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Low glycemic index therapy, ketogenic diet, and supplements as treatments for Angelman syndrome

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Why consider diet?

Epilepsia, 53(9):1498–1502, 2012
doi: 10.1111/j.1528-1167.2012.03537.x

FULL-LENGTH ORIGINAL RESEARCH

Low glycemic index treatment for seizures in Angelman syndrome

Ronald L. Thibert, Heidi H. Pfeifer, Anna M. Larson, Annabel R. Raby, Ashley A. Reynolds, Amy K. Morgan, Elizabeth A. Thiele

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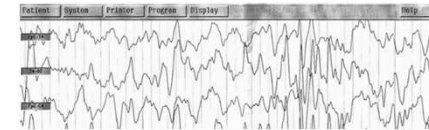
Ketone ester supplementation attenuates seizure activity, and improves behavior and hippocampal synaptic plasticity in an Angelman syndrome mouse model



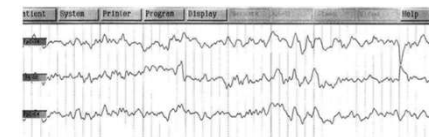
Stephanie L. Ciarlone^{a,b}, Joseph C. Grieco^{a,b}, Dominic P. D'Agostino^b, Edwin J. Weeber^{a,b,*}

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Before KD



2 years following KD initiation

Studies have shown that 30% to 60% of patients with DRE who use the KD have at least a 50% reduction in seizure frequency at 6 months

PEDIATRICS INTERNATIONAL

Official Journal of the Japan Pediatric Society



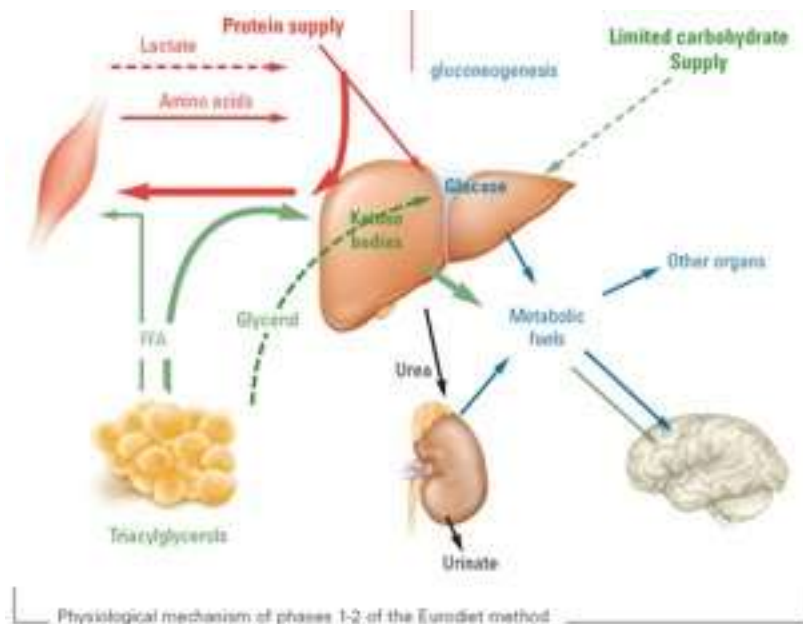
Ketogenic diet in a patient with Angelman syndrome

Athanasios Evangelou, Vai Doulioglou, Katerina Haidopoulou, Maria Aptouramani, Martha Spilioti and Georgios Varlamis
4th Department of Pediatrics, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

The ketogenic diet has been used successfully in the treatment of intractable epilepsy and has been reported to be efficient in the treatment of other conditions such as behavioral disorders,

suffered from frequent daily seizures, both generalized tonic-clonic (3–8 episodes per day) and absences (more than 20 episodes per day).

Mechanism of action



Seizure efficacy

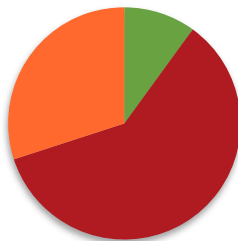
- During ketosis, there is more efficient synaptic removal of glutamate, the brain's major excitatory neurotransmitter. Its conversion to gamma-aminobutyric acid, a major inhibitory neurotransmitter, via the glutamate/gamma-aminobutyric acid–glutamine cycle leads to neuronal inhibition.
- Acetoacetate and BHB inhibit glutamate neurotransmission by inhibiting activation of vesicular glutamate transporters.
- KD also improves mitochondrial dysfunction associated with epileptogenesis.

Types of Diet

Regular Diet



LGIT



KD



Carbohydrates
Protein
Fat

Ketogenic Diet

- Fat to Carb + Protein Ratio

Low Glycemic Index Treatment

- 40-60g low glycemic carbs per day

Modified Atkins

- 10-20g net carbs per day

*All diets are to be medically followed by a doctor and dietitian

Initiation of Diet

Nutritional evaluation

Baseline weight, height, and ideal weight for stature

Body mass index when appropriate

Nutrition intake history: 3-day food record, food preferences, allergies, aversions, and intolerances

Establish diet formulation: infant, oral, enteral, or a combination

Decision on which diet to begin (MCT, classic, modified Atkins, or low glycemic index)

Calculation of calories, fluid, and ketogenic diet ratio (or percentage of MCT oil)

