

CURE Webinar
Epilepsy and Dietary Therapies – How What You Eat May Control Your Seizures
Transcript

- Dr. Laura Lubbers: [00:02](#) Welcome, everyone to today's webinar. I'm Laura Lubbers and I'm the Chief Scientific Officer for Citizens United for Research in Epilepsy or CURE. And I want to thank you all for joining us today. Today's webinar is entitled epilepsy and dietary therapies.
- Dr. Laura Lubbers: [00:17](#) How what you eat may control seizures. And it will discuss how people with epilepsy, their family and their neurologist or epileptologist may utilize dietary therapies to treat some forms of epilepsy. In this webinar, two renowned neurologists will come together to present both the research and clinical perspectives of dietary therapies.
- Dr. Laura Lubbers: [00:38](#) Their presentations will speak to the mechanisms behind the use of dietary therapies to control seizures. And we'll also discuss which patients may benefit from these therapies as well as how patients can work with their doctors to navigate these options.
- Dr. Laura Lubbers: [00:56](#) This is the third installment of our 2019 leaders in epilepsy research webinar series, where we highlight some of the critical research that's being done on epilepsy. Today's webinar is being sponsored by our friends at the BAND Foundation.
- Dr. Laura Lubbers: [01:11](#) CURE's mission is to find a cure for epilepsy by promoting and funding patient focused research. CURE's robust grants portfolio has advanced epilepsy research across areas such as infantile spasms, post traumatic epilepsy, sudden unexpected death in epilepsy or SUDEP, and epilepsy genetics.
- Dr. Laura Lubbers: [01:31](#) Today's presenters are doctors, Eric Kossoff, who is the director of the Child Neurology Residency Program and medical Director of the Ketogenic Diet Program at Johns Hopkins University. And Dr. Jong Rho is the head of the Division of Pediatric Neurology at Alberta Children's Hospital, and Professor of Pediatrics, Clinical Neuroscience and Physiology and Pharmacology at the University of Calgary.
- Dr. Laura Lubbers: [01:58](#) Before Dr. Kossoff starts us off, I'd like to encourage everyone to ask questions. You may submit your questions anytime during the presentation by typing them into the Q&A tab located at the bottom of your Zoom panel, and then clicking send.
- Dr. Laura Lubbers: [02:11](#) My colleague from CURE, Brandon Laughlin will read them aloud during the Q&A portion of the webinar. We do want this

webinar to be as interactive and informative as possible. However, to respect everyone's privacy, we ask that you make your questions general and not specific to a loved one's epilepsy.

- Dr. Laura Lubbers: [02:29](#) I know there are already been a lot of questions that have come through, sent in advance and we'll try to get to everyone's questions. But if we aren't able to, we'll try to follow up with emails. I also want to mention that today's webinar, as well as all previous and future webinars will be recorded and are available on the website. So, with that, I'll turn it over to Dr. Kossoff.
- Dr. Eric Kossoff: [02:52](#) Okay. Great. So, thank you, Laura. It's a pleasure to be here this afternoon. Big fan of CURE and their advocacy and research. And I've been involved with them over the years. And so, it's really nice to be here today and speak to you all who are listening about ketogenic diets which are a hot topic in the epilepsy community.
- Dr. Eric Kossoff: [03:13](#) It's also my pleasure to lecture alongside Professor Rho. We've done this before. And I'll talk about the clinical aspects of ketogenic diets. And then, Jong will take over and talk about the basic sciences and where the field is heading in terms of mechanisms of action.
- Dr. Eric Kossoff: [03:30](#) So, first, I'll go and tell you about clinical approaches to ketogenic diets. These are my disclosures. I'm a consultant for several companies, and I'm on some data safety monitoring boards as well. So, I think before we even start diving into what the ketogenic diet is, I think it's important to realize why do we need non-pharmacologic options as we call them, things other than medications.
- Dr. Eric Kossoff: [03:55](#) Be at diet, be at DNS or neurostimulation or epilepsy surgery. And I think we always go back to the 2000 paper that was published in the New England Journal of Medicine by Kwan and Brody. It's a very famous paper at this point where they talked about what happens after you start treating patients with epilepsy.
- Dr. Eric Kossoff: [04:14](#) And we know that majority 47% will respond to the first drug, 14% if you have to go to a second drug. But if you do have to go to a third, or certainly a fourth drug, sometimes in combination, you have only a 1% chance of becoming seizure free. So, a law of diminishing returns.

- Dr. Eric Kossoff: [04:32](#) And this has been discussed for really the last 20 years about how important it is that if a second drug fails, you're technically then having refractory epilepsy and try other options. But this was 2000. And so, what just recently occurred was a revision of this paper by the same authors where they said, now, with all of the new drugs that are available and there are many new drugs that have come out in the last 20 years, maybe we're doing better.
- Dr. Eric Kossoff: [05:00](#) And maybe even despite having all these other non-pharmacologic options, we have better drugs. So, we may not need them. But what they found in this paper from just again last year was that the results were strikingly very similar. So, even with all of these new drugs on the market, there still is a large number of patients who after the second drug has failed, need to try a third option.
- Dr. Eric Kossoff: [05:23](#) And that's where the topic for today ketogenic diets may play a role for certain patients. We are in the keto community in a very interesting era, strange times that we're living in. People are on these diets for weight loss, for diabetes, for various different issues.
- Dr. Eric Kossoff: [05:44](#) These are just some screenshots of images from supermarkets and bookstores. It seems everyone knows about the ketogenic diet. Lots of patients are doing it on their own. But really, what is the science what do we know? And really, where is the field heading is what I'll talk about here today, to really dispel and really clarify some of the myths and misinterpretations of the ketogenic diet.
- Dr. Eric Kossoff: [06:07](#) And there is a lot of science. We have since 1994, 1995 had an exponential increase in the amount of publications. This is a graph showing the number of publications on the Y axis and the years on the X axis. And you can see, we now have over 300 papers every year coming out on the ketogenic diet.
- Dr. Eric Kossoff: [06:28](#) So, a lot of good science that's out there. One of the big criticisms for many years about the ketogenic diet was that, yes, this is great. Yes, we have lots of publications but we didn't have randomized control trials. And that changed in the last 10 years.
- Dr. Eric Kossoff: [06:45](#) We now have seven randomized control trials. These are screenshots of them from the articles, some on the modified Atkins diet which we'll talk about. Some on the ketogenic diet, some for children, some for adults. But lots of good evidence.

