Outline

• General Nutrition for Patients with Thalassemia:
  – Energy intake, supplements, iron overload
• A few clinical examples:
  – Fat Soluble Vitamin: Vitamin D
  – Trace Element: Zinc

• Benefits of physical activity
• What do we know about exercise & Thalassemia
• How physically active are patients with Thalassemia?
Nutritionists Rule #1

“You can get all the nutrients you need from food alone....”

- Michael Pollak

-- Most patients with thalassemia can’t get ALL the nutrients they require from food alone
North American Dietary Survey in Thal:

n=221
48% male
51% Asian
19.7 ± 11.3 yrs

Conclusion:
Dietary Intake Inadequate
Particularly for folate and the fat soluble vitamins (D,E) and minerals (Ca,Mg)

Fung EB et al, JAND 2012
North American Dietary Survey in Thal:

Conclusion:
Dietary Intake Inadequacy Increases for some nutrients (A,E,B6,C,Th,folate,Ca,Mg,Zn) With advancing age Of patients

Fung EB et al, JAND 2012
Circulating Nutrient Levels in Transfused Patients with Thalassemia

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Normal Range</th>
<th>Value</th>
<th>% Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fat Soluble Vitamins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A, ug/dL</td>
<td>38-98</td>
<td>34.6 ± 12.2</td>
<td>52.4%</td>
</tr>
<tr>
<td>Vitamin D, ng/mL</td>
<td>20-100</td>
<td>17.1 ± 8.5</td>
<td>50.0%</td>
</tr>
<tr>
<td>α tocopherol, mg/dL</td>
<td>5.7-19.9</td>
<td>7.5 ± 7.5</td>
<td>30.0%</td>
</tr>
<tr>
<td>γ tocopherol, mg/dL</td>
<td>&lt;4.3</td>
<td>3.0 ± 5.0</td>
<td>4.2%</td>
</tr>
<tr>
<td><strong>Water soluble vitamins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamin, ug/L</td>
<td>2.4 – 11.7</td>
<td>4.1 ± 4.0</td>
<td>37.5%</td>
</tr>
<tr>
<td>Vitamin B-6, ng/mL</td>
<td>3.3 – 26</td>
<td>7.0 ± 5.9</td>
<td>34.8%</td>
</tr>
<tr>
<td>Vitamin B-12, pg/mL</td>
<td>200-1100</td>
<td>528 ±152</td>
<td>0%</td>
</tr>
<tr>
<td>Folate (ng/mL)</td>
<td>&gt; 8</td>
<td>11.8 ± 7.7</td>
<td>37.5%</td>
</tr>
<tr>
<td><strong>Trace Elements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper, ug/dL</td>
<td>59 – 118</td>
<td>85.1 ± 15.5</td>
<td>0%</td>
</tr>
<tr>
<td>Selenium, ug/dL</td>
<td>110 – 160</td>
<td>99.5 ± 20.7</td>
<td>75.0%</td>
</tr>
<tr>
<td>Zinc, ug/dL</td>
<td>65 – 124</td>
<td>83.0 ± 15.6</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

Mean ± SD

43 SCD, 24 Thal major, Age: 1.5 – 31.4 yrs, Ferritin: 3874 ± 4451

(Adapted from Claster S et al 2009)
Energy Balance Equation

Energy In = Energy Out

$\text{Kcal Intake} = \text{REE} + \text{TEF} + \text{Physical activity}$

Nutrient Intake = Nutrient Requirement - Loses

REE: Resting Energy Expenditure
TEF: Thermic Effect of Food
Elevated energy expenditure decreases after red cell transfusion and is related to [hemoglobin]

n=7
Tx B-thal
22-30 yrs
Pre:
Day of Tx
Post
3 days after

$P=0.02$

Example of Increased “Need”: Increased Oxidative Stress

- Increased “free iron” = pro-oxidant

- Increased markers circulating of oxidative stress

*Walter PB et al BJH 2006, 135:254*
Example of Increased Losses: Urinary Zinc Excretion in Thalassemia

**Fig 2: Urinary Zinc in Thal vs. Controls**

- Thalassemia: Ave. 0.08 ugZn/mgCr
- Control: Ave. 0.03 ugZn/mgCr

- p=0.02

**Urinary Zinc in Diabetics vs. Non-Diabetics**

- Non-Diabetic: Ave. 0.07 ugZn/mgCr
- Diabetic: Ave. 0.13 ugZn/mgCr

- p=0.01

*Fung EB et al AJCN 2013.*
Summary of Nutritional Requirements
What is known in Thalassemia?

