Nutrition Supplements in DMD

Kirana Rao MS, RD, LD
Cincinnati Children Hospital
Objectives

- Arginine
- Co-enzyme Q
- Creatine
- Selenium and Vitamin E
- If time permits
  - Antioxidants like green tea extracts
  - Omega 3 fatty acids
  - Carnitine
Specifically

- Function/Role
- Deficiency
- Toxicity
- DRI/ Upper Limits
- Research
- Availability
L-arginine

- Alpha amino acid
- Semi-essential or conditionally essential
- Synthesized primarily in the intestine and kidneys
Function/Role

- Required for synthesis of creatine, citrulline, glutamate and polyamines
- Immediate precursor for NO, urea, ornithine and agmatine
- Cell division and wound healing
- Removes ammonia from the body
- Role in immune function
- Stimulates release of hormones
  - Insulin, growth hormone, glucagon and prolactin
Nitric Oxide

- Synthesized from L-arginine by NOS
  - Citrulline can be used as a substitute to support NOS
  - Glutamine and Citrulline have competitive roles
- NOS signals smooth muscles to relax, dilates artery and increases blood flow to cells
- Cytotoxic - macrophages produce nitric oxide to kill invading bacteria
- Neurotransmitter in the central and peripheral nervous system - GI
- Stimulates growth hormone
- Decreases inflammation
Deficiency

- Rare
- Premature infants and Newborns
  - Hyper-ammonemia
  - Cardiovascular dysfunction
  - Pulmonary dysfunction
  - Intestinal dysfunction
- Patients with HIV
- Patients with liver dysfunction
Toxicity/Side Effects

- Long term not established
- Implicated in viral replication
  - Higher Arginine:Lysine ratio - increase in HSV infection
- Growth hormone stimulation
- Theoretical increase in schizophrenic symptoms
- Thickening of skin and larynx growth in adults
- Possible increased risk of death in post infarction patients treated with L-arginine
- Possible effects on kidneys
- Joint pain, carpal tunnel like symptoms, fluid retention
Negative effects of NO

- Excess production of NO by macrophages in sepsis
- Maybe responsible for killing brain cells in conditions like stroke
DRI/ Upper Limits

- Not established
- Not an essential amino acid
Research

- Cancer and trauma patients
  - Decreased infection in surgical patients
  - Builds muscle
  - Supports wound healing
- mdx mice
  - Arginine + deflazacort spared injury-induced regeneration
  - In high doses, reduced eccentric contraction induced damage
  - Increased utrophin and gamma sarcoglycan
  - Decreased creatine kinase level
Food Sources

- Typical intake is 3-5 grams from food
- Wheat germ and flour
- Whole grains
- Dairy Products
- Nuts and seeds
- Poultry and wild game
- Seafood
- Beans and Legumes
- Dark Chocolate
- Green leafy and root vegetables*
Availability

- Powder to be mixed with a drink
  - Juven – 90 calories and 7gm arginine/serving
  - Other powders 1-2 gm/ _ teaspoon
- Pills
  - _ to 1 gm/ tablet
- Liquid
  - Arginaid – 250 calories, 4.5 gm/serving
  - Nitrate 3 fuel shot – 3 gm/tablespoon
Summary

- Is there adequate research?
- Is there an established dosage?
- Can I get enough or additional from the diet?
- Are the benefits worth the risk?
- What type of monitoring is needed?
Creatine

- Nitrogenous organic acid
- Synthesized mainly in the liver from three different amino acids
  - Glycine, arginine and methionine
- 95% found in skeletal muscles, rest in brain, heart and testes
Function/Role

- Part of Cell’s energy shuttle
  - Supplies energy to muscle cells
  - Keeps cellular ATP/ADP ratio stable
    - Important for prevention of death of cell
DRI/ Upper Limits

- Not established
Deficiency

- Rare
- Disorders of Synthesis
- Disorders of Transport
- Usually present with neurological defects
- Mental Retardation, Speech delay, seizures
Toxicity

- Not established – long term consequence unknown
- Side effects
  - Muscle cramping, muscle spasms and pulled muscles in athletes
  - Diarrhea and nausea at 10-15gm/d
  - Osmotically active
- Not considered doping but banned in some countries
  - Recommendations to delay till after puberty
Research

