Treatment old & new

Joerg Klepper

UX007
High carb nutrition
Acetazolamide
Modified Atkins Diet
classical ketogenic diet 3:1 / 4:1

1991
2019

Cleo 21 yrs
Revised recommendation of KD from international consensus

Eric Kossoff

2008

2018

Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group

ketogenic diets in Glut1D?

Ketogenic Diet 4:1
- Ketosis: Ø
- Taste: Ø

Ketogenic Diet 3:1
- Ketosis: ✓
- Taste: Ø

Modified Atkins-Diet
- Ketosis: Ø
- Taste: ✓

Low glycemic Index-Diet
- Ketosis: Ø
- Taste: Ø

Regular diet
- Ketosis: Ø
- Taste: Ø

- [Diagram showing ketosis and taste]
KD – what do patients do?

Use of dietary therapies amongst patients with GLUT1 deficiency syndrome.
Kass HR et al, Seizure 2016;35:83-87

Outcome of ketogenic diets in GLUT1 deficiency syndrome in Japan: A nationwide survey.
Fujii T et al, Brain Dev. 2016
Mutations in Disordered Regions Can Cause Disease by Creating Dileucine Motifs

Highlights

- A peptide-based screen detects how mutations affect protein-protein interactions
- Several pathogenic mutations create dileucine motifs and recruit clathrin
- A dileucine motif gain in GLUT1 causes mis trafficking in GLUT1 deficiency syndrome
- Protein mis trafficking via dileucine motif gains is a recurrent cause of disease

Meyer et al., 2018, Cell 175, 1–15
September 20, 2018 © 2018 Elsevier Inc.
https://doi.org/10.1016/j.cell.2018.08.019
Glut1 mistrafficking: transport gone wrong

FACTORY

destination A

Glut1

Destination B

product

„wrong label“

workers

Factory line

destination A
Glut1 mistrafficking: transport gone wrong

Clathrin-dependent endocytosis

Glut1

Glut1*

AP-2

clathrin

formation of clathrin-coated vesicles

plasma membrane

uncoating

fusion

early endosomes

Nucleus

DNA → Translation

RNA

Ribosome

Dileucine motif

Mitochondrion
Glut1 mis trafficking may be treatable!

Clathrin-dependent endocytosis - Blocker

Glut1* 
AP-2 
clathrin 
formation of clathrin-coated vesicles 
Plasma membrane 
uncoating 
fusion 
early endosomes
**Triheptanoin „C7“**

**Triheptanoin:**
- C7-ketoester („artificial ketone“)
- used as tracer for butter in the EU
- liquid at RT with indifferent taste

```
TCA cycle
```
```
Fatty acid
```
```
Triheptanoin
```
```
Odd“ carbons
```
```
Even“ carbons
```
```
ANAPLEROsis
```
```
ATP
```

Randomized controlled Multicenter Study UX007

[Image of a mouse with a checkmark]
Ultragenyx Announces Negative Topline Results from Phase 3 Study of UX007 in Patients with Glut1 DS with Disabling Movement Disorders

Ultragenyx discontinuing development of UX007 in Glut1 DS indication

the study……

• did not achieve its primary endpoint of demonstrating a statistically significant reduction in the frequency of paroxysmal movement events with UX007 treatment compared to placebo,
• did not demonstrate a meaningful difference between treatment groups,
• did not meet its key secondary endpoints,
• The safety profile observed in this study was consistent with what has been previously reported with UX007.
Oral ketones / ketoester

COME IN FOR THE BEST KETO PRODUCTS, ADVICE AND MORE!
Oral ketones /ketoester

On the Metabolism of Exogenous Ketones in Humans

n = 15 healthy volunteers

12g 3OHB KetoSalt ■
24g 3OHB KetoSalt □

12g 3OHB KetoEster ●
24g 3OHB KetoEster ○
Our Research


Shivva V, Cox PJ, Clarke K, Veech RL, Tucker IG and Duffull SB. The population pharmacokinetics of D-3-hydroxybutyrate following administration of [R]-3-

Professor Kieran Clarke

Kieran is Professor of Physiological Biochemistry at the University of Oxford, where she has been since 1991. Prior to this appointment, she was a postdoctoral fellow at Harvard University Medical School and a Group Leader at the National Research Council and lecturer in the Department of Physiology at Ottawa University in Canada.

