

# 2017 Glut1 Deficiency Foundation Conference Summary Report



gratitude and credit to Kris Engelstad and all the speakers for helping prepare the presentation summaries

Glucose Transporter Type 1 Deficiency Syndrome is regularly referenced using a variety of terms, and these individual summaries were no exception. In the interest of clarity and uniformity, we have used the term **Glut1 Deficiency** throughout the summary.

Glucose Transporter Type 1 Deficiency Syndrome is also known and referenced as: Glut1 Deficiency, G1D, Glut1 DS, Glut-1 DS, Glut1, Glut-1, Glut 1, GLUT1, Glut1D, and De Vivo Disease



## 2017 Glut1 Deficiency Foundation Conference Summary

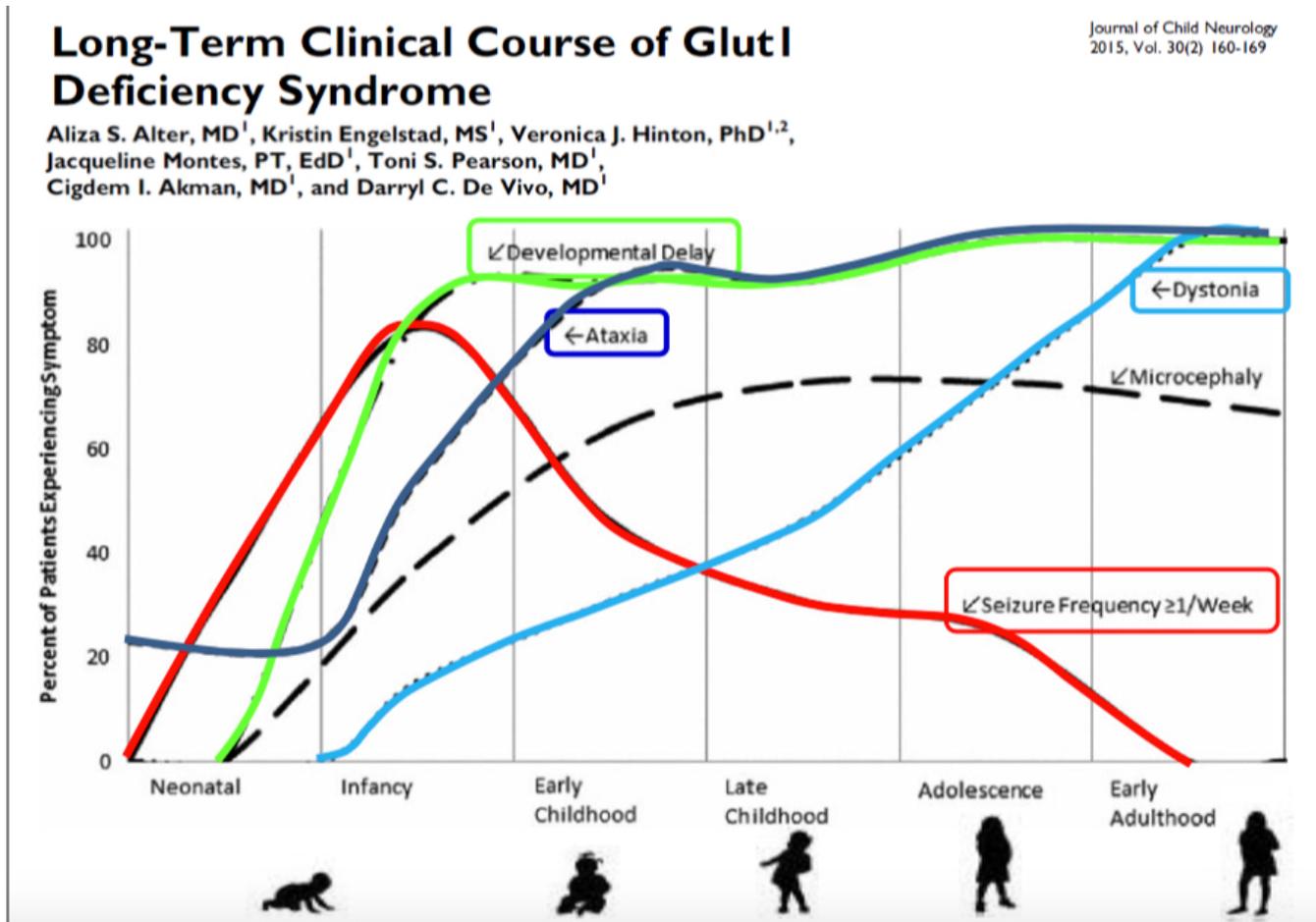
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## Glut1 Deficiency from Pediatrics to Adulthood

### BACKGROUND:

Glucose is the essential fuel for the brain and enters the brain through the glucose transporter Glut1. Without enough glucose there is an energy crisis in the brain: glucose and lactate levels are low indicating Glut1 Deficiency. A novel blood test identifying the reduced number of Glut1 transporters on red blood cells (quantitative Glut1 Deficiency) has recently been developed in France. Mutations the SLC2A1 gene often confirm the diagnosis but the absence of mutations does not exclude Glut1 Deficiency. The “brain energy crisis” results in three cardinal symptoms: epilepsy, movement disorders, and cognitive/behavioral issues. Any combination and any degree of symptoms have been described in Glut1 Deficiency.



**Legend of figure 1:**

In infancy and early childhood seizures and developmental delay are the prominent symptoms that stabilize beyond puberty. In contrast, ataxia, dystonia, and paroxysmal events are issues of childhood and adolescence.

