in the Q&A I can see.

Dr. Jaran Stratford

Yes, I was actually going to jump to that right now. So one of the questions that piggybacks on the discussion that we have just been having is, "Are there known or studied methods for repairing the endothelial injuries caused by an acute infection, at least beyond the body's natural cellular healing mechanisms, which may be hindered by the multisystemic injuries?"

Dr. Jane Reusch

So it may sound counterintuitive, and of course you could expect this answer from me, but it would be exercise. And there is actually even a methodology using inspiratory pressure that's been used in very sick dialysis patients to improve endothelial function. So yes, probably we would like people to get up, get moving and start exercising. That's the best way to improve your endothelial health. Been shown originally in PAD in peripheral arterial disease. But now we and others have shown it in diabetes, in hypertension, et cetera.

But trying to say, meeting somebody where they are in terms of acute COVID syndrome. And it has initials. And I never remember initials because I have dyslexia, but it's an inspiratory exercise of the diaphragm, and it's had systemic improvement in endothelial markers in aging, as well as in dialysis populations. Also there are drugs, but I'll let other people talk about that, including thiazolidinediones.

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Dr. Lucio Miele

I do like the exercise idea.

Dr. Jaran Stratford

So another question that came in during the presentation is, "How can these findings be helpful for primary care doctors in their treatment of patients with long COVID?"

Dr. Lucio Miele

Well, we don't really know how to treat long COVID yet. Sorry. We hope to learn it through RECOVER. At this stage the treatment is going to have to be targeted to the particular consequences of long COVID. So if somebody develops diabetes as a result, then the diabetes needs to be managed and so on and so forth. We don't have a treatment for long COVID yet.

Dr. Clifford Rosen

Yeah. And I think awareness of what dysfunction could occur, endocrine dysfunction, besides glucose intolerance, a number of other factors that we've outlined may be important. So I think for primary care physicians, it's important to do a full workup, pretty much what we're doing in RECOVER in terms of trying to identify potential pathogenic factors that could contribute to symptomatology.

Dr. Emily Gallagher

Yeah. I think primary care perspective, as well, it's important to realize that in young people sometimes the diabetes is actually the first symptom of COVID in people. So if somebody comes in with no known history of diabetes and suddenly comes in with symptoms of hyperglycemia, then they may actually have COVID.

Dr. Lucio Miele

I see a question on, is there a list of long COVID symptoms? There actually is now. It's a long list and I'm taking that one because one of my hats is biomedical informatics. So there's a very nice paper by Emily [inaudible 01:11:33], and coworkers on the N3C dataset that has identified a series of ICD-10 codes. So this is very relevant from the standpoint of primary care that are associated with long COVID manifestations.

They broke it down into three major groups. One of which is GI and metabolic, what we're talking about today. The other one is cardio respiratory. And the third one is neurologic. There is a root ICD-10 code, which I

believe is D 9.9. [inaudible 01:12:09] And a series of codes in association with that can actually tell you how likely it is that somebody has long COVID if they're of new onset.

Dr. Jaran Stratford

Thank you. There's another question here that says, "I understand that minerals often are dysregulated in long COVID, but I don't quite understand the mechanism that is depleting minerals, such as potassium. Is there any evidence or studies that link this as well?"

Dr. Clifford Rosen

I'm not aware of anything beyond acute COVID illness can cause multiple mineral changes, particularly as they're acutely ill. And if they're being treated with insulin and the potassium can go down, they there's a number of other factors, diuretics that can change potassium. I'm not aware of any changes in magnesium other than what we see with acute illness.

And as far as I know, I have not seen any data in long COVID as to what potential mineral elements are there. We do measure calcium in the RECOVER in tier one, but there's no evidence currently that certain calcium levels are low. One thing that has been reported that got a lot of press this week was a report of hypercalcemia, very high calcium for an individual getting more than a 100,000 units of vitamin D a day for long COVID. So there is that potential risk of developing side effects from medications that probably are not effective.

Dr. Jaran Stratford

Thanks. There's also another question that says, "A lot of the data shown was associated with early COVID variants. Is there any evidence that it can be extrapolated to the newer Omicron variants? The symptomatology is very different. Is there the same incidence of diabetes, stratification of severity and PASC risk based on age, race, et cetera?"

Dr. Lucio Miele

The short answer is we don't know yet.

Dr. Clifford Rosen

We don't know.

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Dr. Lucio Miele

Because Omicron is still changing. We just saw what may be among the first instances of two newest sub variants around here. This is going to have to be looked at retrospectively, but there is work ongoing in that matching clinical phenotypes with sub variants. I can tell you that even within sub variants of Omicron there are differences in predicted T cell epitopes. So the immunogenicity is going to be different. This will require a lot of work.

Dr. Jane Reusch

Yeah. There was a recent paper suggesting that PASC is slightly less common in Omicron at six months. But what do you really know about exactly when ... does that mean that it's going to be less common or does that mean it didn't happen yet? And I mean, so I think that these are the questions that frankly RECOVER is not an epidemiological study. It is really all about mechanism and we have to keep our eyes on the goal here. We're investing a lot of money and participants are investing a lot of time. We have to really make sure that whatever questions we can address with RECOVER, we are going after them.