- Mildly increased energy expend.
- Iron overload
  - Increased oxidative stress
  - Sequestration “capture” of trace minerals in the liver (suspected)
- Increased excretion of minerals due to iron chelators

- Limited total calorie intake
- Inadequate intake of essential nutrients
- Little if anything known about absorption

Requirements > Intake
Should patients be taking supplements?

**Answer:** YES. Patients should consider taking a complete multivitamin/mineral supplement that does not contain iron

- Some nutrients can be obtained from diet alone, and are absorbed most efficiently from their natural food source.
- A well-balanced diet is important for other non-essential nutrients such as fiber, phytochemicals etc.
- At this time, there is not sufficient evidence to suggest that a high dose antioxidant supplement would be beneficial above what is found in a multivitamin.

**Caveat:** Not a substitute for adequate chelation or a healthy diet.
Nutritionists Rule #1
You can get all the nutrients you need from food....
--Most patients can’t get all the required nutrients from food alone

Nutritionists Rule #2
“Iron deficiency is the most common nutrient deficiency worldwide”

--Iron overload is the most pervasive issue...
  though dietary iron is not the real villain in transfused patients
What are the “rules” about iron rich foods?

- 2 main forms of iron in the diet:
  - Heme (animal)
  - Non-heme (plant)

- Heme-iron absorbed different from non-heme iron

- Non-heme iron **enhanced** by vitamin C rich foods
  - So avoid eating foods with iron (cereal) with vit C foods (orange juice)

- **Non-heme iron inhibited** by tea consumption
  - One study, n=6 subjects, 40-95% inhibition
    
    {DeAlarcon et al NEJM;1979:300:5-8}
The Dietary Iron Dilemma

Transfusion iron load: 200 mg/Fe per Tx
   2 units every 3 weeks = 19 mg/day
Diet iron load: 4 oz steak 2 x/week
   2.5 mg x 2 (10% absorption) = 0.5 mg/day

**Transfused subjects:** transfused iron >>>>> dietary iron

**Non-transfused subjects:**
1. limit animal sources of iron (heme)
2. consume plant rich sources without vitamin C rich foods
3. drink tea with meals
Nutritional Interventions in Patients with Thalassemia: What has been tried?
Vitamin D Deficiency in Thalassemia

Fung EB et al, Amer J Heme 2011
Vitamin D Supplementation

Regimen:
Test annually
If <20 ng/mL
Supplement
with 50,000 IU D2
q 3 weeks
at time of transfusion

Repeat Vitamin D level
after 6-8 doses

n=66 cases     Mean change=1.4 ng/dL per dose
if 10 ng/dL = 10 doses to > 30 ng/dL

Fung EB et al, Amer J Heme 2011
Zinc Supplementation and Bone Metabolism in Thalassemia
What do Bones Look Like in Young Patients with Thalassemia?

Full Lateral Spine Scans

Distal Radius

Control  Thalassemia
Role of Zinc in Bone Formation & Resorption

Yamaguchi M, Mol Cell Biochem 2010
*Highlights: Zinc & Thalassemia*

- Up to 80% of sampled patients with thalassemia have **depressed plasma zinc** (Iran: Shamshirsaz, 2003; Turkey: Arcasoy 1975; Thailand: Kajanachumpol, 1997)

- Depletion of circulating zinc may be due in part to the presence of proximal tubular damage and **hyperzincuria**, UZn is 4x that of controls (India: Uysal, 1993)

- In iron overloaded patients, one pool of NTBI is bound to albumin, thus decreasing the sites for zinc to bind (Arcasoy, 2001; Turkey)

- Growth abnormalities in thalassemia due to chelation toxicity and/or **zinc deficiency** (Benso, 1995)

- Zinc supplementation (22-90 mg/day) has been shown to increase **height velocity** in young regularly transfused, non-chelated patients with thalassemia (1-18 years) (Iran: Arcasoy, 1987)

- Low bone mass is common & related to **low zinc status** in adolescent females (Bekheirnia 2004, 2007, Iran)
Improving Bone Health in Thalassemia Through Zinc Supplementation: “Think Zinc Study”

It is hypothesized that patients with thalassemia have low bone mass, in part, due to zinc deficiency

**Primary Aim:** To determine the effect of zinc (25 mg/d) vs. placebo on bone health in young patients (6 to 30 yrs) with thalassemia estimated from BMD, and markers of bone formation and resorption.