**GLUT1 DEFICIENCY THROUGH THE DEVELOPMENTAL STAGES:****Infants and Early Childhood:**

The initial presentation of Glut1 Deficiency is often a seizure within the first six months of life. Seizures types are variable and can include cyanotic spells (turning blue), absence (dreaming), focal (one part of the body), generalized (whole body), myoclonic (muscle spasms), and astatic (drop attacks). In infants paroxysmal eye-head movements present as aberrant gaze saccades (jumping like eye movements) with head and eyes moving around. Often they are the first sign of Glut1 Deficiency. In infancy a classical 3:1 ketogenic diet should be used. In early childhood developmental impairment becomes apparent. Gait often is not normal for age (clumsy, wide based, drunken appearance). 10% of absence epilepsies starting in this age have been shown to be Glut1 Deficiency.

**Childhood:**

In childhood and adolescence movement disorders tend to worsen. In school age there can be abnormal gait such as: broad based gait, dystonia, ataxia. Cognition shifts toward lower cognitive range, but not all patients have cognitive issues. Specific impairments may be problems in visual attention, motor skills active language, and whole picture processing (can't see the forest for the trees). In contrast, strengths in Glut1 Deficiency patients include language comprehension, social interaction, gentleness, and slower, but constant progress in development. The use of ketogenic diets is variable, increasingly the modified Atkins Diet (MAD) is used in Glut1 Deficiency, but data on long-term developmental outcome is not yet available.

**Adolescence:**

In adolescence  $\frac{3}{4}$  of Glut1 Deficiency patients report paroxysmal (sudden onset) events such as sudden spells, motor arrest, choreatic or dystonic involuntary movements, drops, or other unspecified discomfort. These episodes often start in puberty. Triggers may be physical activity, loss of ketosis, and sleep deprivation. Often these events occur despite adequate use of ketogenic diets and thus currently are difficult to treat. Adolescents often comply better when the Modified Atkins Diet is used. The low glycemic index diet (LGIT) is not recommended in Glut1 Deficiency.

**Adults:**

In adulthood symptoms of Glut1 Deficiency often stabilize. In most cases epilepsy is controlled by mild ketogenic diets and/or anticonvulsant drugs. Ketogenic diets are often reduced to the modified Atkins Diet (MAD) or discontinued – it still remains unclear how long dietary treatment

should be continued in adults. Paroxysmal events in adults occur and have been termed “Paroxysmal exertion dystonia (PED)”. They are difficult to treat and may also present as migraine, writer’s cramp, and alternating hemiplegia.

Most patients with Glut1 Deficiency will show cognitive impairment of various degrees and will require sheltered environments, although some patients successfully obtained a college degree and are working and living independently. Long-term adverse effects of high-fat ketogenic diet treatment such as kidney stones, growth impairment, or cardiovascular side effects remain a concern, but preliminary results indicate that such side effects may be overrated. We studied 10 Glut1 Deficiency patients on ketogenic diets: after 10 years on the diet lipid parameters remained within the normal range and ultrasound of the carotid arteries did not indicate atherosclerosis (Klepper J et al, submitted).

### **OUTLOOK:**

Glut1 is expressed in other tissues such as muscle, retina, placenta, heart. Potentially the Glut1 defect could also affect these tissues, but so far no involvement of these organs has been reported - there may be compensatory mechanisms by other Glut1 glucose transporters in these tissues.

For patients with Glut1 Deficiency it is recommended to continue the ketogenic diet into adulthood. Additional treatment options may be the use of ketone esters, such as triheptanoin (C7) or other artificial ketones. Ketone esters serve as fuel to the brain just as ketones, but have the additional effect of refilling the TCA cycle (anaplerosis) that generates energy. C7 has been shown to work in Glut1-deficient mice and the first clinical trials in Glut1 Deficiency are currently under way.

Dr. De Vivo and his team at Columbia University, NYC are successfully working on gene therapy for Glut1 Deficiency. Results are promising using a viral vector carrying the Glut1 gene into cells to correct the genetic defect, but gene therapy in patients will not be available for some time.

To generate more data about Glut1 Deficiency worldwide an online patient registry ([www.G1DRegistry.org](http://www.G1DRegistry.org)) has been generated. All families with Glut1 Deficiency are requested to enter their data to provide novel insights into incidence, clinical presentation, spectrum of mutations, dietary treatment, and side effects.

**Juan Pascual, MD, PhD**  
**UT Southwestern Medical Center**  
**Dallas, Texas**

## **Glut1 Deficiency in 2017 and Beyond**

How much energy does the brain consume compared to a light bulb? Think of the energy in a 60W bulb- an adult uses 500W, a child uses 1500W.

Neuroscientists do the following: diagnose, comprehend, and treat. Neuroscientists use many different data sources to study Glut1 Deficiency: mouse models, typical human brain, Glut1 Deficiency patients. We have a lot of data about patients in the G1D Registry.

For energy metabolism the body has many ways to get to the same place (i.e. nourishing the brain). We wonder if there is a different way to nourish the brain. Glucose is metabolized. Neurotransmitters are made (glutamine, glutamate, GABA): if there is a problem with glucose getting into the brain then there is a problem with the construction of neurotransmitters (which are the nerve signaling part of the brain).

Brain metabolism is involved with two mechanisms: 1) building chemicals (called anabolism) or burning/breaking down chemicals (called catabolism) and the building blocks (eg. glucose) must do both. Anaplerosis involves keeping the flame (energy in the brain) going.