Establish nutritional supplementation products based on dietary reference intake

Laboratory evaluation

Complete blood count with platelets

Electrolytes to include serum bicarbonate, total protein, calcium, zinc, selenium, magnesium, and phosphate

Serum liver and kidney tests (including albumin, AST, ALT, blood urea nitrogen, creatinine)

Fasting lipid profile

Serum acylcarnitine profile

Urinalysis

Urine calcium and creatinine

Anticonvulsants (drug levels) (if applicable)

Urine organic acids

Serum amino acids

Ancillary testing (optional)

Renal ultrasound and nephrology consultation (if a history of kidney stones)

EEG

MRI

Cerebrospinal fluid if no clear etiology has been identified

ECG (echocardiogram) if history of heart disease

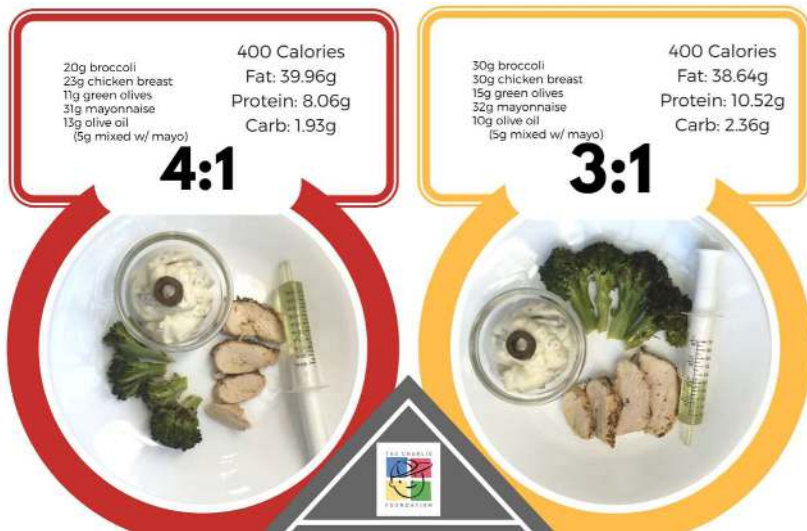


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Ketogenic Diet Therapy



- Based on a ratio of Fat: Carbohydrate + Protein
- Examples of Ketogenic Diet:
 - 3:1 – For every 3 grams of fat, there is 1 gram of protein + carbohydrate
 - 4:1 – For every 4 grams of fat, there is 1 gram of protein + carbohydrate
- MCT oil as part of Ketogenic Therapy
 - MCT oil is made from fats high in Medium Chain Triglycerides (MCT)
 - MCT can help with improving ketosis

Ketone levels are impacted by things outside of diet.

- Increased metabolic rate
 - Growth spurt
 - Fasting
 - Illness
- Constipation
- Use of medications, sunscreens, topical products that cause absorption of carbohydrates

How to start diet

- Consult a dietician and physician
- Usually start at a 3:1 ratio
- Oral diet
 - Recommend small frequent meals
- Tube fed/use of supplements for poor growth
 - Start a formula that is ketogenic friendly
 - Cambrooke: KetoVie products
 - Nutricia: KetoCal products

General Tips

All foods and liquids must be weighed or measured

Use solid meats (skinless), and trim fat of meat before weighing

Fruits should be fresh or packed in water

Read food labels and check them often. Many times the contents of foods can change

Avoid



Using “lite” products (lite means more carbohydrates are in the food)