- Responders and non-responders
- In cell cultures, athletes, and non-DMD animals and humans
  - Increased strength and exercise performance in athletes short term
  - Increased fat free mass and total body mass
  - Antioxidant properties
  - Reduced protein breakdown
Research

- In mdx mice:
  - Improves survival of dystrophic skeletal muscles
  - Increases strength through regulation of calcium homeostasis.
  - Reduces necrosis in type 2 muscle fibers, enhanced oxidative capacity and mitochondrial function
Research

- In DMD Boys
  - Increases measures of strength and reduced marker of bone breakdown (n=15, 3gm/d)
  - Improved strength and body composition (n=31, 0.1gm/kg/d, 15 on steroids)
    - Grip strength
  - No change in bone density or content, FFM, %body fat, CK, serum creatine, renal or liver function
Sources

- Half from diet, mainly meat and fish
  - 1-2 gm/day
- Half from endogenous synthesis in liver
  - 1-2 gm/day
- Vegetables do not contain creatine
- Vegetarians do not have creatine deficiency
Supplement Availability

- Creatine Monohydrate
  - Most common form used in US and used in all studies

- Creatine Ethyl Ester
  - Supposed 10 times better absorption and utilization by cell
  - Benefits are controversial
Availability

- Powder mixed into a drink
  - 1-5 gm per serving
- Liquid
  - 1 tablespoon about 7-10gm creatine
- Pill
  - _ to 1 _ gm per pill
Summary

- Is there adequate research?
- Is there an established dosage?
  - No, Athletes take about 20-30 gm/day to load and then 2-5 gm/day to maintain
  - In DMD boys – 0.1gm/kg/d, 3 gm/d
- Can I get enough or additional from the diet?
- Are the benefits worth the risk?
- What type of monitoring is needed?
Coenzyme Q

- Fat soluble vitamin-like quinone
- Anti-oxidant found in all cell membranes
- Found in tissues with high energy turnover
  - Heart, Brain, Liver, Kidney
- CoQ10 is the most common Co enzyme Q in the human mitochondria
Function/Role

- Vital for proper transfer of electrons in the mitochondrial respiratory chain
- Prevents breakdown of mitochondria
- Antioxidant scavenger
  - Prevents lipid peroxidation
  - Protects against DNA damage and other forms of oxidative damage
- Supports Antioxidant activity of vitamin E
- Indirect stabilizer of calcium channels to decrease calcium overload
- Potential role maintaining the proper pH of lysosomes
Function/Role

- **Children and young adults**
  - Can make from lower ubiquinones like Q6 or Q8

- **Sick and elderly**
  - May not be able to make enough
  - maybe considered a vitamin later in life and in illness

- **Some medications inhibit formation and need supplement**
  - Beta blockers, blood pressure medication, Statins and other cholesterol lowering drugs
Food Sources

- **Oils**
  - Soybean, rapeseed, and sesame

- **Organ meats like heart and liver**
  - Wild, grass fed animals have up to 10 times more coQ10 than organs of grain fed animals

- **Destroyed by heat**
  - Overcooked meat decreased amounts
  - Boiling does not affect, but frying decreased substantially

- **Difficult to maintain CoQ10 levels from diet alone**
Deficiency

- Primary deficiency rare
- Myopathy with Central Nervous system involvement
- Ataxia with cerebellar atrophy
- Exercise intolerance
- Recurrent myoglobinuria
- Developmental delay
- Seizures
Toxicity/Side Effects

- In patients with peripheral neuropathy aggravated pain
- Potential interaction with warfarin
- Potential hypoglycemic and hypotensive effects
- Anecdotal reports
  - Inability to sleep
  - Elevated liver enzymes
  - Rashes
  - Nausea and abdominal pain
  - Sensitivity to light, irritability and headache
DRI/ Upper Limits

- None established
- Max doses used in research is 3000 mg/d
Research

- Decreased oxidative stress
- Benefits seen in
  - Parkinson’s disease
  - CHF
  - Migraine
  - Mitochondrial disorders
  - Some metabolic disorders
  - Questionable benefit in Diabetes
  - Probable relief from cancer treatment side effects
  - Probable benefit from stroke and after cardiac arrest
Research

- mdx mice
  - Ubiquinol 9 and 10 concentrations increased in quadriceps and heart of mdx mice, but not brain