- Dr. Eric Kossoff: [07:00](#) Good trials, randomized trials, including control groups that show the ketogenic diet is, again, very effective in the treatment of epilepsy. Most of these studies are in highly refractory epilepsy. And so, one of the common questions we often get from parents, from caregivers, from patients is just how effective is the ketogenic diet.
- Dr. Eric Kossoff: [07:21](#) If you look at six months in children on the ketogenic diet, and again, this is refractory epilepsy patients, patients who fail 2, 3, 4, many more medications. In general, about 50% to 60%, will end up with a sizable seizure reduction. Anywhere from 50% improved to as you can see, they're seizure free.
- Dr. Eric Kossoff: [07:41](#) About 15% will become seizure free in fact. When you compare this to many of our new anticonvulsant drugs where maybe you have a 30% or 40% chance of having a greater than 50% response. And as I showed you in those famous studies, maybe a 1% chance of being seizure free.
- Dr. Eric Kossoff: [07:59](#) It really puts things into perspective just how effective the ketogenic diet can be and why especially in our pediatric population after two or three drugs have failed, we strongly think about dietary therapy. This really came to a head just about seven years ago in something called a Cochrane Review.
- Dr. Eric Kossoff: [08:19](#) This is a meta-analysis where they looked at all the papers out there. It's done in England. And they really tried to come to a conclusion about just how effective, and they do this for lots of different treatments. And in their review in 2012 of the ketogenic diet, you can see that quote there they felt very strongly that ketogenic diet does have short to medium term benefits comparable to modern anti-epileptic drugs.
- Dr. Eric Kossoff: [08:42](#) And so, really now in 2012, the ketogenic diet is pretty mainstream. Not every hospital offers it, but many do. And it really is used in many centers alongside of our anticonvulsant drugs. It's been an interesting year. And so, what I'll do in the next few slides before I turn things over, excuse me to Dr. Rho is highlight what's new.
- Dr. Eric Kossoff: [09:05](#) What's exciting in the field, where the science is heading. One thing that came out just a little bit less than a year ago was our ketogenic diet consensus paper. This was published in the journal epilepsy open last summer. There were 31 authors including myself and Dr. Rho.

- Dr. Eric Kossoff: [09:23](#) And many from all over the world, not just neurologists but also dietitians. And this was endorsed by the Charlie Foundation, Matthew's Friends, the Child Neurology Society and the Carson Harris Foundation. In terms of what the goal was, it was really primarily to give guidance to ketogenic diet centers.
- Dr. Eric Kossoff: [09:41](#) But also, parents and patients who were reading about the diet in regards to how best to optimally manage patients who are on ketogenic diets. And this was actually a revision of a consensus paper published about 10 years ago. And one of the things we covered in our consensus paper was how do you actually start children, primarily.
- Dr. Eric Kossoff: [10:01](#) This was a consensus paper focusing on pediatrics. But how do we start patients best on the ketogenic diet? And this is the traditional way that we start the diet. It's been around for 100 years and has not changed dramatically in terms of the traditional way to start the diet up until recently.
- Dr. Eric Kossoff: [10:18](#) And so, we typically bring children into the hospital for anywhere from two to four days depending on the center, following a 12 to 24 hour fasting period. And then, we slowly initiate providing foods like you see there on the right. During the admission, we educate the families and dietitians will very carefully calculate the ratio which is the ratio of fat to carbohydrates and protein combined.
- Dr. Eric Kossoff: [10:42](#) And the families will weigh and measure the foods out. And I think one of the things that has really dramatically changed, how we do the diet. And I think made it more accessible to patients all over the world. And I think this was reflected in our consensus paper is flexibility.
- Dr. Eric Kossoff: [10:57](#) That this traditional method that's shown here, really can be altered. It can be altered by center, altered by patients. And so, we now have four different ketogenic diets not just the classic ketogenic diet but the MCT diet, the modified Atkins diet and the diet called the low glycemic index treatment.
- Dr. Eric Kossoff: [11:16](#) And as you can see here, and they're all variants of a theme where they're all primarily high fat, low carbohydrate diets. Some of the biggest differences actually are in the amounts of protein between the different diets and whether they're done as an outpatient, an inpatient and how we counsel families.
- Dr. Eric Kossoff: [11:32](#) But again, showing that there is flexibility and that one size does not necessarily fit all for all patients. In our consensus paper, we

really did highlight some of this that the fluid and calorie restriction that we had been doing for many decades was likely no longer necessary.

- Dr. Eric Kossoff: [11:49](#) We told providers that you can pick which diet you wish to pick. Although, we generally prefer the ketogenic diet for instance due to it being more carefully monitored by dietitians. And then, the modified Atkins or low glycemic index treatment for teenagers and adults.
- Dr. Eric Kossoff: [12:06](#) We asked our centers, do you admit for the diet? And although 80% still do bring children into a hospital for the diet, the overwhelming vast majority said it really is up to you. It's up to the parents and it's up to the center and can be done as an outpatient.
- Dr. Eric Kossoff: [12:20](#) Similarly, we asked if you fast at the start of the diet, and only 28% are still actively fasting children on the ketogenic diet. However, again, it is flexible, 68% said it's optional. And I think we really tried to express this in our consensus paper.
- Dr. Eric Kossoff: [12:36](#) And I think the message to anyone who's listening today is that really, the diet is not one size. Again, it can be very flexible and maybe for one child be very different than for another child, and that's okay. The other important question that's really changed over the last 10 years is who should go on ketogenic diets?
- Dr. Eric Kossoff: [12:55](#) Back in 1993, in the first edition of our ketogenic diet book, this was a great book but it had only two paragraphs devoted to who should go on the ketogenic diet. And as you can see there in this screenshot from that book. The discussion back then was that almost anybody could try the diet, myoclonic, absence, Lennox-Gastaut, partial, just give it a try and see what happens.
- Dr. Eric Kossoff: [13:20](#) And we've come really a long way. This is table one of our new consensus paper, where we do know that there are some epilepsy conditions where the diet is particularly beneficial not just necessarily a 50 or 60% response but maybe a 70% response.
- Dr. Eric Kossoff: [13:36](#) And these are the conditions listed here where we have that evidence that the diet is extremely effective. And then, in the condition as you can see, the fourth... fifth one down, excuse me, Glut 1 deficiency, we have evidence that it's 95% effective.