Dr. Richard Veech

Richard is Chief of the Laboratory of Metabolic Control at the NIH, where he has been since 1969. He studied medicine at Harvard University and obtained his DPhil degree in the Laboratory of the Nobel Laureate, Sir Hans Krebs at the University of Oxford between 1966 and 1969.


Veech RL, Valeri CR and Van Itallie TB. The mitochondrial permeability transition pore provides a key to the diagnosis and treatment of traumatic brain injury. JUBMB Life 2012; 64: 203-207.


**Oral Ketone / Ketoester**

ΔG® is the result of
- 15+ years of research in Oxford/NIH
- 60 million USD + worldwide patent

- 2010 first studies initiated by the US military
- since 11/2017 available for US athletes

65 ml = 100 USD
A REVOLUTIONARY NEW FOOD GROUP WITH THE POWER TO ENHANCE HUMAN PERFORMANCE AND WELL-BEING

DEVELOPED BY TdeltaS® AT OXFORD UNIVERSITY

DeltaG® is the world's first commercially available Ketone Ester.

Operating at a cellular level, DeltaG® provides an alternative source of energy in the form of ketone bodies which break down slowly to provide sustained energy release over several hours. Glucose stores are set aside and used later, enabling endurance athletes to go farther faster.

DeltaG® was developed by TdeltaS®, an Oxford University spin-out, based on pioneering work by Professor Kieran Clarke and Dr. Richard Veech (NIH).

On-Demand Deep Ketosis in a Bottle

NOW AVAILABLE EXCLUSIVELY THROUGH HVMN®
ΔG® improves effectively energy metabolism
Resulting in potential benefit for:

• enhanced endurance
• faster recovery following exercise
• weight management
• anxiety
• Traumatic injury
• cancer
• type II diabetes
• Alzheimer’s / Parkinson Disease and ALS
LETTER TO THE EDITORS

Excellent response to acetazolamide in a case of paroxysmal dyskinesias due to GLUT1-deficiency

Mathieu Anheim · Elisabeth Maillart · Sandrine Vuillaumier-Barrot · Constance Flamand-Rouvière · Fanny Pineau · Claire Ewenczyk · Florence Riant · Emmanuelle Apartis · Emmanuel Roze
# Acetazolamide in Glut1DS

<table>
<thead>
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<td><strong>N=</strong></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1 (#8)</td>
<td>1 (#10)</td>
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<tr>
<td><strong>patient</strong></td>
<td>25y F</td>
<td>18Y F</td>
<td>ND M</td>
<td>16y M</td>
<td>18 y M</td>
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<tr>
<td><strong>SLC2A1</strong></td>
<td>R91W</td>
<td>Ser294Pro</td>
<td>F460LfsX3</td>
<td>Arg269Cys</td>
<td>F263LfsX118</td>
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<tr>
<td><strong>Onset of dystonia</strong></td>
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<td>7.5 y</td>
<td>16y</td>
<td>13y</td>
<td>2y</td>
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<td><strong>frequency</strong></td>
<td>5x/m</td>
<td>ND</td>
<td>12x/m</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td><strong>KD</strong></td>
<td>no</td>
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<td>no</td>
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<td>yes</td>
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<tr>
<td><strong>Acetazolamide dose</strong></td>
<td>750mg/d</td>
<td>500 mg/d</td>
<td>500 mg/d</td>
<td>750-1250mg/d</td>
<td>750-1250mg/d</td>
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<tr>
<td><strong>Follow-up</strong></td>
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<td>12m</td>
<td>ND</td>
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<tr>
<td><strong>response</strong></td>
<td>beneficial</td>
<td>complete</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mild asthenia</td>
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</table>
Current data on anticonvulsant therapy in Glut1DS was rated insufficient to provide recommendations.

Add-on anticonvulsant therapy in combination with KDT used in centers are:

- Levetiracetam (9/13, 69%)
- Valproate (9/13, 69%, not in girls beyond puberty)
- Lamotrigin (5/13, 38%).

Some centers rated ethoxsuximide, carbamazepine and oxcarbazepine, and zonisamide as unhelpful (4/13, 31%).

No recommendations can currently be made on the use of oral ketones or ketoesters.