PET scans in Glut1 Deficiency show low glucose in brain, especially in thalamus and the cerebral cortex, and this isn't normal. All individuals with Glut1 Deficiency have this finding.

### **What does the Glut1 molecule look like?**

#### **Where do the mutations affect the Glut1 molecule?**

The mutations tend to happen on one area of the protein. There seems to be no correlation between mutations and symptoms. We saw 7 patients with the R333W mutation and they are all somewhat different in phenotype.

### **G1D Registry:**

The G1D Registry is useful in obtaining data about patients as they enter their own data into the registry. Data entered includes many questions about patients with Glut1 Deficiency such as: medical history, all issues, patterns, etc. The registry is a secure website, HIPAA compliant, and behind a firewall. Pascual and Ronen published a paper on the registry in Pediatric Neurology 2015 (you can find this on pubmed.com)

Many types of Glut1 Deficiency are noted from this registry and we wanted to know what is the typical patient with Glut1 Deficiency like.

**Listed below is what a patient with Glut1 Deficiency might have at various ages:**

3 months- intermittent involuntary gaze

6 months- fragmentary seizures

1 year – absence seizures

3 years dysarthria

6 years- strong social skills

Puberty- amelioration and movement disorders

Adults- obsessive compulsive traits

**Using mice to learn more about Glut1 Deficiency:**

The mouse with G1D can help us learn about the disease. The G1D mouse has seizures, ataxia, low brain glucose. We can do EEG's on mice and also provide access to blood veins to deliver labeling substances at the same time. With this mouse, we can start to find out information such as: where in the brain these seizures come from?

We know that the whole brain has EEG activity at the same time. We can also use functional MRI's (fMRI) to measure brain activity (not brain structure). In fMRI's we see regions of the brain that are active when you have a seizures. The somatosensory cortex and the thalamus are especially active during a seizure; this is also where we see low glucose on PET scans. We will focus our attention on the cortex and the thalamus.

If you take a section of a mouse brain (just a small section- as long as you have a part of the cortex and the thalamus) the slice can have a seizure.

We ask why are these areas so hyper-excited that they have seizures? We can record electrical activity from a very small slice of brain in the laboratory. If there is a problem with cell to cell communication in the brain a seizure can occur.

Two kinds of activity in the brain are excitation and inhibition and there must be a balance or you will have seizures. Excitation is generally normal in the cortex of Glut1 Deficiency patients. Whereas, inhibition is generally very low in the patients' cortex. The same thing happens in the thalamus.

In the thalamus there is one specific cell type that is disinhibited and is always ready to fire at all times. The cell is the reticular cell of the thalamus. Thus if we can block this cell type from being disinhibited maybe this could help Glut1 Deficiency patients. We will be looking into this. And we will think about if there is anything that we can treat patients with this in mind?

**We know the following about treatment:**

- We need to develop MRI data to look at brain metabolism in mice.
- We can treat Glut1 Deficiency with alternative brain fuel.
- Glucose goes through Krebs cycle (the Krebs cycle is part of the metabolic pathway).

- Triheptanoin is a medium chain triglyceride with 7 carbon atoms (nature makes even carbon molecules) and this is important as it can fuel the Krebs cycle in a way that even carbon chains can't do.

**We are engaged in clinical trials with G1D patients and triheptanoin:**

A standard regular diet is 65% carbs and protein and 35% fat.

A standard ketogenic diet of 4:1 is 90% fat and 10% carbs and protein.

Triheptanoin is provided at 35% with carbs and protein at 60% with an extra 5% essential fats.

We are also trying 45% triheptanoin.

**Vincent Petit, DVM, PhD**  
**METAFORA Biosystems**  
**Evry Cedex, France**

## **Newly Developed Test for Glut1 Deficiency**

### **BACKGROUND:**

Nutrient transporters are used in cells in the process of making energy.

We are in the business of developing ligands that bind to nutrient transporters. We can use these to track the function and effect of these transporters. We can determine if there are under or over consumed nutrients. We develop tests for metabolism including energy demand in cells.

Glut1 Deficiency involves a blood brain barrier protein called Glut1 protein. We know that there is a long time to diagnosis in patients with Glut1 Deficiency. We wanted to develop a test that cuts down that time by evaluating the Glut1 protein function.

We use red blood cells from a patient and attach a specific ligand to the Glut1 protein in the laboratory. Then calculate the amount of Glut1 protein expressed on red cells.

This is a simple blood test that doesn't require fasting and it is fully automated; thus doesn't require much technician time. We have a report on this technique in the journal "annals of neurology" (2017). There were 30 patients and controls in the paper. We determined the normal range of Glut1 expression level in the control population, and demonstrated that in most Glut1 Deficiency patients, the values dropped by at least 20%. Some of the values for the Glut1 Deficiency patients fell in the normal range, but no control value was below 80%. So the sensitivity of the test isn't 100% but it is very specific. This is similar to CSF glucose as a measure.

We ran validity studies-i.e. tests to see if our results would be the same if we re-ran the test data. The test is very reproducible.

Overall the test is: rapid, non-invasive (a few drops of blood needed), and specific. It may be useful in finding patients with non-common phenotypes.

The test is still in production mode. Currently it is not reimbursable by insurance.

We hope to make the test available to the USA, Europe and other countries as soon as possible.