- Dr. Eric Kossoff: [13:51](#) So, the ketogenic diet is really the best treatment for that condition. And so, this message was really instrumental when we created our consensus paper to get this word out about how effective it can be for these epilepsies. One of the hot new topics that we touched on a little in our consensus because there had been a prior guideline consensus published in 2016 discusses infants.
- Dr. Eric Kossoff: [14:15](#) For many years, infants were not seen as a population that should be put on the ketogenic diet for various reasons. And now, we've come almost a complete opposite that we have evidence that infants may be the ideal population to go on a ketogenic diet due to all of the ketogenic formulas that are available nowadays.
- Dr. Eric Kossoff: [14:32](#) And this was published again about three years ago from a group in Europe showing just how effective it can be. And then, going to the opposite extreme, there's been a lot of interest in using ketogenic diets for adults with epilepsy. A lot of adults certainly have intractable epilepsy.
- Dr. Eric Kossoff: [14:48](#) They may have pediatric syndromes that they did not outgrow. And so, they're very interested in trying ketogenic diets. And we've had an adult diet epilepsy center at Johns Hopkins since 2010. It's extremely active with over 300 adults seen.
- Dr. Eric Kossoff: [15:03](#) And about a fifth of those patients are on a diet when they come to us. But 80% have not been. I think giving us really the message. And I think most centers are seeing this that there is an interest out there amongst adults who have never been offered a diet before but are highly motivated to try a modified Atkins or ketogenic diet to improve their epilepsy.
- Dr. Eric Kossoff: [15:25](#) And when Dr. Mackenzie Cervenka who runs our Adult Epilepsy Diet Center looked at her results, you can see they look relatively similar to what we see in pediatrics, with about 15% to 16%, becoming seizure free. And about overall half of those patients having a meaningful or over 50% response rate.
- Dr. Eric Kossoff: [15:45](#) The diet is not without side effects. It is important. And as we, as neurologists spend time with families that we explain to them that the diet needs to be monitored carefully by a ketogenic diet center looking for these side effects. And there are some common ones that tend to be often GI related like reflux or constipation.

- Dr. Eric Kossoff: [16:04](#) But then, some of the more sporadic and rare side effects, kidney stones, effects on cholesterol, vitamin D, bone fracture, some of them are some of the long-term effects. There's a lot of active research being done to try to find ways to make these side effects less common. Most of them seem to involve supplementation.
- Dr. Eric Kossoff: [16:24](#) So, most of our ketogenic diet families, when we start the diet, begin other supplementation, the most common ones being multivitamins with calcium and vitamin D. But as you can see here, there are many optional extra supplementations that you can provide that may be advantageous and help prevent some of those side effects from happening.
- Dr. Eric Kossoff: [16:44](#) So, we do spend a lot of time making sure that our ketogenic diet families are getting all of their supplements to keep them safe and keep them healthy while they're on ketogenic diets. This is actually our table six in our consensus paper. And you can see here that there's a lot of management, a lot of follow-up that occurs when we see a child and their family back in our ketogenic diet clinic.
- Dr. Eric Kossoff: [17:06](#) Some of that includes making sure that the supplements are being provided. But also, checking lab work, making sure the diet is really meeting the goals of each individual child. So, we do spend a lot of time in our clinic making sure families know that there are risks as well as potential benefits to dietary therapy.
- Dr. Eric Kossoff: [17:25](#) And so, before I hand over to Dr. Rho, just to summarize. We've had a lot of good experience over now about 100 years showing that the ketogenic diet, be it ketogenic or modified Atkins or variants work for about half of all patients, children and adults with epilepsy.
- Dr. Eric Kossoff: [17:41](#) Really, we're in an era now of lots of flexibility both in terms of which diet you pick and how you start the diet and how you follow them up. And I think this is really made the diet more accessible and available all over the world. We do know what the indications are and we're trying to get those children and adults on the diets sooner rather than later.
- Dr. Eric Kossoff: [18:01](#) And then, finally, that there are side effects. This is a diet that does have medical potential risk. But most of these side effects are predictable. And with supplementation, may be very preventable as well. So, thank you. This is our ketogenic diet center. And I will be available after Professor Rho's presentation to help answer questions. So, thank you.

- Dr. Jong Rho: [18:26](#) Thank you, Laura and Eric. Thank you all for participating in the webinar. In the next 10, 15 minutes, I'm going to cover the basic science and the basic translational subject of how does dietary therapy like the ketogenic diet actually work.
- Dr. Jong Rho: [18:41](#) And while this may sound a very esoteric question, in many ways, the professional communities throughout the world and even the lay public are really interested in the fascinating clinical effects of the diet. What I'm going to do is walk you through, I think, a broad overview of how we think the diet might work in in a simplified way.
- Dr. Jong Rho: [19:02](#) The concept notion is very straightforward. Why do epilepsies occur? Why do seizures occur? In part, probably because of abnormal metabolism in brain cells. You need energy to think and act normally. But you also need energy to produce seizures and perhaps some abnormalities in that context, may be a contributory factor.
- Dr. Jong Rho: [19:27](#) So, at the end of this very brief overview, you'll appreciate the fact that there's increasing evidence that the ketogenic diet works in part by improving metabolism and through some unique pathways that have not been really fully explored in the epilepsy research world.
- Dr. Jong Rho: [19:44](#) So, when we look at the treatments for epilepsy, we often think of anti-seizure drugs or anticonvulsants as they're known. And we know that they act on certain targets within the cells. This is a picture of a typical neuron with all of the dendrites, here are the processes.
- Dr. Jong Rho: [20:03](#) And then the axon and then the connections to the adjacent neurons. And we do know that there are inhibitory connections as well as excitatory connections. And that the balance between inhibition and excitation may be critical towards whether abnormal discharges occur, such as we see with seizure activity.
- Dr. Jong Rho: [20:23](#) If we look at what's happening at a molecular level, for instance, at this inhibitory synapse, we see that there's a presynaptic terminal, there's postsynaptic membrane, got receptors on the postsynaptic side. And that if we look at key neurotransmitters such as GABA or gamma aminobutyric acid, this is a transmitter that's important for controlling inhibition in the brain.
- Dr. Jong Rho: [20:49](#) We can see that a number of different drugs that we use clinically such as benzodiazepines, barbiturate compounds like phenobarbital can actually augment or potentiate GABA A

