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

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Why consider diet?

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.

Ketogenic diet in a patient with Angelman syndrome

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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 (1-8 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**

### 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
- EKG (echocardiogram) if history of heart disease
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)

**Breakfast:** 70 g heavy whipping cream, 20 g strawberries, 40 g scrambled eggs, 4 g cheese, 8 g butter

**Lunch:** 70 g heavy whipping cream, 20 g cooked broccoli, 21 g beef patty, 7 g cheese, 7 g melted butter

**Dinner:** 70 g heavy whipping cream, 15 g cooked green beans, 19 g grilled chicken, 6 g cheese, 11 g mayonnaise

**Snack:** 27 g heavy whipping cream, 17 g berries, cantaloupe, pineapple

**Snack:** 27 g heavy whipping cream, 90 g sugar-free gelatin dessert

**Snack:** avocado
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

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### Low GI Foods (20-69)

<table>
<thead>
<tr>
<th>Breakfast Cereals</th>
<th>Low Carbohydrates</th>
<th>Fruits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bran flakes</td>
<td>All Bran Fruit &amp; Nut Bran</td>
<td>Blackberries</td>
</tr>
<tr>
<td>Oat bran</td>
<td>All Bran Fruit &amp; Nut Bran</td>
<td>Blueberries</td>
</tr>
<tr>
<td>Steel cut</td>
<td>All Bran Fruit &amp; Nut Bran</td>
<td>Cranberries</td>
</tr>
<tr>
<td>Corn flakes</td>
<td>(not dried)</td>
<td>Dates</td>
</tr>
<tr>
<td>Quinoa flakes</td>
<td></td>
<td>Grapes</td>
</tr>
</tbody>
</table>

### Moderate GI Foods (60-99)

<table>
<thead>
<tr>
<th>Breakfast Cereals</th>
<th>High Carbohydrates</th>
<th>Fruits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bran flakes</td>
<td>High Bran Cereal</td>
<td>Apple</td>
</tr>
<tr>
<td>Oat bran</td>
<td>High Bran Cereal</td>
<td>Bell peppers</td>
</tr>
<tr>
<td>Steel cut</td>
<td>High Bran Cereal</td>
<td>Mango</td>
</tr>
<tr>
<td>Corn flakes</td>
<td>(not dried)</td>
<td>Pineapple</td>
</tr>
<tr>
<td>Quinoa flakes</td>
<td></td>
<td>Pomegranate</td>
</tr>
</tbody>
</table>

### High GI Foods (100+)

<table>
<thead>
<tr>
<th>Breakfast Cereals</th>
<th>High Carbohydrates</th>
<th>Fruits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn flakes</td>
<td>Instant Oatmeal</td>
<td>Apple</td>
</tr>
<tr>
<td>Oat bran</td>
<td>Instant Oatmeal</td>
<td>Banana</td>
</tr>
<tr>
<td>Steel cut</td>
<td>Instant Oatmeal</td>
<td>Orange</td>
</tr>
</tbody>
</table>

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The Glycemic Index, or GI, is a measure of how foods raise our blood sugars after eating them. Food rates go from 0 to 100 with the highest performer being 100. The GI of foods reflects the impact of the carbohydrates in the food on blood sugar. The GI number of foods of carbohydrates can have a larger 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

<table>
<thead>
<tr>
<th>Food Group</th>
<th>Foods Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grains</td>
<td>Almond flour; coconut flour; hazelnut flour</td>
</tr>
<tr>
<td>Protein</td>
<td>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</td>
</tr>
<tr>
<td>Dairy</td>
<td>Heavy whipping cream; unsweetened yogurt; cheese; sour cream; cream cheese; unsweetened nut milks (almond, coconut); Fairlife products (pay attention to carbs)</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Non-starchy vegetables (artichoke, asparagus, broccoli, carrots, cauliflower, celery, cucumber, eggplant, green beans, lettuce, pepper varieties, spinach, summer squash, tomatoes and zucchini.</td>
</tr>
<tr>
<td>Fruits</td>
<td>Blueberries, strawberries, raspberries, blackberries. Cherries, grapefruit, apples, pears, plums, avocados</td>
</tr>
<tr>
<td>Oils</td>
<td>Butter, ghee, MCT oil, coconut oil, avocado oil, nut oils, olive oil, mayonnaise</td>
</tr>
<tr>
<td>Beverages</td>
<td>Water, broth, calorie free sports drinks</td>
</tr>
<tr>
<td>Supplements</td>
<td>Fairlife protein shakes, Ketocal, Ketovie</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>Meal</th>
<th>Menu</th>
</tr>
</thead>
</table>
| Breakfast | 1 ounce ham  
|          | 2 scrambled  
|          | 1.5 tablespoon butter  
|          | ¼ cup berries  
|          | water         |
| Lunch   | Lettuce  
|          | Tuna salad: 3 ounces canned tuna, ¼ cup 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

**Make**
Make sure safe to introduce solids

**Start**
Start with purees: often low starch green vegetables are a good place to start

**Introduce**
Introduce one new food at a time

**Work**
Work with dietitian if on a diet therapy to obtain appropriate food list
Poor growth

- Formula supplementation
- Dietitian can help with selecting appropriate choice
- Examples:
  - Cambrooke: KetoVie products
  - Nutricia: KetoCal products
  - MCT oil
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
- Definitively 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 Ube3am⁻/p + mice
- Dose 100-200 mg daily

https://doi.org/10.1016/j.nbd.2015.03.024
Treatment with probiotics or prebiotics

- Prebiotics 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\textsubscript{A} receptors
- Dose 20 mg-2000 mg daily
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:

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References