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## **Assaying Drugs for Safety in Glut1 Deficiency Syndrome**

Glucose is required for brain function. Glucose is transferred from the blood to the brain through the blood brain barrier. Glucose is metabolized through glycolysis. If there is less glucose entering the brain then there is less glycolysis. Glucose is broken down into acetyl Co-A and produces ATP as well as neurotransmitters. One of the neurotransmitters is glutamate; which is an excitatory neurotransmitter (when neuron is exposed to glutamate it fires). Glutamate is also converted into an inhibitory neurotransmitter, gamma-amino butyric acid (GABA). When a neuron is exposed to GABA it is silent (doesn't fire). Neurons need a balance between excitation and inhibition, and seizures happen when the balance is tilted in favor of excitation over inhibition.

### **Therapeutic options- Anti-Epileptic Drugs (AED's):**

There are no good therapeutic options for Glut1 Deficiency; seizure drugs are not very useful. Sometimes normal anti-epilepsy drugs that apparently work by boosting inhibition can paradoxically worsen outcomes.

We can test anti-epileptic drugs (AED's) in the laboratory with animal models to see what happens.

There is a mouse model of Glut1 Deficiency. These mice are more prone to generalized tonic clonic seizures which is often one of the initial presentations of Glut1 Deficiency. In the mouse model, we inject mice with chemicals that can cause seizures. What is the minimum amount of a seizure inducing chemical a normal mouse require to have seizures versus Glut1 Deficiency mouse? The minimum amount at which 50% of the animals have seizures is called the effective dose (ED5). We find this effective dose by injecting animals with different doses of drugs and then statistically analyzing the response outcomes (dose response relationship). Wild type (non-diseased) mice need more drug to have a seizure than a Glut1 Deficiency mouse.

When we give the chemical pilocarpine to induce seizures in the mice, we see that Glut1 Deficiency mice are more prone to GTC seizures. We evaluate whether triheptanoin might prevent seizures. We also evaluate whether diazepam can terminate seizures in Glut1 Deficiency mice.

### **Diazepam:**

When pilocarpine is injected and we add diazepam 30 seconds later - what happens?

In wild type mice there is cessation of seizures with diazepam. However, if we wait long enough to start diazepam there is a problem with seizures.

For Glut1 Deficiency mice, post pilocarpine, there is no response to diazepam; and as the animal ages the response to even higher dose of diazepam is even worse. We know that these animals do not respond to diazepam.

### **Phenobarbital:**

If pilocarpine is injected and then phenobarbital (1 or 30 minutes later); we get dose response in the wild type animal. We get ED50 value in the wild type mice.

In Glut1 Deficiency mice there is respiratory distress with normal doses of phenobarbital that causes ED 50 in wild type animals with phenobarbital.

### **Triheptanoin:**

On the other hand, we have seen that triheptanoin elevates the seizure threshold (i.e makes it more difficult to have a seizure). The ED50 dose for Glut1 Deficiency animals is greater than without triheptanoin.

### **A proposal for a High Throughput screening:**

Taken together with data from Dr. Klepper's research, we believe that diazepam and phenobarbital may antagonize the function of the Glut1 transporter potentially worsening seizure outcomes.

Not only is this sort of negative interaction possible with anti epilepsy drugs, but it is just as possible with other drugs that Glut1 Deficiency patients may be exposed to for the management of illnesses other than seizures. Our desire and proposal is to create a library of the commonly used drugs that may potentially contraindicate Glut1 function. Such a library of potential contraindication of commonly used outpatient drugs does not currently exist. It's availability can inform and make physicians and patient families aware of potential negative interactions – in some cases there may be an opportunity to choose another drug for the condition that does not have these negative effects.

### **A high throughput way to identify harmful drugs by studying Glut1 translocation. uptake assays:**

When Glut1 is on the surface of the cell membrane, it can function properly. When it is within the cell, then it is not available to transport glucose. We could use a high throughput laboratory assay to test drugs that can potentially worsen symptoms in Glut1 Deficiency by translocating them from the cell surface to the inside of the cell. This can be accomplished using cultured neurons on which the Glut1 protein is fluorescently tagged, and depending upon location in the cell (i.e. its presence on the cell surface or within the cell) will emit a strong or weak signal. We can add different drugs and drugs in different concentrations to determine which drugs and at what dose may potentially

antagonize Glut1 function. We can also use this system to understand how long it may take for a drug to potentially affect Glut1 location.

**A second way of identification for these harmful drugs is uptake assays:**

It is also possible that drugs may just impact glucose uptake without getting translocated. We have a glucose uptake assay using astrocytes/neuron cultures that can be exposed to different concentrations of different kinds of drugs. We can create a dose response curve to find drugs that inhibit glucose uptake. We hope to find a group of drugs that are and are NOT to be used in patients with Glut1 Deficiency.

Finally we can test drugs identified to affect Glut1 translocation or uptake in the animal model of Glut1 Deficiency. Here we can test whether Glut1 Deficiency animals treated with these drugs would be more prone to seizure and movement disorders. We can test these things in Glut1 Deficiency mice with EEG's and also look for movement disorders. We can look for ataxia in these mice on a "catwalk" (a test for ataxia in mice).

We really should look at common pediatric medications and see if they cause a problem in Glut1 Deficiency patients. No one has really evaluated medications for fever, asthma, allergies, ADHD, etc. There are commonly used medications in patients but no one has evaluated them for Glut1 Deficiency patients. Many of the drugs commonly used may cause seizures in Glut1 Deficiency patients. We will look at drugs that Glut1 Deficiency patients may be using. We are waiting for funding at this point.