receptor function at a postsynaptic level. And so, this is our conceptual notion of how most of these drugs work.

Dr. Jong Rho: [21:07](#) They have specific targets on cell membrane receptors or transporters and that that's somehow dampens excitation in various ways. However, if we look at the deep within the cell and how the cell functions to achieve homeostasis, we see a much more complicated scenario of biochemical pathways, substrates and enzymes that actually are important for normal functioning.

Dr. Jong Rho: [21:34](#) And that when we look at a particular portion of the so called metabolic complex landscape, we see a lot of different things happen in many different ways with intersections and bifurcations and bidirectional type of interactions, which make it really hard to determine how tweaking any part of this might produce a positive effect.

Dr. Jong Rho: [21:54](#) And this is really where I think the ketogenic diet because we think of this as not so much a single mechanism but multiple mechanisms when taken together provided beneficial anticonvulsant effect. Back in 2007, this was our schematic view of how the ketogenic diet through elevations in fatty acids and reduction in glucose through parallel and potentially synergistic ways, collectively put together an anticonvulsant action.

Dr. Jong Rho: [22:21](#) Five years later, this got a little more complicated with some inclusion of mechanisms that were described by investigators brought newly into the field of epilepsy. And this has been one of the advantages that the scientific curiosity underlying how the diet works actually brings forth a lot of qualified scientists that can give us insights into this.

Dr. Jong Rho: [22:40](#) And here, one of the other things that was posed as a question was, because of the neuroprotective activity of the diet, can the ketogenic diet produce a disease modifying effect? So, called anti-epilepsy genesis. And certainly, some of the targets that have been described would provide a scientific rationale for thinking of that.

Dr. Jong Rho: [23:02](#) In more recent years, we've come to appreciate the notion that the brain cell, the neuron doesn't really sit in isolation. And that it really involves the interplay between the micro vasculature or the circulatory system within the brain, as well as glial cells or astrocytes in particular, composing the so-called neurovascular unit.

- Dr. Jong Rho: [23:22](#) These things work together to provide energy for normal cellular function. And when things go badly, then there's a disruption in key processes. Again, we focus on the excitatory or inhibitory synapses because that's what mediates activity. And we've often thought of epilepsy as partly consequence of too much excitation, too little inhibition, et cetera.
- Dr. Jong Rho: [23:46](#) And that EI balance is what dictates the genesis of seizures. But metabolic substrates such as ketone bodies that are made by the ketogenic diet can produce ATP molecules that are useful for functioning. These energy molecules can also dampen excitation through receptors such as adenosine receptors.
- Dr. Jong Rho: [24:05](#) And they can also link with particular types of ion channels such as ATP sensitive potassium channels that can hyperpolarize the cell membrane or dampen excitation through that mechanism. There are other things that have been described by leading investigator such as determinants of whether cell lives or dies.
- Dr. Jong Rho: [24:25](#) They're not just involved with this process called apoptosis, but they can also modulate membrane bound channels such as KTP channels. And then, ketones can have effects in blocking excitatory neurotransmitter relief. So, we dampen the excitation that way.
- Dr. Jong Rho: [24:41](#) Alternatively, medium chain triglycerides such as decanoic acid can act an anti-seizure drug and actually block excitatory receptors such as AMP receptors. There's a drug called Perampanel which we use in clinical practice that is thought to act principally on blocking these so-called AMP receptors.
- Dr. Jong Rho: [25:01](#) On the inhibitory side, up in the upper right, we see the ketone bodies have been proposed to be important for the production of inhibitory molecules like GABA. And then, when it's done in the presynaptic terminal, it increases inhibition at the postsynaptic terminal enhancing hyperpolarization thus dampening excitation.
- Dr. Jong Rho: [25:21](#) There are other things that happen too. Simple molecules like glucose which are critical for brain function can be metabolized to various downstream substrates such as pyruvate and lactate. And the enzymes that regulate this are thought to be a key target for regulating excitability.
- Dr. Jong Rho: [25:37](#) And that can be done through various actions that bring together the astrocyte and the neuron together. And one of the classic ways that does that is a so-called lactate shuttle. So, that

the energy that the neuron needs to fire normally may impart rise from lactate being pumped into to the neuron by a mono carboxylic acid transporter.

- Dr. Jong Rho: [26:00](#) And then, these studies which have been published leading journals have given us a new view at how metabolism affects synaptic activity through the so-called tripartite neurovascular units. And if we look a little bit more deeply into mitochondria, we can see that since mitochondria are responsible for the vast majority of ATP molecules being produced, we know that substrates such as ketone bodies for example, can enhance ATP production. can reduce the formation of negative species such as reactive oxygen species.
- Dr. Jong Rho: [26:36](#) And facilitate greater energy production and reserve within the brain. And the way to think about this is that the cells functions much like a city. And so, that you have the energy grid and then we got the energy stations that if one blows perhaps, the city will still be functional.
- Dr. Jong Rho: [26:54](#) But if a sufficient number become dysfunctional, then the city shuts down because they you don't have enough to keep the lights on, so to speak. And many of these mechanisms that have been proposed over the years have evolved upstream pathways such as glycolysis.
- Dr. Jong Rho: [27:11](#) And, then, we have alternative pathways where you can divert glucose into the pentose phosphate chunks. We have increased fatty acid oxidation which could also be related to enhance neurotransmitter synthesis.
- Dr. Jong Rho: [27:32](#) Increasing TCA cycle function and providing so-called ANA parodic substrates for carbon restoration can also be anticonvulsant. And there are a number of other mechanisms downstream within the mitochondrial inner membrane that can help with homeostasis as well. And these are some of the studies that have been published.
- Dr. Jong Rho: [28:02](#) So, if we take a simple molecule like ketone bodies after which the ketogenic diet is named, this is just a schematic on the left-hand side, a presynaptic terminal, where all the sites of action that have been recently reported are relevant to ketogenic diet action or ketone bodies in particular. Now, on the right, it's a schematic of a cell.
- Dr. Jong Rho: [28:21](#) So, you can look at the mitochondria in the lower left. And it even has epigenetic actions at the level of histones that could

