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Nutrition & Exercise

Thal at Cal Lecture
10/06/2014

Ellen B. Fung, PhD RD CCD
Associate Research Scientist
Children's Hospital & Research Center, Oakland

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?

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Children's Hospital Oakland Research Institute

HEDCO Health Science Bldg

Nutrition Advice- Upside Down

Nutritionists Rule #1

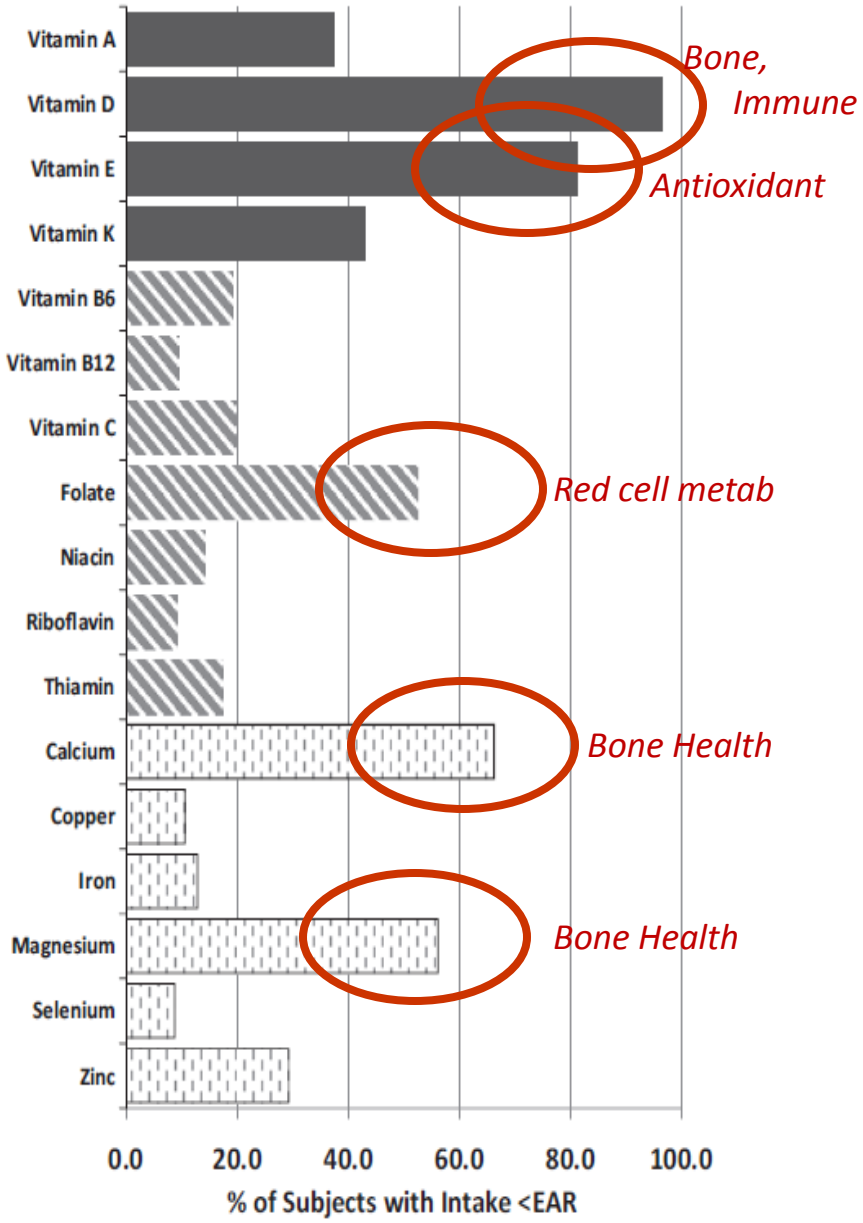
"You can get all the nutrients you need from food alone…."

- Michael Pollak

-- Most patients with thalassemia can't get ALL the nutrients they require from food alone

North American Dietary Survey in Thal:

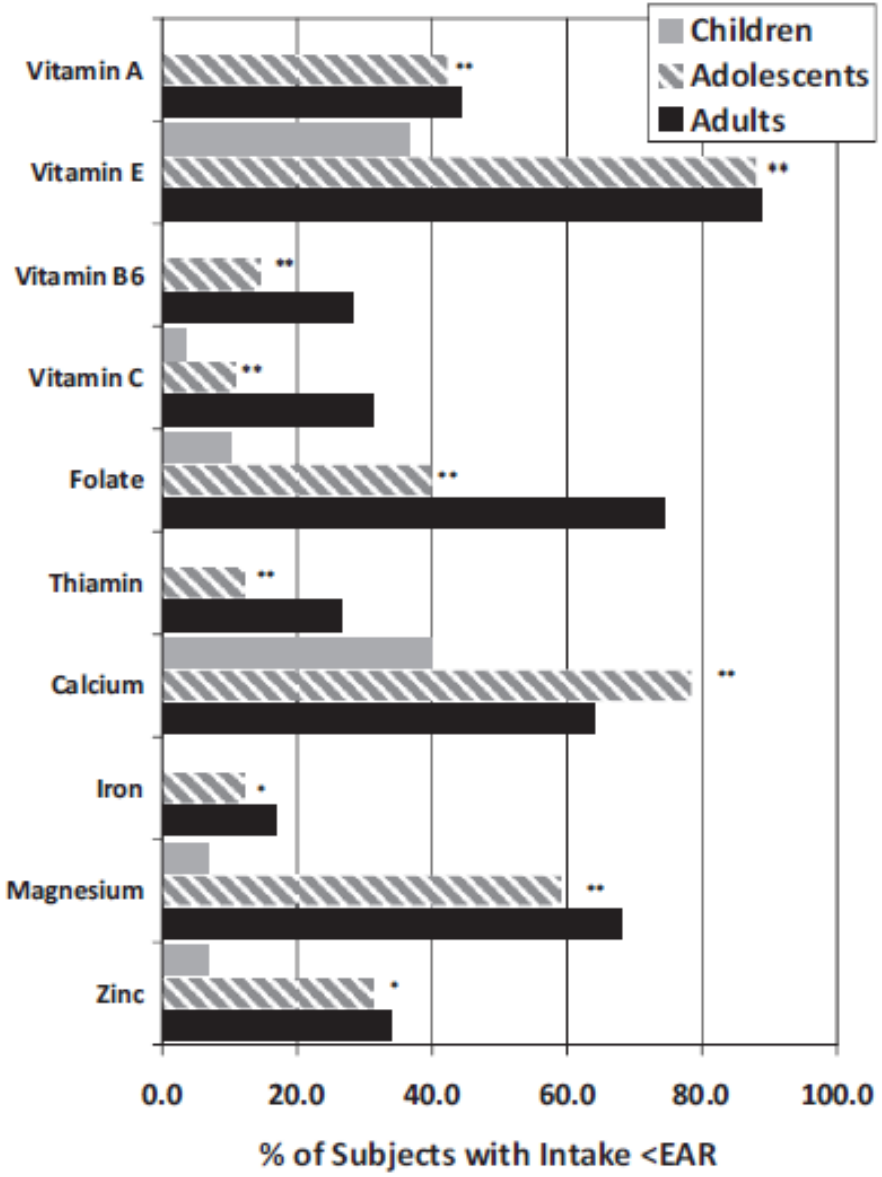
n=221
48% male
51% Asian
19.7 ± 11.3 yrs



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

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

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

Kcal Intake = REE + TEF + Physical activity

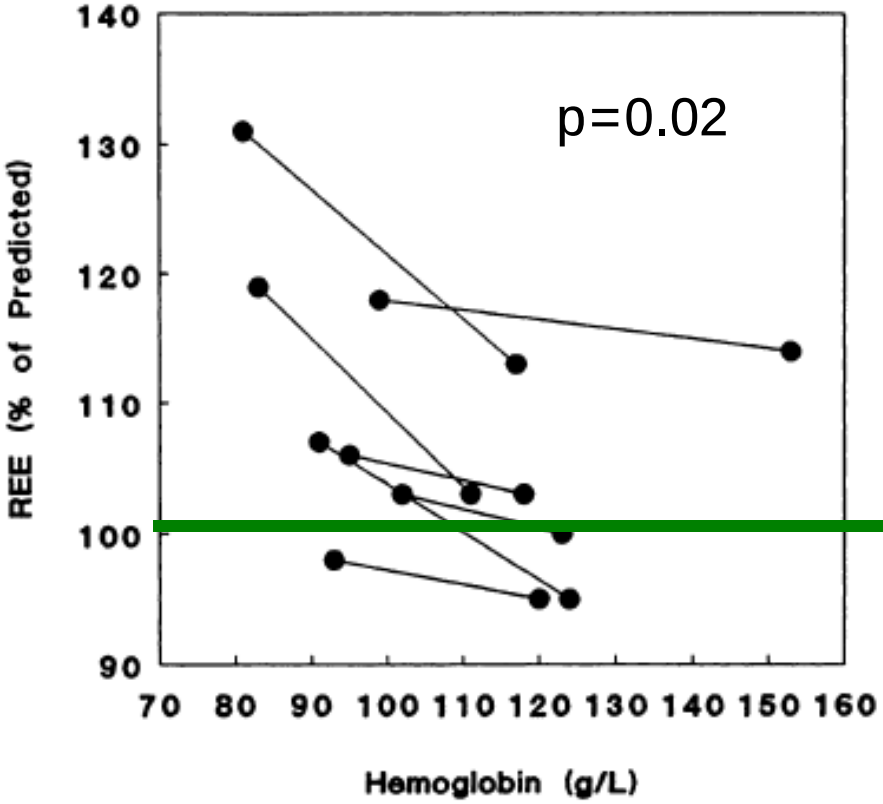
Nutrient Intake = Nutrient Requirement - Loses