- Boys
  - Muscular dystrophies and neurogenic atrophies (n = 12 and 15)
  - Treated with 100 mg/d
  - Improved physical performance
  - Improvement in well being
  - Improvement in cardiac function
Forms Available

- Soft gels 60 – 300 mg
- Tablets
- Liquids
- Cosmetics
Summary

- Is there adequate research?
- Is there an established dosage?
  - Mitochondrial disorders – 150mg/d or 2 mg/kg/d up to a maximum of 3000 mg/d
  - Parkinson 300-1200 mg/d
  - Cardiovascular 50-200 mg/d
  - Diabetes 100-200 mg/d
  - Muscular dystrophies – 100 mg/d
- Can I get enough or additional from the diet?
- Are the benefits worth the risk?
- What type of monitoring is needed?
Vitamin E

- Fat Soluble Vitamin
- Family of 8 antioxidants
- Most common form in American diet is gamma tocopherol
- Greatest nutritional significance alpha tocopherol
Function/Role

- Antioxidant
  - Intercepts free radicals and prevents lipid destruction
  - Protects LDLs from oxidation i.e. heart disease
  - Vitamin C and other antioxidants are capable of regenerating anti-oxidant capacity of alpha-tocopherol
- Expression and activity of immune and inflammatory cells
Deficiency

- Rare
  - Severe malnutrition, genetic defects, fat mal-absorption or disorders of fat metabolism, and in premature or VLBW infants
- Impaired balance and coordination
- Muscle weakness
- Neurological problems due to poor nerve conduction
Toxicity/Side Effects

- Long term safety not established
- No reported side effects taking up-to 35 times DRI for 4 months
- Can act as an anti-coagulant and increase risk of bleeding problems
- Potential for liver toxicity
## DRI/ Upper Limits

<table>
<thead>
<tr>
<th>Age (boys only)</th>
<th>DRI (mg/d)</th>
<th>UL (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>4</td>
<td>ND</td>
</tr>
<tr>
<td>7-12 months</td>
<td>5</td>
<td>ND</td>
</tr>
<tr>
<td>1-3 years</td>
<td>6</td>
<td>200</td>
</tr>
<tr>
<td>4-8 years</td>
<td>7</td>
<td>300</td>
</tr>
<tr>
<td>9-13 years</td>
<td>11</td>
<td>600</td>
</tr>
<tr>
<td>14-18 years</td>
<td>15</td>
<td>800</td>
</tr>
<tr>
<td>19 and above</td>
<td>15</td>
<td>1000</td>
</tr>
</tbody>
</table>
Research

- In mdx mice
  - Mice on wood shavings or wheat kernel beds on conventional or vitamin E diets
- In DMD boys
  - No benefits on muscle force or function
  - No benefits for muscular strength and cardiopulmonary function
  - No benefits compared to placebo
Sources

- Vegetable oils
  - Palm, sunflower, corn, soybean and olive, wheat germ
- Nuts
  - Sunflower seeds, peanut butter
- Wheat Germ
- Whole grains
- Fish
- Green Leafy Vegetables
- Fortified breakfast cereal
Supplements/ Availability

- **Fully Synthetic**
  - Contains several different isomers
  - Most common and least expensive
  - Less potent and bio-available

- **Semi-synthetic – esterified natural source**
  - More stable
  - Found in tablets and MVIs and cosmetics
  - In healthy people easily de-esterfied over several days

- **Natural – RRR-_-tocopherol**
  - Most bio-available form of _-tocopherol
  - Preferred isomer for use by the body
Availability

- Soft-gels, tablets or liquid
- With selenium, vitamin C, and/or other antioxidants
- 200-1500 IU per serving
Summary

- Is there adequate research?
- Is there an established dosage?
- Can I get enough or additional from the diet?
- Are the benefits worth the risk?
- What type of monitoring is needed?
Selenium

- Chemical element related to sulfur and tellurium
- Essential in small quantities but toxic in large
Function/Role

- Required for the function of selenoproteins
- Component of amino acids
  - selenocysteine and selenomethionine.
- Functioning of the thyroid gland
  - Cofactor for thyroid hormone
- Cofactor for reduction of antioxidant enzymes
- Interacts and supports with every nutrient that affect the pro-oxidant/antioxidant balance of the cell
  - Vitamins E and C
- Interacts with other components of antioxidant enzymes
  - Copper, zinc, and iron
Deficiency