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## **Signaling Properties and Therapeutic Effects of Ketones**

### **BACKGROUND:**

The US Office of Naval Research (ONR) has sought to explore and provide metabolic counter measures to improve the safety and performance in extreme environments (such as deep sea diving) for Navy SEALs.

Navy seals can stay at 50 feet of seawater depth for 10 minutes and after that they will have the potential for seizures due to central nervous system (CNS) oxygen toxicity. The Navy has experimented with several drugs to help reduce seizures in Navy divers, such as anti-epileptic drugs, but these drugs have unwanted side effects and can impair warfighter cognition ability.

There needs to be a strategy for oxygen toxicity for Navy SEAL divers who use oxygen rebreathers.

The hyperbaric oxygen seizure model is important to use in research as tonic-clonic seizures occur; these seizures are reversible and reproducible.

We can research this in the laboratory by using hyperbaric oxygen chamber; however rodent seizure models in research are informative but not always predictive.

### **RESEARCH:**

We can evaluate seizures in a slice of rodent brain tissue (in the laboratory). We are interested in the hippocampus area for learning and memory issues.

We expose the rodent brain slice tissues to high levels of oxygen (like a Navy SEAL might need for deep sea dives); we see seizures in the brain slice and can study this phenomenon in the absence and presence of ketones. Ketones help to reduce seizures even when evoked by various neurotoxins.

We can also study this at the level of the mitochondria, in EEG's, EKG's, physiological data, and neurological data. We can measure the latency of seizures in response to extreme environments through this method.

In this research we noticed that fasting ketosis caused neuroprotective effects when subjected to high levels of oxygen. We wondered what the brain energy change was in the context of fasting.

There was a published study from Harvard Medical School where subjects were fasted for 40 days. When fed a normal diet most of the fuel is from glucose. Yet when fasting for 40 days, 2/3 of the

brain energy metabolism is from ketone bodies. When large amounts of insulin is provided to a person on a normal diet, severe hypoglycemia would result and this is fatal. Yet when insulin was provided to these fasted patients they all survived and were asymptomatic to hypoglycemia. This represents a dramatic demonstration that the brain can use ketones for fuel even in the face of what would typically be severe hypoglycemia.

Metabolic therapy protection to high oxygen level states can be achieved with nutritional ketosis. Getting into ketosis- involves sustained adherence to a very low carbohydrate diet where there is a depletion of liver of glycogen. This can also be achieved with prolonged fasting, but this is not sustainable. . Ketone salts are formulated with sodium, potassium, calcium and magnesium attached to ketones, primarily beta-hydroxybutyrate. Exogenous ketones can circumvent dietary established ketones to get into ketosis.

Ketones may be important signaling metabolites such as: suppress ion of oxidative stress (epigenetic), suppress inflammation (NLRP3, reduced IL1B), increase the GABA to glutamate ratio, and increase the conversion of glutamate to GABA by activating glutamic acid decarboxylase (GAD)

The term anaplerotic applies in that metabolites are feed into metabolic pathways to make neurotransmitters. Ketones can bypass GLUT1, GLUT3 and pyruvate dehydrogenase deficiency (PDH). They use the use the MCT transporter to enter the brain, and this transporter is increased over time with sustained adherence to nutritional ketosis

The liver is the site of production of ketones. It makes ketones but can't use ketones as source of fuel. Ketones can cross the blood brain barrier and the mitochondrial outer wall very easily. Thus, ketones produced endogenously and exogenously are highly efficient and readily available fuels for tissues and organs, especially the brain.

We have demonstrated that Ketone supplementation delays oxygen seizures in rats. If a ketone ester is provided; it is similar to the rats having been fasted for 1 week (i.e the level of ketosis is high). This rapid (within 30 minutes) and sustained (over 4-8 hours) ketosis was a desired feature of the military because it could rapidly induce a state of neuroprotection.

The human application would be as high as 1 gram/kg/day of ketone esters, divided into 2-4 doses. Within 30 minutes we see a high rise in ketones and reduced glucose. Both can be measured with a Precision Xtra blood glucose/ketone (BHB) meter (Abbott labs). device. Additionally, acetoacetate and beta-hydroxybutyrate can be measured in the lab or by a variety of other devices that are hitting the market (e.g. Kaomoji).

We study the neuroprotective effect of exogenous ketones under the 100% oxygen model in rats. This is similar to 10 times the amount of oxygen than we normally have. Rats given ketone esters demonstrated remarkable resilience against CND oxygen toxicity (tonic-clonic seizures). We used 5 ATA of oxygen, which typically produced seizures within 10 minutes (control animals); whereas those treated with ketone esters were able resist the seizures for over 1 hour. This

neuroprotection and anti-convulsant effect is higher than and know antiseizure compound that we know of.

We feed rats with exogenous ketones mixed with standard diet (10-20% of the food by weight)

In mice fed with ketone esters and normal diet; blood glucose goes down when ketones go up and we are not sure why this happens. Ketone esters increases BHB and acetoacetate in a 1:1 ratio. Ketone esters (1,3-butanediol acetoacetate diester) significantly elevates the acetoacetate; this is important to seizure activity. Elevations of acetoacetate are also seen when ketone salts are administered, but not to the same levels as with this ketone ester.

### **Glut1 Deficiency mice findings with ketone esters:**

Glut1 Deficiency mice plus ketone esters show high variability in response and they tend to dispose of ketones fast. This seems to be a positive indication that their tissue (brain especially) are starved of fuel.