**Study Design:** Randomized Placebo Controlled Trial

**Stratification:** Gender & Pubertal Development

**Protocol Length:** 18 months

**Estimated Sample Size:** 60 / 50 to complete

_Fung EB et al AJCN 2013_
## Study Time Line

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Baseline</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc/Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vit D &amp; Copper</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXA &amp; pQCT</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bone Age</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Puberty</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anthros</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood/Urine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Health ?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Adherence (pill counts, urinary zinc, calendars)

**Encouragement Tools:** Birthday cards, phone calls, reminder emails, pill containers, lunch boxes, pens, magnets, gift certificates
DXA Assessments: Think Zinc Study

BMC:
  Bone Mineral Content
BMD:
  Bone Mineral Density
Z-Score:
  Standard Deviation Score
IVA Analysis:
  Vertebral Fracture
Assessed for Eligibility (n=105)

61 Excluded: ineligible (n=34)
    not interested (n=15)
    other reasons (n=12)

Consented & Randomized (n=44)

2 dropped: tx reaction (n=1), too busy (n=1)

Baseline Completed (n=42)

Zinc Group (n=24)

n=6 dropped:
    1 ineligible
    1 pregnant after baseline
    1 nausea after baseline
    1 lost to follow-up after 6 mo
    1 sister of deceased
    1 did not return for 18 mo

Zinc (n=18)
Completed 18 month time point

Placebo Group (n=18)

n=4 dropped:
    1 ineligible
    1 pregnant after 12 mo
    1 lost to follow-up after 12 mo
    1 death after 12 mo

Placebo (n=14)
Completed 18 month time point

_Fung EB et al AJCN 2013._
### Baseline Subject Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Zinc (24)</th>
<th>Placebo (18)</th>
<th>Control (34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>17.5±5.6</td>
<td>17.4±4.7</td>
<td>17.5±5.2</td>
</tr>
<tr>
<td>B-Thal</td>
<td>62%</td>
<td>77%</td>
<td>-----</td>
</tr>
<tr>
<td>% Asian</td>
<td>75%</td>
<td>61%</td>
<td>42%</td>
</tr>
<tr>
<td>% Female</td>
<td>50%</td>
<td>50%</td>
<td>55%</td>
</tr>
<tr>
<td>Ht Z-score</td>
<td>-1.8±1.1</td>
<td>-1.6±1.3</td>
<td>-0.1±1.1</td>
</tr>
<tr>
<td>Ferritin, ng/dL</td>
<td>1994</td>
<td>2033</td>
<td>-----</td>
</tr>
<tr>
<td>Chelation</td>
<td>Desferal (7)</td>
<td>Desferal (3)</td>
<td>Combo (1)</td>
</tr>
<tr>
<td></td>
<td>Exjade (10)</td>
<td>Exjade (12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combo (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-OH VitD</td>
<td>23±11</td>
<td>26±11</td>
<td>32±8</td>
</tr>
<tr>
<td>&lt;30 ng/mL</td>
<td>71%</td>
<td>67%</td>
<td>47%</td>
</tr>
<tr>
<td>Dietary Zn, %RDA</td>
<td>133%</td>
<td>137%</td>
<td>138%</td>
</tr>
<tr>
<td>Plasma Zn, &lt;70 , ug/dL</td>
<td>82±14</td>
<td>82±16</td>
<td>79±8</td>
</tr>
<tr>
<td></td>
<td>23%</td>
<td>28%</td>
<td>11%</td>
</tr>
</tbody>
</table>

*Fung EB et al AJCN 2013*
Adherence to Zinc Supplement
by time of study in those who returned supplement bottles

No difference between zinc & placebo groups in
% adherence at anytime point

Fung EB et al AJCN 2013
Plasma Zinc With Time of Study
Placebo vs. Zn Supplementation in Patients with Thalassemia

Fung EB et al AJCN 2013
% Change in Whole Body Bone Mineral Content compared to baseline value in Placebo vs. Zinc Groups*

*Data controlled for puberty and baseline value

Absolute Difference 4.3%

Fung EB et al AJCN 2013
% Change in Whole Body Bone Mineral Density compared to baseline value in Placebo vs. Zinc Groups*

*Data controlled for puberty and baseline value

Fung EB et al AJCN 2013
% Change in Lateral Spine BMC & BMD compared to baseline value in Placebo vs. Zinc Groups

*Data controlled for pubertal development and baseline BMC value

Fung EB et al AJCN 2013
Adjusted spine & hip BMD Z-scores were 0.3 SDs lower in placebo compared to zinc group by the 18 month time point.