- Rare in healthy well-nourished individuals
- Can occur in patients with severely compromised intestinal function, HIV
- Can occur in patients fed solely by total parenteral nutrition
- Can occur in people dependent on food grown from selenium deficient soil
  - Keshan disease – myocardial necrosis, weakening of heart
  - Kashin disease – atrophy, degeneration and necrosis of cartilage disease
  - Goitre, cretinism, recurrent miscarriages
No abnormalities seen in DMD boys
No change in disease activity on 6 micrograms, 20 micrograms or 1mg/d
Most research in cancer, heart disease, arthritis, HIV and other chronic diseases
Toxicity

- Malnourished status can enhance selenium toxicity
- Pro-oxidant in large amounts
- Selenosis
  - Gastrointestinal upsets
  - Hair loss
  - White blotchy nails
  - Garlic breath odor
  - Fatigue and irritability
  - Mild nerve damage
  - Hair and nail brittleness and loss
## DRI/ Upper Limits

<table>
<thead>
<tr>
<th>Age (boys only)</th>
<th>DRI ug/d</th>
<th>Upper limit ug/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>15</td>
<td>45</td>
</tr>
<tr>
<td>7-12 months</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>1-3 years</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>4-8 years</td>
<td>30</td>
<td>150</td>
</tr>
<tr>
<td>9-13 years</td>
<td>40</td>
<td>280</td>
</tr>
<tr>
<td>14 years and above</td>
<td>55</td>
<td>400</td>
</tr>
</tbody>
</table>
Sources

- Dependent on selenium levels in the soil
  - Liver*
  - Brazil nuts*
  - Whole Grain Cereals
  - Green Leafy Vegetables
  - Garlic
  - Meat
  - Fish
  - Eggs
Availability

- Organic form found in foods
  - Selenomethionine
  - Best absorbed and utilized form of selenium
  - Increase blood concentrations to a greater extent than inorganic form

- Inorganic form found in supplements
  - Sodium selenate and sodium selenite
  - High selenium yeasts - selenomethionine
  - 1000 – 2000 micrograms selenium/gram
Summary

- Is there adequate research?
- Is there an established dosage?
- Can I get enough or additional from the diet?
- Are the benefits worth the risk?
- What type of monitoring is needed?
Antioxidants

- Reactive Oxygen Species
  - Natural byproduct of normal metabolism of oxygen
  - Important for cell signaling
  - However stress can increase ROS levels greatly causing damage to cell structures
  - Normally cells are able to defend themselves against ROS damage by using antioxidants and scavenging free radicals
Diseases implicated due to ROS mediated tissue injury

- Cancer
- Atherosclerosis
- Degenerative neurological diseases
  - AML, Parkinson’s, Alzheimer’s
- Ishcemia
- Aging
- Inflammatory and auto-immune diseases
Green Tea

- Rich in anti-oxidant epigallocatechin gallate
- 2 studies in mdx mice showed the extract improved muscle function
- 0.01-0.05% green tea extract
- Corresponds to about 1 and _ L (6 cups)/day
### Top 20 foods rich in anti-oxidants

<table>
<thead>
<tr>
<th>Small red beans dried</th>
<th>Strawberries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild blueberries</td>
<td>Red delicious apples</td>
</tr>
<tr>
<td>Red kidney beans</td>
<td>Granny smith apples</td>
</tr>
<tr>
<td>Pinto beans</td>
<td>Pecans</td>
</tr>
<tr>
<td>Cultivated blueberries</td>
<td>Sweet cherries</td>
</tr>
<tr>
<td>Cranberries</td>
<td>Black plums</td>
</tr>
<tr>
<td>Cooked artichokes</td>
<td>Cooked russet potatoes</td>
</tr>
<tr>
<td>Blackberries</td>
<td>Dried black beans</td>
</tr>
<tr>
<td>Prunes</td>
<td>Plums</td>
</tr>
<tr>
<td>Raspberries</td>
<td>Gala Apples</td>
</tr>
</tbody>
</table>
Summary

- Is there adequate research?
- Is there an established dosage?
- Can I get enough or additional from the diet?
- Are the benefits worth the risk?
- What type of monitoring is needed?
Omega 3 Fatty Acids