REE: Resting Energy Expenditure
TEF: Thermic Effect of Food

Resting Energy Expenditure (REE)
Pre & Post Transfusion in Thalassemia

Elevated energy expenditure decreases after red cell transfusion and is related to [hemoglobin]

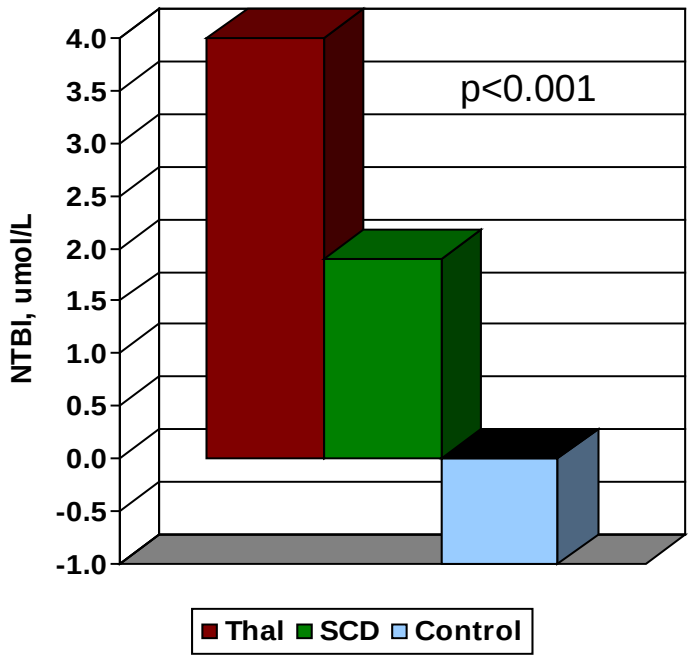
n=7
Tx B-thal
22-30 yrs
Pre:
Day of Tx
Post
3 days after



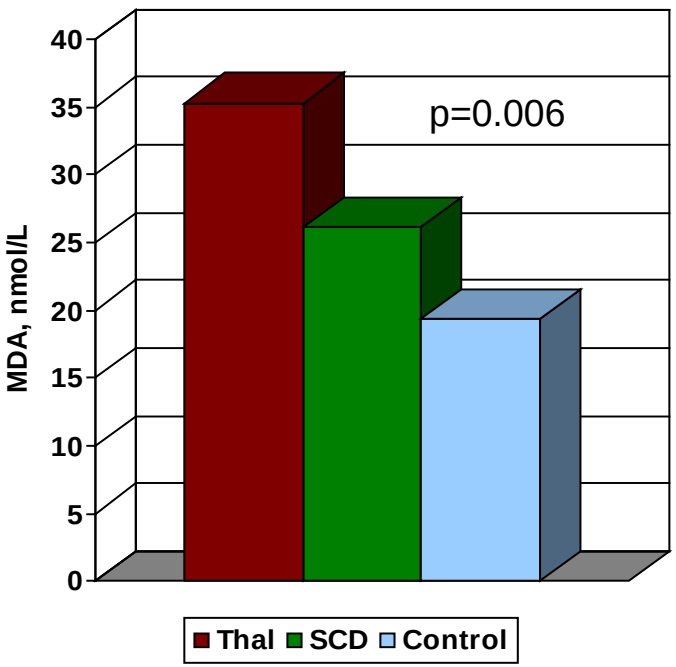
Indirect Calorimetry

Vaisman N et al. AJCN 1995;61:582-4.