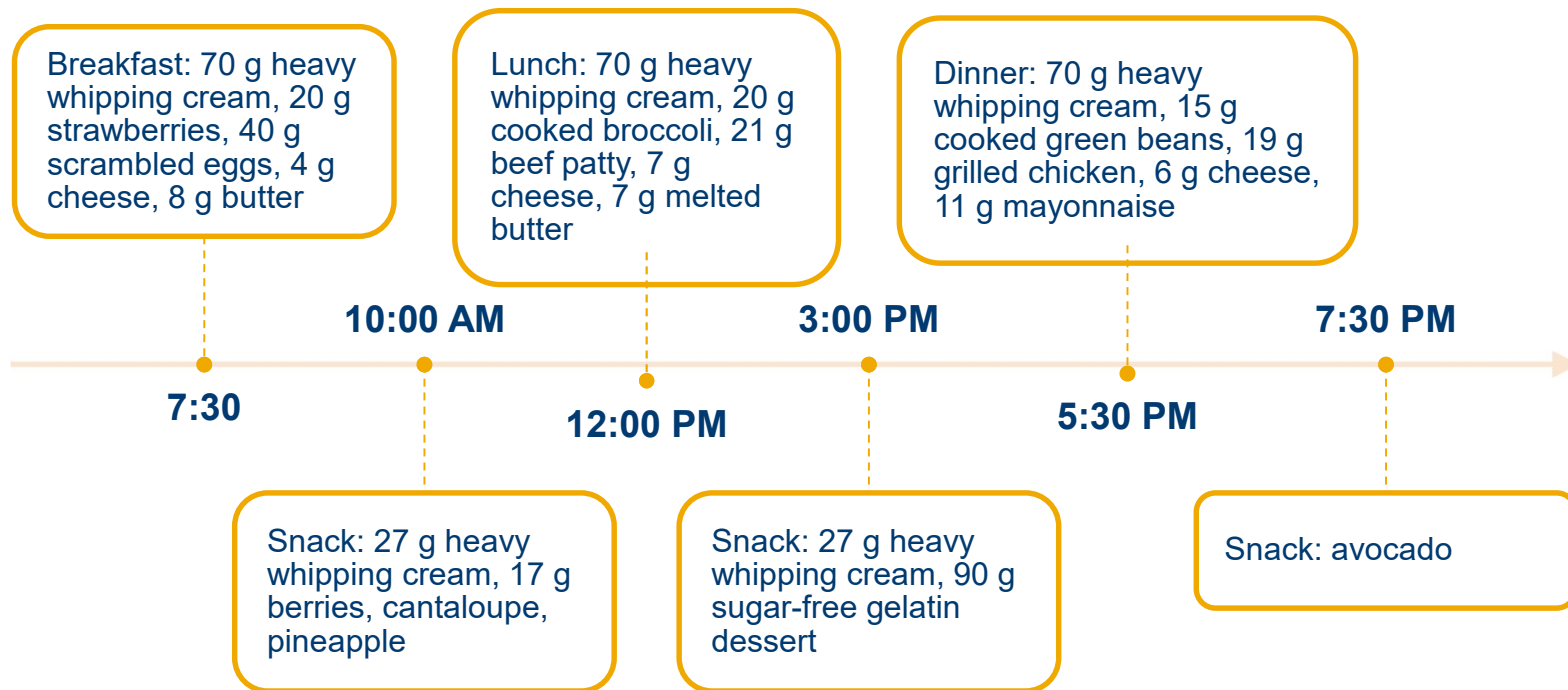


Adding coating to foods, and use salt only for seasoning – even pepper has carbohydrates, since it comes from a plant

Drinking water is important.



Typical Ketogenic Diet for example patient (5-year-old)



Modified Atkins Diet Therapy

- Emphasizes a low carbohydrate, high fat, and adequate protein diet
- Does allow for more freedom with food choices
- Usual goal of 10-20g net carbs per day
 - Net carbohydrate = total carbohydrates – total fiber

Low Glycemic Index Therapy

- High-fat low carbohydrate diet
- Glycemic index ranks foods by how fast they raise blood sugar
- 40-60g low glycemic carbs per day
- The Glycemic Index is a tool developed when testing how different foods effect blood sugars. Foods that are low glycemic have a less dramatic effect on blood sugar when eaten.
- Low GI with ranking <50

Low GI Foods (20-49)	Moderate GI Foods(50-69)	High GI Foods : (70-100)
<p>Breakfast Cereals All Bran All Bran Fruit' n Oats Fiber One Oat Bran Oatmeal(not instant)</p> <p>Fruits and Fruit Juices (Limit 1-2 Fruits/day) Apples, Apple juice Apricots Blackberries Blueberries Cherries Cranberries (not dried) Grapefruit Grapefruit juice Peaches Pears Prunes Plums Raspberries Tangerine Strawberries Tomato juice</p> <p>Beans and Legumes black eyed peas, butter beans chick peas, green beans, kidney beans, pinto beans, lentils, lima beans, navy beans, snow peas, hummus</p> <p>Non-starchy vegetables asparagus, artichoke, avocado, broccoli, cabbage, cauliflower, celery, cucumber, eggplant, greens, lettuce, mushrooms, peppers, tomatoes, okra, onions, spinach, summer squash, zucchini, turnips.</p> <p>Grains barley, rye, bulgur, wild rice, wheat tortilla, wheat pasta</p> <p>Nuts, olives and oils almonds, peanuts, pecans, sunflower seeds, hazelnuts, olives walnuts, oils that are liquid at room temperature</p> <p>Dairy, fish, meat, soy and eggs skim milk, soy milk, almond milk, lowfat cheese, yogurt (lowfat or greek) lean red meat, fish, skinless chicken and turkey, shellfish, egg whites, egg yolks(up to 3/week) soy products, Egg Beaters</p>	<p>Breakfast cereals Bran Buds Bran Chex Just Right Mini Wheats Special K Swiss Museli</p> <p>Fruits: Banana (under ripe) figs grapes kiwi Mango oranges raisins Cranberry juice, orange juice</p> <p>Beans and legumes: boston type baked beans canned pinto, kidney or navy beans, green peas</p> <p>Vegetables: beets, carrots, Sweet potato, yam, corn on the cob</p> <p>Breads: pita pocket oat bran bread pumpernickel bread rye bread wheat bread high fiber bread</p> <p>Grains: cornmeal brown and white rice couscous</p> <p>Pasta: macaroni ravioli (meat filled) pizza (cheese) spaghetti (white)</p> <p>Nuts: cashews macadamia</p> <p>Snacks: chocolate muffins low fat ice cream popcorn</p>	<p>Breakfast cereals Cheerios Corn Flakes Corn Chex Cream of wheat Grape Nut Flakes Grape Nut Flakes Grits Puffed wheat and rice Rice Chex Rice Krispies Raisin Bran Shredded Wheat Total</p> <p>Fruits: Dried Dates Pineapple Watermelon Over ripe bananas</p> <p>Beverages: soda, sweet tea, pineapple juice</p> <p>Vegetables potato, baked, broiled, fried, mashed, french fries canned or frozen corn, parsnips, winter squash</p> <p>Breads most breads (white and whole grain), baguette, bagels, bread sticks, Kaiser roll, dinner roll</p> <p>Grains rice, instant, tapioca</p> <p>Snacks candy, crackers, chips, cookies, syrups, jelly, jam Donuts, corn chips, tortilla chips, pretzels, jelly beans, rice crackers, pastries, cakes, nutrigrain bars, Pop tarts.</p> <p>Restaurant and Ethnic Foods Most Chinese food (sugar in stir fry sauces) Teriyaki meats and vegetables, Fried rice Mexican foods with white rice, tortilla, etc Any foods with white sugar or white flour</p>