regulate gene expression. So, I think a major point here is that a simple molecule like ketone bodies, for example, can have a number of different actions at many different levels that collectively taken together can produce anti convulsive as well as neuroprotective effects.

- Dr. Jong Rho: [28:47](#) Now, the most intriguing study that has come out over the last few years has been the notion that when you eat a high fat low carb diet, it affects the gut microbiome. And it's been known for many years that the microbiome was established very early in life usually typically between birth and the first year of life.
- Dr. Jong Rho: [29:11](#) And that it has the correlative changes with regard to synaptic plasticity and neuronal development. It's also been linked to the onset of mental health disorders not just normal brain development. And now, interestingly, last year, investigators at UCLA proposed that the primary mechanism by which the ketogenic diet works is through by alterations of the gut microbiota.
- Dr. Jong Rho: [29:34](#) And in this very intriguing paper, what they did was to basically feed a couple animal models of epilepsy with the ketogenic diet compared it to control fed animals. And they analyzed the various bacterial species that were there over the course of a two-week treatment.
- Dr. Jong Rho: [29:50](#) And what they found were prominent changes in a few key species. If you note the light blue there, the Akkermansia muciniphila species appeared to be one that stuck out over the course of the study. What they went on next was to examine the blood metabolome, and they found a decrease in so-called gamma-glutamyl amino acids.
- Dr. Jong Rho: [30:10](#) And which basically means that the change in the blood metabolome would predict a change in brain metabolites. And specifically, an increase in GABA and a decrease in glutamate, which was shown when they looked at the hippocampal levels of GABA and glutamate using analytical techniques.
- Dr. Jong Rho: [30:28](#) And so, their thesis was that a high fat ketogenic diet alters the gut microbiome, changes the metabolome and that this subsequently changes the neurochemistry of the brain to favor the production of GABA and to lessen the glutamate which is on the excitatory side.
- Dr. Jong Rho: [30:45](#) Now, while this is very intriguing and certainly one that has led to quite a bit of interest and speculation as well as research, we

need to ask the question, what are the human data with regard to ketogenic diet and the gut microbiota? As it turns out in this small paper that was published earlier this year, the various species that were changed by the ketogenic diet vary considerably.

- Dr. Jong Rho: [31:09](#) And in fact, where sometimes discrepant with what the animal literature has shown. And if you look at other studies outside of epilepsy, notably autism, the ketogenic diet appears to induce changes that are quite different than what was seen in the rodent models of epilepsy.
- Dr. Jong Rho: [31:26](#) So, we have a lot more to learn about the impacts of the diet on the microbiome. And to determine whether this is really epiphenomenon or whether this is causally related to an anticonvulsant action. So, we took this schematic of the key research over the last few years.
- Dr. Jong Rho: [31:43](#) And now, we have to consider whether the blood metabolome changes induced by the gut microbiome has a direct effect on controlling seizures. Finally, in the last couple of minutes, I want to just highlight the fact that there is growing evidence that the ketogenic diet and in variations thereof induce neuroprotective actions through a number of different mechanisms.
- Dr. Jong Rho: [32:07](#) And these are not single, they're parallel. They interact with each other. But at the end of the day, if you look at the bottom portion of the slide, you can see that favoring bioenergetic stability, reducing free radical formation, and maintaining synaptic integrity or homeostasis all work together to provide neuroprotection and resistance against disease.
- Dr. Jong Rho: [32:28](#) And certainly, in this intriguing study published a few years ago, which looked at whether the ketogenic diet actually affects the process of epilepsy development, IE epilepsy genesis. This animal study showed that if you fed one group a ketogenic diet, but then another group, you fed the diet, but then you converted them back to a controlled diet, the protective effects against kindling were actually preserved despite discontinuation of the diet.
- Dr. Jong Rho: [32:56](#) So, in summary, I hope that I've given you a little taste of the emerging science that shows that metabolism-based treatments for epilepsy, they induce a number of different molecular and cellular actions quite distinct from what we see with regard to anti-seizure drugs.

- Dr. Jong Rho: [33:12](#) And that even simple molecules like beta hydroxybutyrate can have a whole number of different actions both within and outside the nervous system that can provide some measure of protection. And that many of the so-called mechanisms of actions of diet-related substrates and enzymes are relevant to neuro protection, which then I think poses the question are they antiepileptogenic.
- Dr. Jong Rho: [33:34](#) And really the bottom line to all of this is that the science underlying dietary therapies for epilepsy is now mainstream and validated compared to 10, 15 years ago when we had very little information to go on. And with that, thank you for your attention.
- Dr. Laura Lubbers: [33:50](#) Terrific. Thank you, doctors Kossoff and Rho. Really appreciate your presentations. We will now begin the Q&A session. If you have questions again, please submit them in the Q&A tab located at the bottom of your Zoom panel and send them and Brandon will read them aloud. I know we already have a lot of questions that have come in. So, why don't we go ahead and get started?
- Brandon Laughlin: [34:13](#) Absolutely. And you are correct. We have. As you might guess, many of these questions are clinically based. But I'm going to go ahead and put these out to both of you and field as you see fit. One of the questions that came in based off metrics, is the research around the timeline on how long the average person stays on the ketogenic diet? And then, the second part of that question is, what are some of the factors that that you look into when coming off the ketogenic diet?
- Dr. Eric Kossoff: [34:52](#) So, I can answer that, can people hear me beyond? Yes. Okay. Great. So, yeah. The duration of the ketogenic diet is a question that has been looked at with some research both in terms of the minimum time, how long you should give it and perhaps the case where it's not effective.
- Dr. Eric Kossoff: [35:12](#) But also, maybe more interestingly, the maximum time at which point is maybe the ketogenic diet outlived its usefulness or maybe it's led to the benefit you're going to see and you can come off the diet without negative effects. And so, most of the time, we will tell families give the diet at least two to three months.
- Dr. Eric Kossoff: [35:32](#) There is some scientific evidence that if you're having seizures frequently enough, even within two to three weeks, you're going to see potential benefit. Unlike some therapies, the

ketogenic diet seems to work relatively quickly, maybe again within a week or two.