A glucose tolerance test shows how fast the glucose is taken up by the system. Similarly, a “ketone tolerance test” is a good indication that Glut1 Deficiency mice have a high capacity to use ketones for fuel, and this may result in lower than expected levels in the blood and tissues (i.e. they are burning ketones)

When given ketone esters mixed in with food; ketone levels did not rise to the levels typically seen in non-disease animals.

Ketone salt 20% up was much easier to administer because the mice did not self-restrict and this was well tolerated.

There were little changes in body weight over time in ketone esters which taste bad, so mice might not like them. However, mice given ketone esters were better at hanging wire (strength) test and on Rotarod (motor function) test. Overall they had more robust physical capabilities when in a state of nutritional ketosis compared to untreated.

### **Ketone supplementation in patients:**

Is it safe to use ketone salts in patients? They would need to consume a large dose.

Ketone salts have been used for decades in various metabolic disease states. New technologies are making it possible to develop bio-identical ketone salts that are made with a balanced mineral formula that would be well tolerated, safe and pleasant to taste in forms that resemble fruit punch or a chocolate shake. This would also make large doses more feasible.

Compliance is one of the main issues with the ketogenic diet and as new companies develop pre-packaged foods and “comfort keto-foods” this will be much less of an issue. Also, work by Dr. Eric Kossoff has shown that in some cases the less restrictive modified ketogenic (Atkins) diet (MAD) may be just as good. A MAD consumed with MCT oil and supplemental ketones could be the ideal strategy for treatment and compliance

The ketogenic diet does suppress seizures in many different disorders; such as Angelman syndrome. There is a published report of using ketone esters in the Angelman syndrome mouse model (2016). Research at USF is moving this therapy into clinical trials at multiple centers.

Results indicated an elevated presence of enzymes that can convert more glutamate (excitatory) into GABA (stabilizing) with nutritional ketosis. High GABA levels have a calming effect and the ability to suppress seizures.

We want to do a study in Glut1 Deficiency patients, especially since exogenous ketones have been shown to reduce some of the symptoms that may be associated with this disease including, enhancing motor function, reducing anxiety and also suppressing seizures (including absence seizures). The combination of Medium Chain Triglycerides and ketone mineral salts have the biggest effects on anxiety reduction. There are commercial products on the market that combine BHB salts + MCT and these would be the formulas we would be interested in testing.

When a patient with Glut1 Deficiency exercises, symptoms can worsen. Maybe if we give ketone esters as a source of fuel when exercising it can shift fuel preference such as in elite level athletes. Ketosis shifts energy metabolism from glucose to ketones with a 50% reduction in lactate. This observation has significant implications for patients and their ability to be more metabolically resilient during exercise. Feeding prior to exercise could be important.

Ketones have been shown to be involved with several powerful signaling pathways, leading to therapeutic effects. Feeding exogenous ketones increase GABA to glutamate ratio, increase in neurotransmitters, antioxidants are elevated, decrease in glucose (suggests increase in glucose disposal). Many of these effects are desirable traits for a drug compound, but nutritional ketosis tends to stimulate all of these effects (in a mild way) with little or no side effects.

Implementation of nutritional ketosis through diet should be the front line approach for Glut1 Deficiency, whereas exogenous ketone supplementation will be available in the future as a prescription medical food. Several companies now sell them as nutritional supplements, but only products approved by a 3<sup>rd</sup> party (NSF, Informed Choice, etc) should be considered. There is a blood ketone meter on the market now (Precision Xtra). The Dexcom Patch sticks to the skin and picks up glucose, and these results can be sent to a smart phone. The same technology is under development for ketone monitoring. Diet initiation of ketosis takes approx. 3-10 days whereas taking exogenous ketones is a fast way to get into ketosis and to sustain therapeutic levels.

**Eric Kossoff, MD**  
**Johns Hopkins Hospital**  
**Baltimore, Maryland**

## **Diet Therapy for Glut1 Deficiency**

The current state of dietary therapy for disorders, including Glut1 Deficiency was discussed.

A lot of papers are being published on the ketogenic diet (KD).

There is more flexibility in the diet now and this helps with expanding the use of dietary therapy.

There are 4 major randomized clinical trials using KD that have been published.

The Cochrane Collaboration (2012) is a published paper that is useful in getting insurance to pay for the KD as it classifies dietary therapy as valuable and efficacious.

90% of Glut1 Deficiency patients have at least 50% seizure reduction with the KD in major studies.

There is a nice paper by Masino and Rho 2012 which explains why the diet works.

The KD is now more flexible and accessible. There are a lot of different formulas on the market. You can use these as baking mixes also and many companies are creating different keto foods.

### There are 4 major diets

- 1) Classic ketogenic diet
- 2) Medium chain triglycerides diet (MCT)
- 3) Modified Atkins diet (MAD)- created at Hopkins
- 4) Low glycemic index treatment – created at Massachusetts General

We use the Modified Atkins diet at Hopkins as an alternative primarily. This includes less fat, a bit more carbs, more protein, no admission to hospital and no calorie or fluid restriction compared to the classic ketogenic diet. There is no weighing foods on gram scale- patients can have 15-20 grams of carbs per day.

Under age 2 years the ketogenic diet was slightly better than the MAD diet for kids with seizures. Most centers use the classic KD for children under age 2.

## **What do we know about Glut1 Deficiency?**

3 key issues that parents commonly ask keto centers for their children with Glut1 Deficiency include:

- 1) The KD is as effective as the MAD?
- 2) What are the appropriate ketone levels?
- 3) Can I stop the diet ever?