The **glycemic index**, or **GI index** is the measurement of how foods raise our blood glucose after eating them. Foods raise glucose to varying levels (carbs increase blood sugar the most, fats and protein second). Actual (sugar) has a glycemic index of 100 and other foods measured are ranked as low, moderate and high GI foods. Although GI index is helpful to meal planning. **The TOTAL number of grams of carbohydrate can have a bigger impact than GI index on blood sugar levels.**

Consuming low GI foods + calculating carbohydrate intake = the most stable blood sugar levels!!!

Starting LGIT



Cut out simple sugars such as juices, sodas, candy, other sweets



Cut out more hidden carbohydrates such as barbeque sauce



Change carbohydrates to low glycemic carbohydrates



Limit carbs to 40-60g per day

Recommended Foods

Food Group	Foods Recommended
Grains	Almond flour; coconut flour; hazelnut flour
Protein	Beef, lean cuts; chicken and turkey; eggs or egg substitute; fish; nuts and seeds; nut butters; legumes in moderation such as beans, soybeans, kidney beans, lentils and chickpeas
Dairy	Heavy whipping cream; unsweetened yogurt; cheese; sour cream; cream cheese; unsweetened nut milks (almond, coconut); Fairlife products (pay attention to carbs)
Vegetables	Non-starchy vegetables (artichoke, asparagus, broccoli, carrots, cauliflower, celery, cucumber, eggplant, green beans, lettuce, pepper varieties, spinach, summer squash, tomatoes and zucchini).
Fruits	Blueberries, strawberries, raspberries, blackberries. Cherries, grapefruit, apples, pears, plums, avocados
Oils	Butter, ghee, MCT oil, coconut oil, avocado oil, nut oils, olive oil, mayonnaise
Beverages Supplements	Water, broth, calorie free sports drinks Fairlife protein shakes, Ketocal, Ketovie

Sample diet 9 years old

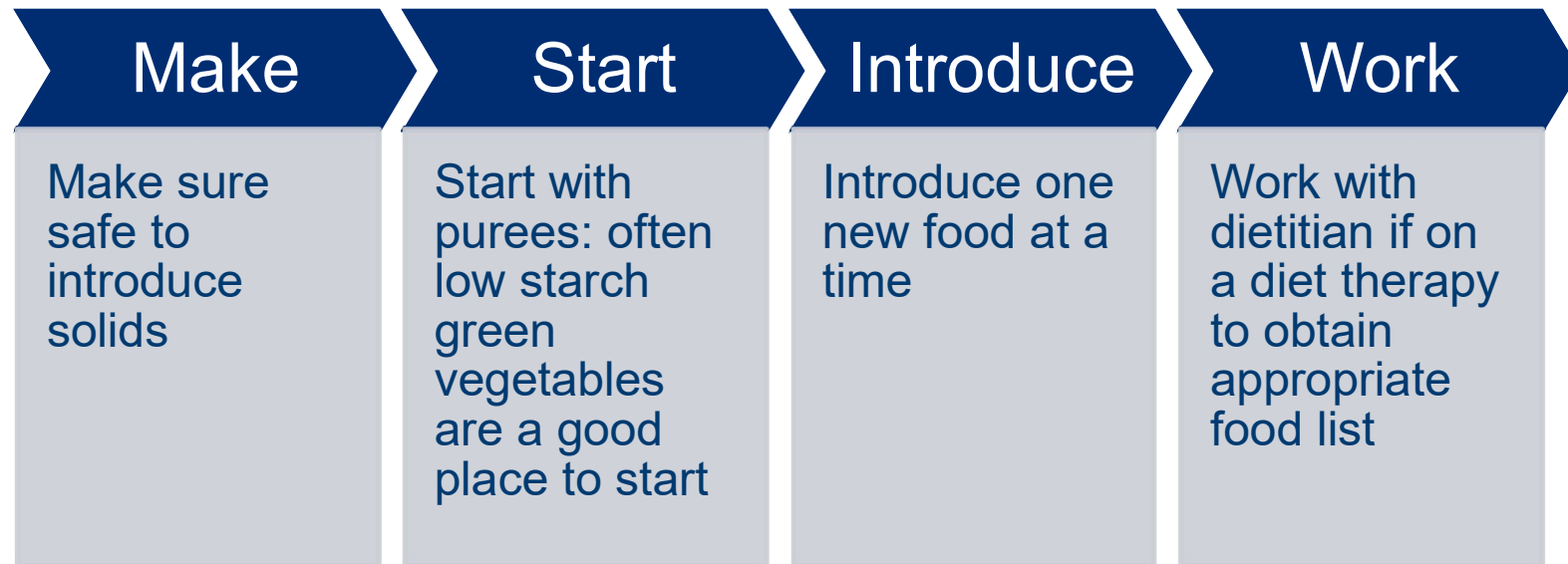
- 1400 calories
- 31 grams of carbohydrates (9% of total calories)
- 109 grams of fat (70% total calories)
- 80 g protein (22% total calories)