- Dr. Eric Kossoff: [35:48](#) And so, we generally do still recommend for families that make the commitment and engage in the ketogenic diet as a therapy to give it two to three months before giving up if they perhaps don't see any benefit. On the opposite end in terms of how long to stay on the diet, the tradition, at least in the pediatric world is two years similar to medications.
- Dr. Eric Kossoff: [36:10](#) And so, if you're doing well or especially if you're seizure free, at about two years on the ketogenic diet will often check in EEG. And if you have an epilepsy that potentially could be outgrown, we will slowly wean the diet by reducing the ratio usually every week or two until the diet has been stopped and you're back on regular foods.
- Dr. Eric Kossoff: [36:31](#) For certain epilepsies like Glute 1 deficiency where diet may be helpful even into adulthood, you may stay on the diet much, much longer. For some epilepsies like infantile spasms, there was a randomized trial comparing six months to two years and they found six months was just as effective in terms of diet duration.
- Dr. Eric Kossoff: [36:51](#) And so, for that epilepsy, we may go shorter periods of time. But in general, on average, it's about one or two years in the pediatric world. In the adult world, they often stay on for longer if it's helping. But in pediatrics about two years.
- Brandon Laughlin: [37:06](#) Wonderful. Thank you. Going along with that, somebody actually asked a follow-up question about what are the steps that someone might take to initiate the diet? Meaning, blood work, other tests, et cetera.
- Dr. Eric Kossoff: [37:24](#) Right. And it gets to the point I was peeking at some of the questions as they were coming in that it really is important that this should be done with supervision at an epilepsy center. We do have families that are starting on their own.
- Dr. Eric Kossoff: [37:37](#) And sometimes it works out but other times they can have adverse effects or even just not the efficacy they were hoping for. So, it really should be done in an epilepsy center. There are labs that are recommended to be done in advance to make sure there's no reason that the diet could potentially cause a problem.

- Dr. Eric Kossoff: [37:56](#) As Dr. Rho mentioned it is a metabolic big change to the neurons into your body. And so, it can have some adverse effects if there is a problem in metabolizing the fats. So, we usually recommend labs to be done in advance. We usually as well spend a lot of time talking to the families just about goals, expectations.
- Dr. Eric Kossoff: [38:17](#) What's going to happen during the week, maybe changing their medications to a tablet formulation, so there's less carbohydrates. We often will do that. And so, there's a fair bit that goes in before the ketogenic diet is started. And a lot of that does involve neurologists, it involves dieticians and really families just reading and getting information before jumping down the road of the ketogenic diet.
- Brandon Laughlin: [38:44](#) Okay, great. I'm going to ask this question next, because we actually received this question prior to the webinar and then actually by a few folks attending the webinar, is there potential harm be it cardiovascular risks, renal risks, hepatic risks of somebody on the ketogenic diet long term?
- Dr. Eric Kossoff: [39:05](#) Yeah. I can answer that and maybe Jong can too. This is actually a topic that we're really actively looking at. There are a lot of investigators trying to look into the long-term side effects. At least right now, the three major long term effects that have at least been reported are bone density changes and bone fractures can happen if you're on ketogenic diets for over five to six years.
- Dr. Eric Kossoff: [39:29](#) This is true for a lot of our anticonvulsant drugs. And it may be, again, as many patients are on both more related to drugs. But we do certainly see that this can happen with ketogenic diet therapy. So, bone health is one. Growth is something that we do see as a problem in children who were on ketogenic diets for prolonged periods of time.
- Dr. Eric Kossoff: [39:51](#) And this may have more to do with again the bones than the actual diet components. But children who are on the ketogenic diet, sometimes their height velocity can be affected if they're on it for many years. And then, the last one, at least so far appears to be kidney stones.
- Dr. Eric Kossoff: [40:07](#) And so, if you're on the diet for long periods of time, we make sure that your kidneys are being monitored. We often will use a supplement called polycitra to help prevent kidney stones. And so, those are the three at least current in 2019 long term side effects that we're aware of.

- Dr. Eric Kossoff: [40:24](#) But there's a lot of research being done looking at cardiovascular health, carotid artery changes and looking at long term effects that we really just don't know about. But not knowing doesn't mean it's not a potential risk or side effect. So, stay tuned. And I think we'll have more research in this to come.
- Brandon Laughlin: [40:45](#) Great. Speaking of research and the long-term effects, if there has been success on a medically managed ketogenic diet, has there been any research or does science suggest that a person could have a higher chance of experiencing seizures again?
- Dr. Eric Kossoff: [41:08](#) Does the question mean, if they've become seizure free on the diet and-
- Brandon Laughlin: [41:12](#) Correct.
- Dr. Eric Kossoff: [41:12](#) And off? Yeah. I mean, there's been a little research into how you wean the diet and what happens. And before I jump to that question I guess, most of the studies would say about 80% of the time, what happens on the diet will remain when you come off a diet.
- Dr. Eric Kossoff: [41:30](#) So, for example, if you're seizure free, you stop the diet, and this is again in pediatrics. 80% of the time, your seizures will remain gone when you come off the diet. And if you're 90% better and you wean the diet in odds, you'll stay 90% better without it. But there certainly are children,
- Dr. Eric Kossoff: [41:48](#) it tends to be more in the short term as you wean the diet, their seizures can get worse and you go back on the diet. But we, getting to the question, there are some patients who maybe years later depending on the epilepsy they have may have a recurrence. We are certainly seeing in our adult epilepsy diet center...
- Dr. Eric Kossoff: [42:07](#) some patients who were on the ketogenic diet when they were young children were taken off the diet, maybe tried a few more medications over their adolescence. Now, they're adults and they go back on the diet in adulthood. It's a small number of patients, but certainly, it happens in the diet. Again, it seems to be equally effective in adults as in children.
- Brandon Laughlin: [42:29](#) Great, thank you. Next question actually is a little bit more mechanism based. Are there ways to increase ketosis when you follow a diet that's more based on meat?