In Glut1 Deficiency we are talking about a brain energy failure thus giving more ketones could be better. However this is anecdotal.

Maybe at a younger age higher ketones are better.

There are some negatives to this concept mainly that ketones are high but some patients still have some seizures, suggesting it's more than just ketones helping.

What about the classic KD versus the MAD diet? Some patients switch to the MAD diet and did better. This is all complicated and could vary from patient to patient. There isn't a simple way to treat all patients.

## **Kossoff (2016) has a report regarding dietary therapy and seizures in Glut1 Deficiency:**

92 families completed a survey regarding their use of dietary therapy for their children with Glut1 Deficiency. It was completed at the 2015 Glut1 Deficiency Foundation meeting in Orlando.

The age range of patients was 1-24 years with a mean of 9.9 years and 90 patients had been treated with dietary therapy 2 patients did not have dietary therapy.

The breakdown of diets utilized were KD n=59, MAD n=29, MCT n=4, and LGIT n=2.

Switching was common; many switched from KD to MAD, often on their own.

Some went from MAD to KD. For the KD there was a wide variety for ratios; many were not on 4:1 (about 2/3's of patients), choosing lower ratios

46% said their child was seizure free on the diet and 80% had a greater than 90% reduction of seizures. This confirms just how effective dietary therapy can be for children with Glut1 Deficiency.

Why might some patients still have seizures? Not clear from the survey

Other findings:

- 1) Age at diagnosis- the younger the better at starting the diet.
- 2) Current age makes a difference in having seizures (younger did better).

- 3.) The MAD equals the KD for seizure activity in this survey according to parents.
- 4.) A 4:1 fat to carb/protein ratio did not make a difference in seizures  
(lower ratio improved seizures equally).
- 5) Checking blood ketones versus urine ketones makes no difference in seizure outcome.

**Extra supplements taken in patients in survey:**

Carnitine (n=62), oral citrates (n=25), MCT oil (n=20), no one was on C7  
36% were on AED's

76/76 with movement disorders improved the movement disorders and cognition on a diet.

Ketones: Checking ketone levels varies a lot among patients. 34% checking blood, 34% said check urine, 21% both, and 11% checked not at all. Didn't seem to matter for seizure control. Worth future study.

Puberty: 22 patients were at or finished puberty and 64% said they had a change in seizure activity.

Side effects of dietary therapy include some patients who had gastrointestinal issues and 1 person with a cholesterol issue.

5.5 years was the average time on diet (1 family had been on for 20 years).

67% were unsure whether the patient should come off the diet in the future. Also worth future study.

Since our 2016 study, there have been more looking at the diet and Glut1:

New study by Amalou (2016)

10 children were started on MAD diet (2 infants).

Data showed there was similar improvement with MAD compared to KD.

Japan study: Data showed that the MAD diet is more palatable for Glut1 Deficiency and was comparable or better in some patients to classic KD.

**G1D Registry:**

Data in the registry consists of 181 patients. Again a lot of varying diets. 54% were on the KD.

**Summary:**

It is ok to make a change as 4:1 KD does not fit all patients

Outcomes on diets are spectacular for Glut1 Deficiency and they are excellent for seizures, cognition and movement disorders.

Management of diet is also variable, including ketones and supplements.

We need further study for puberty, discontinuation, correlation with ketosis, and supplements.

In the future we will evaluate cognition and also adults with Glut1 Deficiency.

**Future Possible Novel dietary approaches to Glut1 Deficiency:**

Triheptanoin

C10

Ketone esters

Modified cornstarch

**Mackenzie C. Cervenka, MD**  
**Johns Hopkins Hospital**  
**Baltimore, Maryland**

## **Ketogenic Diet Treatments and Transition Strategies**

Glut1 Deficiency was discovered in the 1990's and the first patients diagnosed are all now adults.

Adults with Glut1 Deficiency can have atypical symptoms such as migraine, writer's cramp, and alternating hemiplegia which may not be recognized as symptoms of Glut1 Deficiency.

Adult patients with Glut1 Deficiency can also have the following symptoms: chronic mild encephalopathy, infrequent seizures, varying spasticity, ataxia and paroxysmal exertional dystonia (PED).

Genetic mutations are typically autosomal dominant and are most often de novo (not transmitted from a parent).

Some patients have a decrease in seizures during childhood and when we meet them as an adult they are only having other types of events such as PEDs. However, the adult clinical picture is often not so different than in children. But we want to know just how they are different than children?

### **Dietary considerations:**

The standard American diet for most adults in our society includes eating a lot of carbs. The developing brain needs more energy. However, the adult need for energy is less than that of a young child.

Patients with Glut1 Deficiency are on the ketogenic diet but we don't really know the quantity of ketones these patients need.

The classic ketogenic diet is 90% calories from fat. The ratio of fats to carbohydrates and protein combined is 4:1 or 3:1. The modified ketogenic diet and the Modified Atkins Diet (MAD) are less restrictive than the classic diet and used by some patients but they still measure ketones. The ratio of fats to carbohydrates and protein combined is typically 2:1 or 1:1.

Many adult patients start these diets on their own; as many of the ketogenic diet centers don't offer diets to adults and most adult epilepsy centers do not use ketogenic diets for treatment. This isn't always the best way to do things.

It was reported by Pong, 2012 that 62% of patients with Glut1 Deficiency became seizure free on the ketogenic diet. Compliance was 84%.

There is little in literature regarding effectiveness of the modified ketogenic diet in adults.