Meal	Menu
Breakfast	1 ounce ham 2 scrambled 1.5 tablespoon butter ¼ cup berries water
Lunch	Lettuce Tuna salad: 3 ounces canned tuna, 1/4 cu celery, ¼ cup pickles, 2 tablespoons mayonnaise water
Snack	String cheese water
Dinner	3 ounces steak 1 cup steamed broccoli 4 tablespoons olive oil 1 cup calorie free drink
snack	½ avocado 3 celery sticks water

Monitoring Lab Work

- Patient will have lab work monitored closely especially while the most restrictive diets
 - Electrolytes (especially calcium), measures of acidosis, liver function, blood glucose, ketone levels, carnitine
 - Home ketostix depending on how strict a diet
- Labs assist in giving a good picture of the effectiveness of therapy
- Labs also tell if changes can or may need to be made after adjusting the body's fuel source to fats
 - May need to adjust recipes, food list or add supplements

Transitioning to Solids



Poor growth

- Formula supplementation
- Dietitian can help with selecting appropriate choice
- Examples:
 - Cambrooke: KetoVie products
 - Nutricia: KetoCal products
 - MCT oil



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Metabolic disturbances

- Dehydration
- Low blood sugar
 - blood glucose of <40 mg/dL and symptomatic hypoglycemia are treated with carbohydrate-containing beverages such as orange juice
- Excessive ketosis
- Metabolic acidosis
 - Treatment with bictra often needed in AS
- Decreased diet activity and gastrointestinal symptoms such as abdominal pain and vomiting are usually transient and rarely require diet discontinuation, but may require reducing the KD ratio

GI Side Effects

- High-fat content prolongs the gastric emptying time and can cause vomiting.
- Constipation occurs due to low fiber and food intake. KD at a 3:1 ratio is associated with fewer gastrointestinal symptoms compared to the 4:1 ratio.
- Hepatitis and pancreatitis are rare yet fatal complications (avoid starting diet in individuals on medications that increase risk of pancreatitis such as valproic acid).

Kidney stones

- Risk of kidney stones range from 2% to 6% and may be as high as 25% in those who have been on KD for longer than 6 years.
 - Administration of potassium citrate can reduce the risk to .9%
 - Measurement of urinary calcium-to-creatinine ratio at baseline and every 3 months is recommended. Renal ultrasound should be considered if there are signs and symptoms concerning for kidney stones.

Growth and Vitamin Deficiencies

- Growth failure may occur in children on KD, and it is treated by lowering the KD ratio.
- Vitamin and mineral deficiencies have been reported.
 - Calcium and vitamin D deficiency can lead to osteopenia and osteoporosis.
 - Periodic dual energy X-ray absorptiometry screening should be considered in children using long-term KD.
 - The use of **low-carbohydrate multivitamins** with minerals and calcium along with vitamin D supplementation is recommended.
 - **Carnitine deficiency** may occur and supplementation may be needed.
 - Cardiomyopathy and corrected QT interval prolongation have been seen in children on KD, and the underlying mechanism may be **selenium deficiency**.

Dyslipidemia

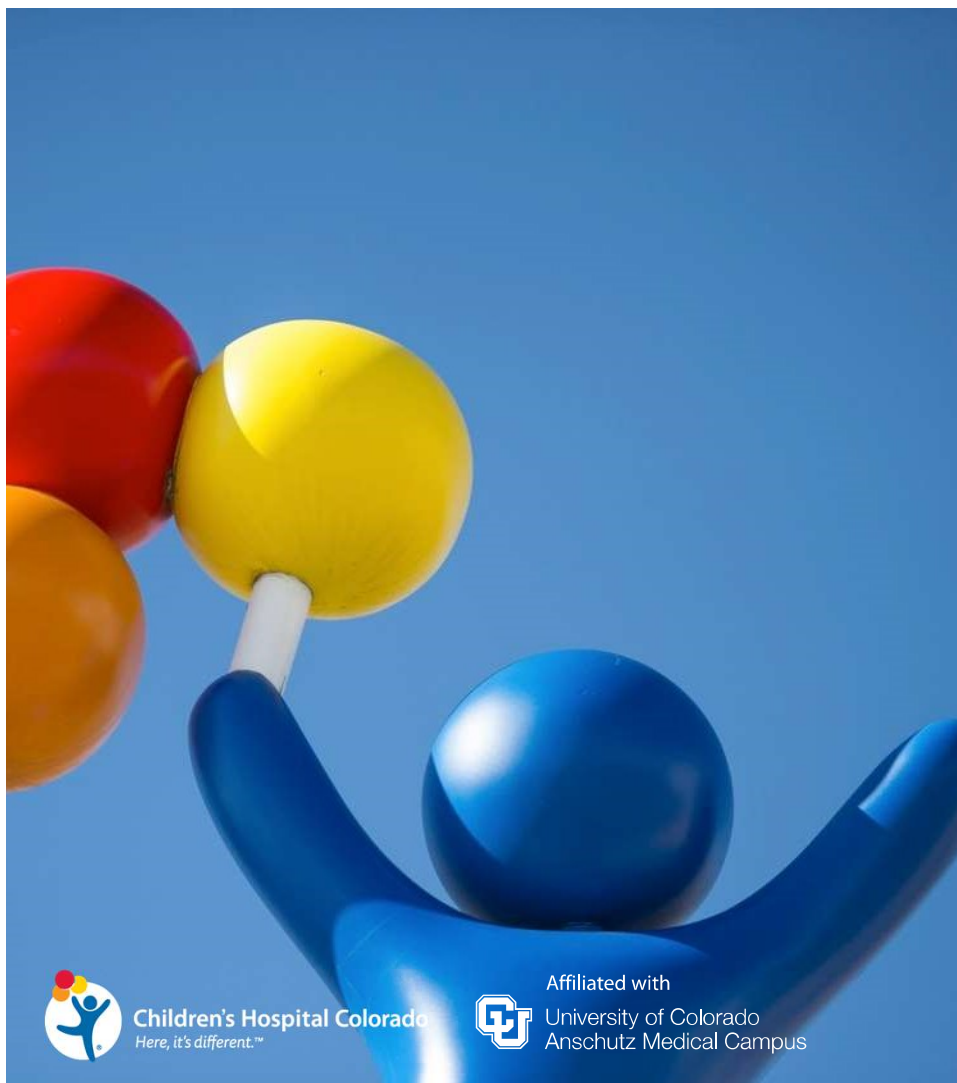
- Hypercholesterolemia
- Hypertriglyceridemia
- Doppler studies and echocardiogram may be necessary in the presence of chronic dyslipidemia and to screen for cardiomyopathy.
- A higher proportion of unsaturated to saturated dietary fats, the addition of **MCT oil, a lower KD ratio, and carnitine supplementation** may help prevent the risk of dyslipidemia.