- Dr. Jong Rho: [42:43](#) So, there are several ways you could do that. Obviously, fasting calorie restriction is the classic way you induce ketosis. If you take the diet and it's high in fats then the fatty acid oxidation will produce the ketone bodies. There's a growing number of sources for ketone supplements that are currently available through the web.
- Dr. Jong Rho: [43:06](#) And the number of experimental studies looking at various formulations of ketone bodies such as ketone esters that have been shown in animal models to be effective. We don't have any human data yet, but those are being planned. The ketone esters are interesting because they're orally ingestible. They can be broken down by the body through enzymes that are resident in the gut as well as in the bloodstream, the so-called ester ACES.
- Dr. Jong Rho: [43:36](#) And that what that does is it produces ketones to be elevated in your blood. There are also certain foods that have a higher tendency, perhaps to produce ketone bodies, the so-called MCT diet, for example, has been historically observed to maybe induce greater ketosis.
- Dr. Jong Rho: [43:54](#) But again, in terms of whether that's a proven fact or not. I think Eric can certainly comment on that better than I can. So, I think ketones because of their pleiotropic mechanisms that have been described in the last five years, there's a growing interest in trying to figure out a way of providing ketone supplements, enhancing ketosis without necessarily going to the traditional diets themselves.
- Dr. Jong Rho: [44:21](#) It's still early days. I would be cautious in the sense that not all available formulations are necessarily safe in large quantities and these things are constructed also with various salts and ways of making them ingestible. So, they may produce some degree of toxicity as well. And keep also in mind that the relative amount of ketosis is important.
- Dr. Jong Rho: [44:45](#) Mild to moderate degrees of ketosis that we see in clinical therapy with the diet is tolerated. Although, certainly diabetics who go into major ketoacidosis, something we don't see in ketogenic diet treatments, high levels can actually induce health problems and in the extreme case, coma. So, dose does differentiate a remedy from a poison. So, as a famous pharmacologist from centuries ago would say.
- Brandon Laughlin: [45:15](#) Great. Thank you, Dr. Rho. So, the next question actually, we received in in many different forms. So, I'm going to try to generalize it as best I can, is there research into the

effectiveness of the diet for those who experience nocturnal seizures versus those who experienced seizures during the day?

- Dr. Eric Kossoff: [45:38](#) Yeah. I mean, it's an interesting question. It hasn't really been looked at in that manner before. We certainly see a lot of pediatric patients who have more seizures at night than during the day. And the diet seems to be effective for those types of epilepsies as well as those that have more during the day. It doesn't seem to make much of a difference.
- Dr. Eric Kossoff: [46:03](#) We do sometimes target the way we provide the diet based on when the seizures are happening. So, in some children who have predominantly nocturnal seizures, we may give a higher ratio or an extra fat supplement at bedtime to try to get their ketones higher during the evening that can sometimes be successful.
- Dr. Eric Kossoff: [46:22](#) But to my knowledge, I don't know if Jong knows. I don't know anyone who's looked specifically at treating those only with nocturnal seizures versus those with daytime or with maybe a combination. I think we just don't know that yet.
- Dr. Jong Rho: [46:35](#) It's a very interesting question, certainly. The topic for more focused future clinical studies. What I can say from the basic science side is that it's known that the epileptic brain has derangements in sleep wake cycling and rest activity cycling. So, there's perturbations that occur and it's not surprising that many forms of epilepsy actually manifest at night for example or during sleep wake transitions.
- Dr. Jong Rho: [47:02](#) When you actually feed epileptic mice or animals with the ketogenic diet, there are restoration of the sleep wake cycling and the rest activity cycling such that the prediction would be that would have perhaps efficacy, perhaps on those that tend to manifest mostly during sleep, for example. But we don't have any real strong clinical data to show that, that'd be a subject for an interesting clinical study for sure.
- Brandon Laughlin: [47:34](#) Great, thank you both. Next question. An interesting question. Are there quantifiable EEG changes once somebody is on the diet?
- Dr. Eric Kossoff: [47:47](#) Yeah, that's actually somewhat controversial topic. There has been some evidence that supports that. That suggests that there can be changes in the EEG sometimes within a few weeks. There's one study out of Texas that suggested that if there was a decrease in the amount of slowing, slowing someone

suggesting a diffuse change to the brain, not necessarily an epileptiform one.

- Dr. Eric Kossoff: [48:12](#) But if there were changes to slowing within that first month, they were much more likely to respond in terms of seizure reduction later on to the ketogenic diet. And there have been some studies that have looked at certain epilepsies where they follow the EEG and shown that yes, the EEG can improve just like the clinical seizures can improve.
- Dr. Eric Kossoff: [48:30](#) But on the other hand, there actually have been other papers that have really said there's a big disconnect. The seizures may seem like they're clinically improved but the EEG may actually not have changed very much. There's one epilepsy called ESES or Epilepsy with Status Epilepticus and Sleep.
- Dr. Eric Kossoff: [48:50](#) Where really the goal of that treatment for that condition is to improve the nocturnal EEG. And the data is actually relatively mixed about how just affected the diet is and improving that EEG. Patients may be better but the EEG doesn't always change very much. So, it's a hot topic. There's a lot of debate and discussion.
- Dr. Eric Kossoff: [49:09](#) When we see families and we talk to them about the ketogenic diet at our center, we really focus primarily on the clinical seizures. And actually, there's some good data now about cognitive benefits out of the Netherlands. But usually, we don't promise or guarantee for any patient that the EEG is necessarily going to change.
- Brandon Laughlin: [49:30](#) Great, thank you. Actually, we've received a few questions based off the effectiveness of the ketogenic diet with certain medicines and things of that nature. Has there been research into the use of the ketogenic diet with AEDS? And also, does the ketogenic diet work without any... when somebody is not on any AEDs?
- Dr. Eric Kossoff: [49:58](#) Yeah. I can tackle that. It's usually a partnership. We tell families that for most patients, and actually we have a recent study that suggests that it's again, about 82%, 83% of our families still remain on medications, it might be fewer medications, but it's usually not the ketogenic diet by itself.
- Dr. Eric Kossoff: [50:18](#) Although, that did happen in about 20% of patients who usually did very well. We were able to wean them off their medications. But we tell families for the most part, it is a partnership. There is