Dr. Emily Gallagher

I think with age, like we saw that in that paper went from the group at UPENN, where they looked at the statistics over the different waves that the mortality in the oldest group later improved over time with the different waves, but that was probably related to vaccinations in the different groups over time. So there has been a definite improvement in survival with older people, but it's probably vaccination related.

Dr. Clifford Rosen

Right. And still not clear whether vaccination reduces the risk of long COVID.

Dr. Jaran Stratford

So there's another question here that says, "There's recently been a lot of work about the role of the mitochondrial in long COVID and other post-infection conditions. Are there any evidence for the role of mitochondria in regulating the metabolics of patients with long COVID?"

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Dr. Jane Reusch

I think that when you have as much sarcopenia post COVID, you would expect that you would have decreased mitochondrial function. And that's where Lucio's data on the metabolomic profiles, particularly on the semi targeted metabolomic profiling may offer some really key insights there.

Dr. Clifford Rosen

Yeah. And John Kerwin has some data that oxidative phosphorylation is impaired in some of T-cell function in individuals that go on to have sustained disease beyond 28 days. So depending on the tissue, there may be significant differences in respiratory capacity.

Dr. Emily Gallagher

Now, remember early on, there were papers coming out on like Metformin and improved outcomes. I don't know if anybody has a comment on whether that has panned out, or if there's any mitochondrial effects of Metformin that might have changed outcomes.

Dr. Jane Reusch

So Caroline Vermonte, who is part of the N3C diabetes domain with me, she has, I don't know if it's in press or out paper with Metformin in terms of outcomes. And she has a 1,500 person cohort that she's going to be reporting on soon. What news specific byline before the official FDA paper release looks exciting.

Dr. Jaran Stratford

So there's another question that says, is there any research completed or ongoing research regarding weight gain in long COVID patients that may be unexplained by some of these other factors or maybe related to some of the metabolic topics that we've discussed today?

Dr. Philipp Scherer

I think that's going to be a very difficult one to deconvolute because there are so many things coming together in long COVID that it is nearly impossible to put a finger on a specific long COVID induced weight gain. I think it's very likely, but that will be difficult to prove convincingly a direct relationship to that. And Lucio might be in a better position to comment on the statistics behind that.

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Dr. Lucio Miele

So to the extent that it has been looked at in the N3C cohort, new onset obesity was one of the codes that were part of the metabolic constellation of long COVID. However, the mechanisms could be multiple. It could simply be due to inactivity because of fatigue. So we don't really know that there is a direct link, but that's something definitely worth studying.

Dr. Philipp Scherer

And there have been a number of studies really focusing on weight gain over the course of COVID now without a consensus at the end of the day. There are papers that will argue for an increase in overall weight. But I think there are just as many papers that will argue that the net increase in weight gain and loss is actually no different from a period preceding the three years before COVID. So I think this is going to be a difficult one because it's a very heterogeneous response as well. We have unquestionably individuals that have gained weight, and there are individuals that have lost weight during that time and whether or not this was a function of infection versus lifestyle changes over the time beyond that is going to be a tough one.

Dr. Jane Reusch

The only group where it's been a little more consistent is youth. So in the kids, not specifically related to whether they had the burden of a COVID infection, but throughout the pandemic, there has been more weight gain in kids.

Dr. Philipp Scherer

Agreed. Yeah, that is true.

Dr. Jaran Stratford

So we have one follow up question to the response about endothelial repair, "Exercise intolerance is a common symptom of patients with long COVID, and this is understood to be related to overactive sympathetic responses. Is the inspiratory device more of a parasympathetic support form of exercise, and can this paradox be addressed a little bit more?"

Dr. Jane Reusch

Well, so that's a big question that our lab is trying to unravel in diabetes, but I would just say that this does appear to increase parasympathetic tone, or at least RR variability. I haven't yet done it. We have a proposal

that just got a good score. So maybe we will be doing it in youth with type 2, and maybe we'll do it in this group, but it seems that when you're taking a relatively frail or deconditioned population, it's good to start with an exercise intervention that's both portable and also not overwhelming to them. So I like its odds of being potentially useful and it should, although I really ... the data from the aging population, the push in our variability was really ... it was statistically significant, but whether it was clinically significant is hard to say.

Dr. Jaran Stratford

We'd like to thank all of our presenters today and thank you to our audience for attending the seminar and engaging with the Q&A. As a reminder, a recording of today's seminar will be available on RecoverCOVID.org within a few weeks. We will also be posting a Q&A document that has responses to the questions that we received today that we were not able to address during our allotted time.

We also want to note that today we had a focus heavily on metabolic function in PASC, and at future sessions we'll have a focus also on the GI function that we didn't cover as much today. This slide lists the topics for future sessions. So our three seminars are on the second and fourth Tuesdays of the month from 12:00 to 1:30 Eastern time. We have some exciting topics coming up, and we hope to see you at these future sessions. And with that, we thank you and hope you have a great day.

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