Other considerations

- Dextrose-containing intravenous fluids are a common cause of seizure relapse
- In an intensive care unit, KD should be avoided in children receiving propofol infusion due to the risk of complications
- Over-the-counter medicines may have carbohydrates and can lead to ketosis reversal and seizure breakthroughs

Fevers/illness

- Give sugar-free, fever-reducing medicine (acetaminophen suppositories are good and don't interfere with the ketogenic diet).
- If the fever does not go away and fever reducing medicine does not help, see your child's doctor or go to the nearest Emergency Department.
- Have a back up rescue medication at home (clonazepam, diazepam)
- If your child is prescribed an antibiotic, be sure it is carbohydrate-free, if possible.

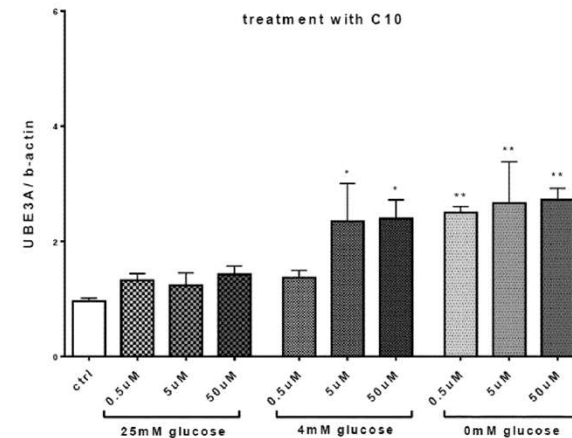
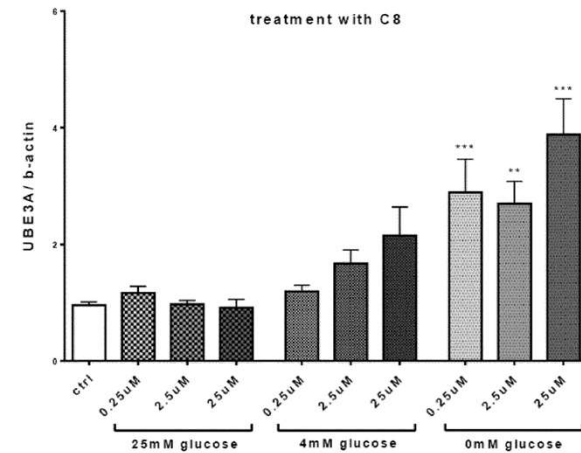


Supplements

- MCT oil
- Levocarnitine
- Prebiotic/Probiotic
- Exogenous ketone
- Taurine
- Black currant
- B12
- Melatonin
- DHA
- Iron
- L-Threonine

MCT Oil

- Medium-chain triglyceride (MCT) diet increases UBE3A expression in the brain
- MCT diet improves cognitive performance.
- Some data may suggest isolated C8 (caprylic acid triglycerides) has added benefit > C10 (no published data)
- Helps constipation
- Start 1 tsp daily and can titrate up as tolerated