- Essential Fatty Acid
  - Body cannot synthesize and so required in the diet
  - Alpha- Linolenic Acid, EPA, DHA
  - Antioxidant in small quantities
Food Sources

- Cold Water Fish
- Nuts
- Flax seed and oils
- Oils
- Green Leafy Vegetables
DRI/ Upper Limit

- Adequate Intake
  - Men 1.6 grams/day
  - Women 1.1 gm/d
- FDA recommends <3 gm omega 3 per day of which <2 come from supplements
  - 1-3% of total energy from omega 3 and omega 6
- Oxidant in large quantities
- Pro-arrhythmic
- May cause deficiency of omega 6 fatty acids
- May lead to increased bleeding time
Health Benefits

- Mostly done with Cardiac Disease
- None done on DMD population
- May reduce risk of coronary artery disease
- Bipolar disorder and depression
- Healthy visual function in babies
- Implicated in inflammatory diseases
Summary

- Is there adequate research?
- Is there an established dosage?
- Can I get enough or additional from the diet?
- Are the benefits worth the risk?
- What type of monitoring is needed?
Carnitine

- Quaternary ammonium compound
- Derived from Lysine or methionine
- Responsible for transport of fatty acids from the cytosol into the mitochondria
- Vitamin C is essential for synthesis
- Antioxidant
- Conditionally essential nutrient
Food Sources

- Red Meat and Dairy Products
- Nuts and seeds
  - Pumpkin, sunflower, sesame
- Legumes and Beans
  - Beans, peas, lentils, peanuts
- Vegetables
  - Artichokes, asparagus, broccoli, Brussels sprouts, garlic, okra
- Fruits
  - Apricots, bananas
- Whole grains
  - Buckwheat, rice bran, rye, whole wheat, wheat bran, wheat germ
- Green Leafy vegetables
  - Beet greens, collards, mustard greens, kale, parsley
- Bee Pollen, Brewer’s yeast and Carob
Deficiency

- Biologic effects may not be noticed till 10-20% of normal
- Maybe primary or secondary
- Primary or secondary
  - Impaired entry of LCFAs into mitochondria
  - Beta oxidation, energy production and ketone body production is impaired
  - Cardiomyopathy, encephalopathy and skeletal muscle myopathy
  - Excessive lipid accumulation in muscle, heart and liver
  - Hypoketotic hypoglycemia
  - Muscle weakness, gastric dysmotility and hypochromic anemia
- Maybe seen in end-stage renal dz and hemo-dialysis
DRI/ Upper Limits

- None reported
- ~3000 mg/d may cause fishy body odor in adults
- 40-100 mg/kg/d in children is normally recommended dose
Toxicity

- None reported
- Gastrointestinal symptoms
  - Nausea, vomiting, abdominal cramps, diarrhea
- Fishy body odor
- Potential effect on liver, kidney and heart
Research

- **Preliminary benefits seen in**
  - Primary and secondary carnitine deficiencies
  - End stage disease and hemodialysis – overall well being
  - Cardiovascular disease – decreased mortality
  - Peripheral arterial disease – improvement in exercise performance of ischemic muscles
  - Diabetes- may improve insulin sensitivity
  - Treatment of mild cognitive impairment and mild alzheimers
  - Treatment of lipoatrophy in HIV patients
  - Cancer- improvement of fatigue

- **Probably beneficial only to someone whose carnitine levels are decreased**
In DMD

- Muscle carnitine deficiency reported in 12 boys with DMD
Availability

- Liquid and tablet form
Summary

- Is there adequate research?
- Is there an established dosage?
  - Usual 40-100 mg/kg/d
- Can I get enough or additional from the diet?
- Are the benefits worth the risk?
- What type of monitoring is needed?
Summary

- Arginine
- Co-enzyme Q
- Creatine
- Selenium
- Vitamin E
- Antioxidants
- Omega 3 fatty acids
- Carnitine
Summary

- Healthy diet should provide all the nutrients needed by your body.
- Use supplements to provide any additional benefits that it may provide, not to make up for a poor diet.
- Best absorbed form of nutrient is usually from the food.
- As of yet, there are no magic bullets for DMD boys, unless a supplement is provided for a primary or secondary deficiency.
- If you choose to start a supplement, have clear set objectives and time goal before you start - enlist team in defining objectives and progress.
- Managing MD to monitor necessary signs and labs for toxicity or effects on other organs.
Questions