*BMD Z-scores adjusted for baseline BMD value and pubertal stage

Fung EB et al AJCN 2013
Relevance to Other Bone Mineral Density Treatment Options in Patients with Thalassemia

Current Study (Fung et al AJCN):
- Time period: 18 months
- Intervention: 25 mg/day Zinc
- Whole body change: 2–4%
- Lateral spine change: 5–9%
- Spine BMD Z-score: +0.37 SD

Previous Publications using Bisphosphonate Therapy

Voskaridou E (Br J Haematol 2003):
- Time period: 12 months
- Pamidronate
- Spine change: 4%

Mamtani M (Osteoporosis Int 2010):
- Time period: 2 years
- Zoledronate
- Spine change: 10%
- Spine BMD Z-score: +0.69 SD

## Adverse Events by Group in Subjects with Thalassemia who completed the 18 month protocol

<table>
<thead>
<tr>
<th>Sign / Symptom</th>
<th>Placebo (n=14)</th>
<th>Zinc (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>14.5%</td>
<td>18.4%</td>
</tr>
<tr>
<td>Stomach Cramping*</td>
<td>17.7%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9.7%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>4.8%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Skin Rash</td>
<td>9.8%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9.8%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Low serum Cu ≤70 ug/dL**</td>
<td>8 of 14</td>
<td>8 of 19</td>
</tr>
</tbody>
</table>

### Admissions & Other
- Death due to iron-related heart failure (n=1)
- Fever (n=1)
- Gastroenteritis (n=1)
- Diabetic Teaching (n=1)
- Asthma exacerbation (n=1)
- Distal radius fracture (n=1)

*Fung EB et al AJCN 2013*
Summary of Zinc Study:

- We found zinc supplementation was well tolerated in young patients with thalassemia, and that it increased bone mass particularly at the spine and whole body.

- Low bone mass is common in patients with Thalassemia and may be caused in part by a sub-clinical zinc deficiency.

- The potential to provide an anabolic stimulus to bone through a simple, safe nutritional intervention is promising and worthy of study in a larger cohort with a broader age range and disease severity.

Fung EB et al AJCN 2013
Exercise
Benefits of Physical Activity

**Physical activity can...**

- Can help maintain body weight, increase muscle mass
- Physical activity can also help with weight control
- Improve balance, decrease risk of falling/fracture
- Increase bone mass & alter bone geometry
  - Immobility causes rapid bone loss
- Lower your risk of heart disease, stroke, type 2 diabetes and some cancers
- Improves mood and decreases depression
- Improve academic achievement in students
Physical Activity Guidelines

Adults
150 min/wk of moderate exercise \{or\}
75 min/wk of vigorous exercise
30 minutes a day, 5x/wk
“10 min at a time is fine”

Adolescents
60 min of exercise each day!

Less than half of all adults meet the guidelines
Less than 3 in 10 high school students get at least 60 min of physical activity every day.
What do we know about Thal & Exercise?

- Exercise intolerance & fatigue common – patient reports
- Presumed to be inactive or highly sedentary due to low Hb (though no supporting evidence...)
- Exercise capacity is reduced in Thal- due to anemia and iron-mediated cardiotoxicity (Mavrogeni S et al 2009)
- Heart rate and cardiac output are abnormally high during exercise, compared to controls (Grant et al 1987)
- Cardiac iron is negatively associated with maximum heart rate response and VO2 max (Sohn EY et al 2013)
Relationship between Hemoglobin, VO$_2$Max & Heart Rate

Sohn EY et al AJH 2013

Females= solid bars, Males= cross-hashed bars
Relationship between Cardiac Iron and VO$_2$ Max and Heart Rate

more iron overloaded = worse exercise tolerance

Sohn EY et al AJH 2013
Energy Balance Equation

Energy In = Energy Out

Kcal Intake = REE + TEF + Physical activity

REE: Resting Energy Expenditure
TEF: Thermic Effect of Food
Describing Physical Activity Patterns in Thalassemia

GT3x+ Actigraph to Assess Physical Activity

Ongoing Study, CHRCO 2014
Results are Unpublished

n=50 Thal
50% Tx
50% Non-Tx
n=30 Controls
No need for physical activity extremes
Summary

NUTRITION

• A well-balanced, nutrient dense diet is key ... in addition to adequate chelation for transfused subjects
• Patients are unlikely able to obtain all needs through diet alone- a multivitamin/mineral supplement w/o iron needed
• Vitamin D is of particular concern, consider 2,000 IU/d, and check levels twice a year
• Dietary iron should be monitored in all patients, and tea consumed with meals
• Consider additional zinc supplement, particularly in those with low bone mass

PHYSICAL ACTIVITY

• Patients should start with small attainable goals, work up to 30 min/day, 5x/wk... Make it fun, something they can stick to
• Realize they may be more tired before Tx...
Special Thanks To...

**Children’s Hospital Oakland**
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- Catherine Aguilar
- Ida Micaily
- Laurice Levine
- Shaghig Tchaparian

**Subjects & Families Who Participate in the Research!!**

**Thalassemia Clinical Research Network**

**Cooley's Anemia Foundation**
- Leading the Fight Against Thalassemia

**National Heart Lung and Blood Institute**