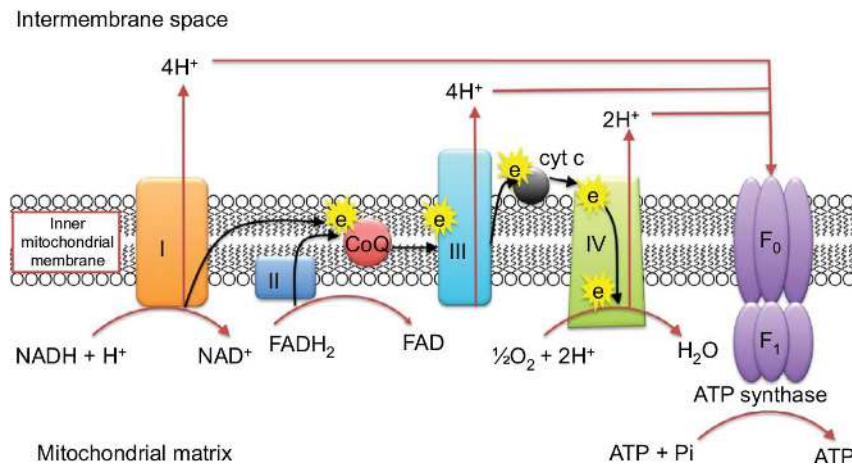


Levocarnitine

- Check level particularly when starting restrictive diet and yearly thereafter
- May help prevent dyslipidemia
- Autism onset can be connected with carnitine deficiency.
- IV indicated for valproate (VPA)-induced hepatotoxicity
- Definitely indicated if there is a low carnitine level
- Carnitine plays a critical role in **energy production**. It transports long-chain fatty acids into the **mitochondria** so they can be burned to produce **energy**.

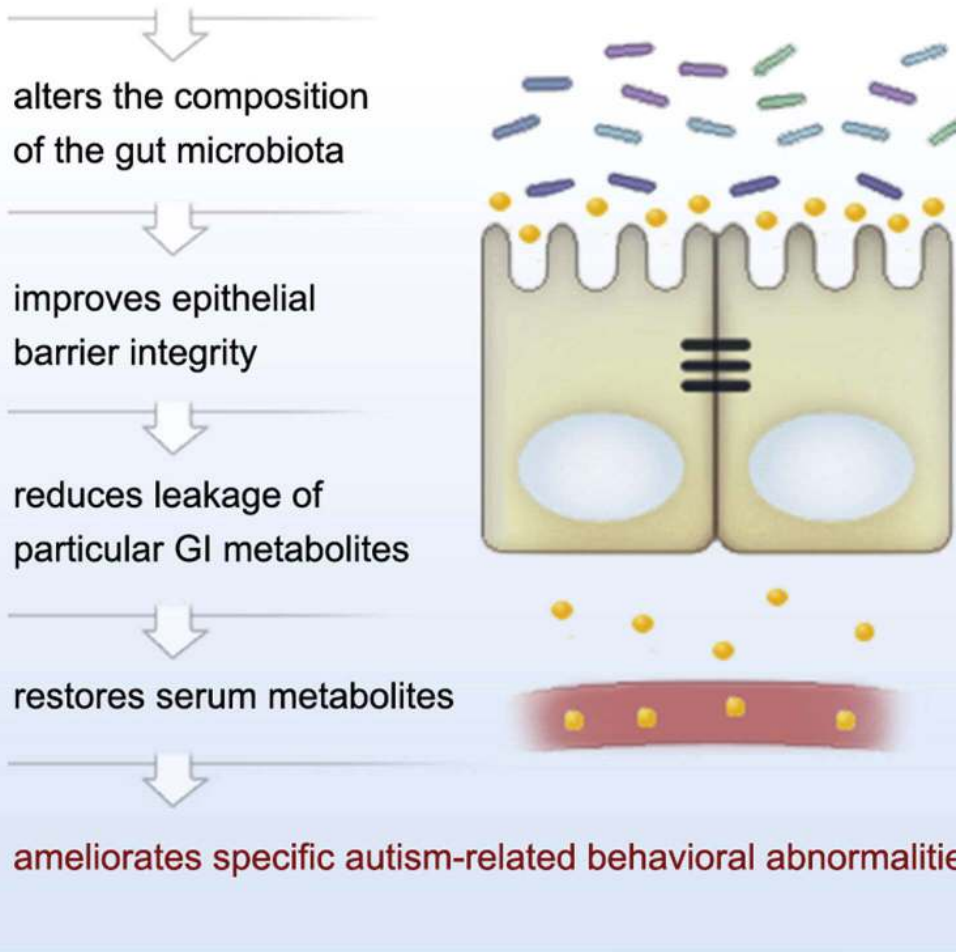
Coenzyme Q10

Mitochondria function



- CoQ10 supplementation restores the electron flow to the mitochondrial respiratory chain (MRC) to ultimately increase mitochondrial antioxidant capacity.
- Administration corrected motor coordination and anxiety levels, and improves the expression of complexes III and IV in hippocampus CA1 and CA2 neurons and cerebellum in these *Ube3a^{m -/p +}* mice
- Dose 100-200 mg daily

probiotic treatment of mice with autism features



Treatment with probiotics or prebiotics

- Probiotics are like fertilizer to feed the gut flora present
 - Inositol
- Prebiotics reestablish new bacteria
 - B. Fragilis
 - Active cultures in yogurts
- Establish healthy gut flora
- May help with constipation



Exogenous ketone

- Clinical trial completed in January
 - 13 individuals completed the study
- Results of clinical trial continue to be analyzed
 - Change in delta power noted with large effect in some patients (overall not statistically significant)
 - Changes in event-related potential seen in the frontal region
 - Impact on constipation
 - Impact on appetite in several patients with increased food seeking of carbohydrates



Taurine

- Recovered motor capacity, learning and memory skills in a mouse model of **Angelman syndrome**, indicating the compound may be a potential therapy to treat motor and cognitive deficits in **Angelman** patients.
- Known that taurine is an agonist of GABA_A receptors
- Dose 20 mg-2000 mg daily



What are the benefits of Threonine?