The Modified Atkins Diet is used at John Hopkins Hospital and several other adult diet centers nationwide. For the MAD, adults take 20 grams net carbs per day (fiber doesn't count!). Patients aren't required to take a certain amount of fat, just enough to get into ketosis. The MAD diet equates to about a 1:1 to 2:1 ratio of fats to carbohydrates and protein combined. When adults reduce carbs, many will go into ketosis with just this. If the patients do not have improvement in seizures and other symptoms, we ask them to start thinking about using a classic ketogenic diet.

### **How the MAD is used in Glut1 Deficiency patients:**

In the G1D registry of patients with Glut1 Deficiency, 2/3 of patients used modified diets. We know that the MAD can reduce oxidative stress.

The MAD has also been used for movement disorders. Adults with Glut1 Deficiency often have issues with movement disorders and less problems with seizures. Patients with a betahydroxybutyrate level of 0.2-2 mmol/L had a reduction in movement disorders in one study (Leen et al., 2013).

### **Transitioning to an adult diet center from a pediatric diet center:**

The transition means that many patients with Glut1 Deficiency will be more independent as adults. They may be asked to choose appropriate foods, check ketones, and monitor symptoms.

Adult patients often want to drive. However, to be allowed to drive, the patient must be seizure free. There is a requirement for length of time being seizure free to gain permission to drive and these vary from state to state. This is also true for movement disorders that may impact driving ability.

Parents or other adults can obtain guardianship of Glut1 Deficiency patients once they turn 18 years of age if they are not able to make decisions for themselves.

Disability in Glut1 Deficiency adults can be significant. Adult patients may be taken off of their parents' health insurance (age varies by insurance carrier and state). Make sure he/she has Medicare and Medicaid in place.

Transition planning prior to the onset of adult age is important for several reasons. Graduation from the public school system happens from 18-21 years and patients may plan to participate in day programs or require care/supervision at home. Some colleges will help make keto foods available in dining halls.

### **Transitioning to Adulthood:**

At age 10-13 years start taking about a transition plan with the pediatrician and pediatric neurology team.

At ages 14-15 years continue to plan.

At ages 16-17 years start working for independence or guardianship and find job programs. Consider advance meeting of the child with the adult neurologist.

At 18 years initiate the transition.

**Transition Tips:**

- Plan ahead to prevent gaps in care.
- Avoid reinventing the wheel (taking the same tests or trying old treatments again that didn't work the first time).
- Planning improves patient and health care provider satisfaction.
- Have a transition diet clinic. There are several diet clinics through the nation.

Drs. Kossoff and Cervenka wrote a paper on "Transitioning pediatric patients receiving ketogenic diets for epilepsy" describing this experience in 10 patients with epilepsy on ketogenic diets (2013).

**Tips to improve dietary compliance:**

- Consider modifying the diet to make it less restrictive and easier to follow.
- Ketogenic diet resources such as cooking classes, cookbooks and websites with recipes, and diet monitoring mobile applications are available.
- Many ketogenic foods are commercially available or as medical foods (require a prescription).
- Potential side effects of these diets can be constipation and kidney stones can be avoided with good hydration.

**What happens if a woman on the ketogenic diet gets pregnant?**

Is there teratogenicity (harm to the fetus)? There is very little information in the literature about this (van der Louw, 2017).

**There are some potential long term side effects to avoid:**

Vitamin deficiency (known risk)

Carnitine deficiency (known risk)

Kidney stones (known risk)

Osteopenia/Osteoporosis (known risk)

Cardiovascular disease (risk unknown)

Cerebrovascular issues (risk unknown)

**Preventative measures to help prevent side effects:**

Replace heavy cream with olive oil or medium chain triglyceride oil in patients with elevated lipids

Reduce calories in obese patients

Multivitamin supplements

Oral citrates (for kidney stones)

Check for hyperlipidemia as (in MAD) blood LDL and total cholesterol often go up in first 6 months, then trend back to normal in 1-2 years on diet therapy. Studies in children have shown that in 12 months there was some decrease in vascular elasticity but this improves and was not significant at 24 months (Kapetanakis, 2014; Coppola, 2014).

**We still need to learn more about adults using ketogenic diets for epilepsy and Glut1 Deficiency:**

How long should adults stay on these diets?

What about supplements?

Which diet is the best?

What ketone levels are best?

Are there other side effects that we don't already know about?

Both Dr. Umrao Monani and Dr. Abraham Al-Ahmad are recipients of research grant awards from the Glut1 Deficiency Foundation and they presented updates on their work at the Nashville conference. Due to Kris Engelstad's travel schedule, she was unable to attend their presentations. We have some resources related to their talks to share below.

**Dr. Umrao Monani, PhD**  
**Columbia University Medical Center**  
**New York, New York**

Dr. Monani presented on **Gene Replacement Therapy for Glut1 Deficiency**.

Dr. Monani's team has published a paper related to their research on gene therapy. You can access the full text article [here](#):

**Abraham Al-Ahmad, PhD**  
**Texas Tech University Health Sciences Center**  
**Lubbock, Texas**

Dr. Al-Ahmad presented on **Modeling the Blood-Brain Barrier using Patient-Derived Stem Cells: A Focus on Modeling Glucose Transport**.

Dr. Al-Ahmad provided the power point slides for his presentation, which you can access [here](#).

### **Other Conference Resources:**

You may also find additional conference resources at our [website](#), including the agenda, presentation slides, photos, and a list of exhibitors and sponsors.