no one drug that is negatively interacted per se by the ketogenic diet.

- Dr. Eric Kossoff: [50:35](#) We know that certain drugs you have to be a little bit more cautious for side effects. So, topiramates, zonisamide, you have a slightly higher chance of acidosis. Valproic, you may see a higher chance of carnitine deficiency. You might see reduced ketosis if you're on valproic.
- Dr. Eric Kossoff: [50:51](#) But these drugs are not contra indicated so to speak, it's not a situation where they have to stop those medications. And on the other hand, we also don't have any evidence that any one drug seems to be really effective with the ketogenic diet.
- Dr. Eric Kossoff: [51:06](#) There are lots of drugs often tried. But we don't have any one drug in particular, that seems to be particularly beneficial. If anything, we have some older data that the Vagus nerve stimulator may in combination with the ketogenic diet be potentially synergistic, but that's obviously not a medication.
- Dr. Eric Kossoff: [51:23](#) So, I think as more patients are put on different therapies, we can look for those beneficial synergistic effects. But at least right now, we tell families that any drug is fine, no drug is perfect with the diet, and we'll just do it case by case.
- Brandon Laughlin: [51:39](#) Interesting. I actually going back to ketosis, Dr. Rho, is there a range that's recommended for ketosis in terms of blood meters?
- Dr. Jong Rho: [51:51](#) Well, I think much like when we use anti-seizure drugs and we do blood levels of the drugs, we have a rough idea based on clinical experience where patients should be or could be, but these are guides. There are no absolute numbers and everyone's response is going to be a little bit different.
- Dr. Jong Rho: [52:10](#) And in fact, the same level in two different patients, one may tolerate very well, the other one may get very sleepy or tired. So, I think the levels themselves are really a guide, maybe Eric can comment on that as well.
- Dr. Laura Lubbers: [52:27](#) Yeah. No, I totally agree with Jong. We tell families that the ketone levels are like a drug level and every child is different. Some children only need to have relatively low ketone levels and the low glycemic index, which is one of our dietary therapies.

- Dr. Laura Lubbers: [52:43](#) You have extremely low ketone levels and actually in the urine, they're undetectable, yet these children do very well. And so, I think, especially when we hear the mechanistic potential options for why the diet works as Dr. Rho presented, there's so many mechanisms at work that ketones may just be part of it.
- Dr. Laura Lubbers: [53:03](#) And it may suggest the body has made this metabolic change but it may not really be the true aspect of why the diet's effective. So, I think every child is different. We try to keep a calendar of what their ketone levels are, and in a sense for where maybe, okay, the ketone levels seem to correlate with seizure control and try to achieve that for every child individually.
- Brandon Laughlin: [53:26](#) Right, thank you. We actually have time for one final question. But like Laura said, we'll do our best to get back to those questions that maybe were unanswered. But I thought a good final question might be to discuss maybe some of the resources that somebody who is considering the ketogenic diet or is maybe new to the ketogenic diet, what resources are available to those patients and to those families?
- Dr. Jong Rho: [53:55](#) Well, one major website that I would recommend is the Charlie foundation for ketogenic therapies website. So, <https://charlifoundation.org>. All one word, charlifoundation. It's a good place to start. They've been around for a long, long time. And the fact the Charlie Foundation was founded in the mid-1990s. And it was really seminal in catalyzing both clinical interest in research in the ketogenic diet. That would be my recommendation. Eric?
- Dr. Eric Kossoff: [54:30](#) Yeah. Absolutely, Jong. And we've actually looked at this in a research way and really families find out about the ketogenic diet from the internet nowadays is not all from books and magazines and other resources. It really is the internet. So, I always recommend the Charlie Foundation webpage. There's another organization in England called Matthews Friends.
- Dr. Eric Kossoff: [54:52](#) So, it's site, S-I-T-E, [.matthewsfriends.org](https://matthewsfriends.org). That like the Charlie Foundation is a parent support with great resources and articles that patients can download. I also have helped the Epilepsy Foundation through their webpage, which is epilepsy.com. Good information about ketogenic diet along with all the other therapies as well. But those are probably my top three.
- Brandon Laughlin: [55:20](#) Great. Well, thank you both. Laura, I'll turn it back over to you.

- Dr. Laura Lubbers: [55:25](#) Well, thank you so very much for all the very helpful information. This concludes our webinar about epilepsy and dietary therapies. Again, I want to thank our presenters, Dr. Kossoff and Rho for your presentations and the BAND Foundation for sponsoring today's webinar and the rest of our webinars throughout this year.
- Dr. Laura Lubbers: [55:43](#) I'd also like to thank the audience for your amazing attention, your terrific questions both during the session and prior to it. If you have additional questions about the topic, wish to learn more about CURE's research programs or future webinars, please visit our website, www.cureepilepsy.org.
- Dr. Laura Lubbers: [56:02](#) I also encourage you to check out this month's Seizing Life podcast at seizinglife.org which tackles the same topic by exploring the clinical aspects of the ketogenic diet. Finally, we hope you will join us for our future webinars including our next webinar, which is on July 10, which is surgical approaches in epilepsy. With that, I want to thank you all. Enjoy the rest of your day.