1. Essential for Vitamin B12 production
2. Supports the immune system
3. Prevents fatty liver
4. Allows Celiac patients to eat wheat
5. Possibly effective in treating tyrosinemia type 1 (3), spinal spasticity (4) and phenylketonuria
6. May treat Lou Gherig's Disease
7. Contributes in the normal function of intestines
8. Supports muscles and connective tissues
9. Speeds wound healing
10. Alleviate anxiety
11. Stabilize blood sugar
12. Useful in Krebs cycle
13. Aids in sleep

L-threonine

- Essential amino acid (building block of protein)
- Used to treat spasticity in other disorders
- No specific data in AS
- May help with anxiety

Black currant

- Anecdotally, parents report behavioral improvements, cognitive progress
- Doses used are one capsule a day for deletion kids or once every second day
- Also available as a powder
- Some reports of increased anxiety
- No published studies to date



B vitamins



- B6 can help with the irritability associated with the use of Keppra
- B12 is important for neurological development
 - For unclear reasons many with AS have high levels of B12 even when not on a supplement
 - Study published in 2012 looked at multiple vitamins including B12 and saw no impact
 - 1 mg by mouth per day for all weights and ages



Melatonin

- Hormone naturally produced in the pineal gland
- Initiates sleep
- Not effective to help keep you asleep
- Worth trying as part of routine at bedtime

Docosahexaenoic acid (DHA)

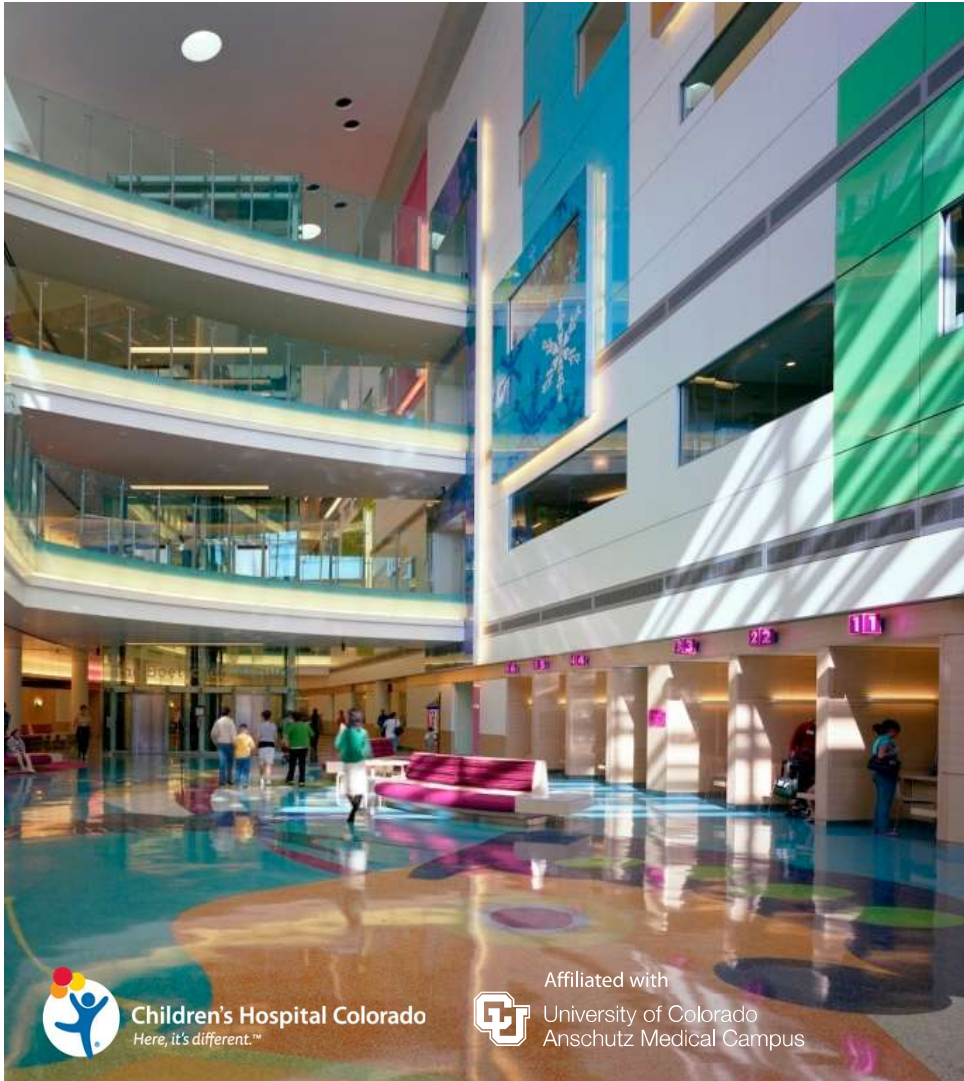
- omega-3 fatty acid essential for brain development during pregnancy and early childhood
- Some products have it added
- Improved ability to climb in AS-fly model



Iron



- Important to check iron stores (ferritin), especially if there are concerns for restless sleep
- If low try to increase with foods in the diet or add a multivitamin with iron
- Supplement can make constipation worse



Questions?

Thank you!!!

Don't hesitate to email with any questions:

Jessica.duis@childrenscolorado.org

References

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