Example of Increased "Need": Increased Oxidative Stress



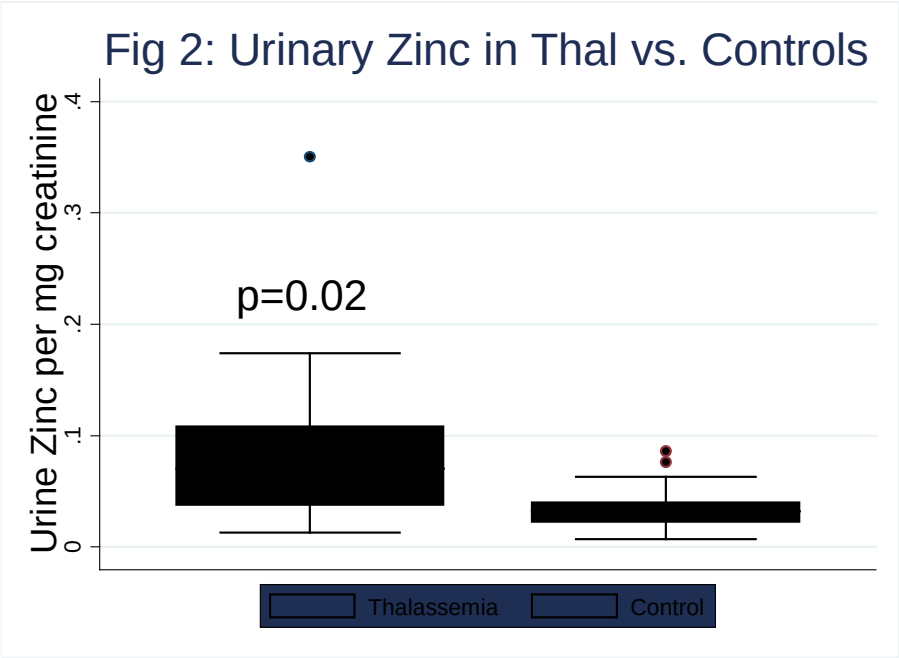
Increased "free iron" =pro-oxidant



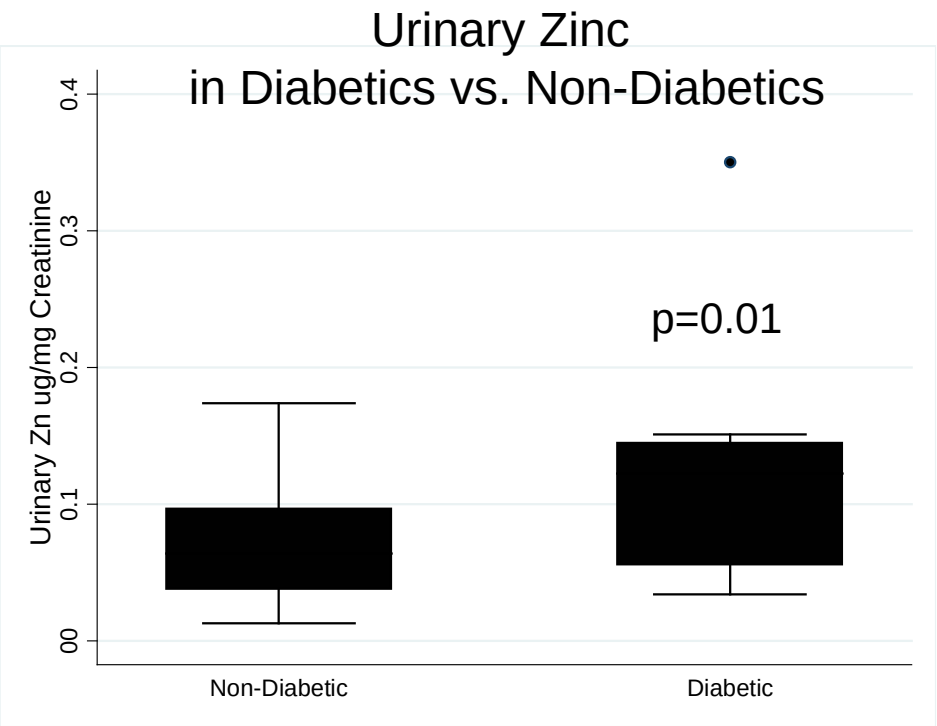
Increased markers circulating of oxidative stress

Walter PB et al BJH 2006, 135:254

Example of Increased Losses: Urinary Zinc Excretion in Thalassemia



Ave: 0.08 ugZn/mgCr 0.03 ugZn/mgCr



0.07 ugZn/mgCr 0.13 ugZn/mgCr

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

Nutrition Advice- Upside Down

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 <u>dietary iron</u> 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 <u>enhanced</u> by vitamin C rich foods
  - So avoid eating foods with iron (cereal) with vit C foods (orange juice)

- <u>Non-heme iron inhibited</u> 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

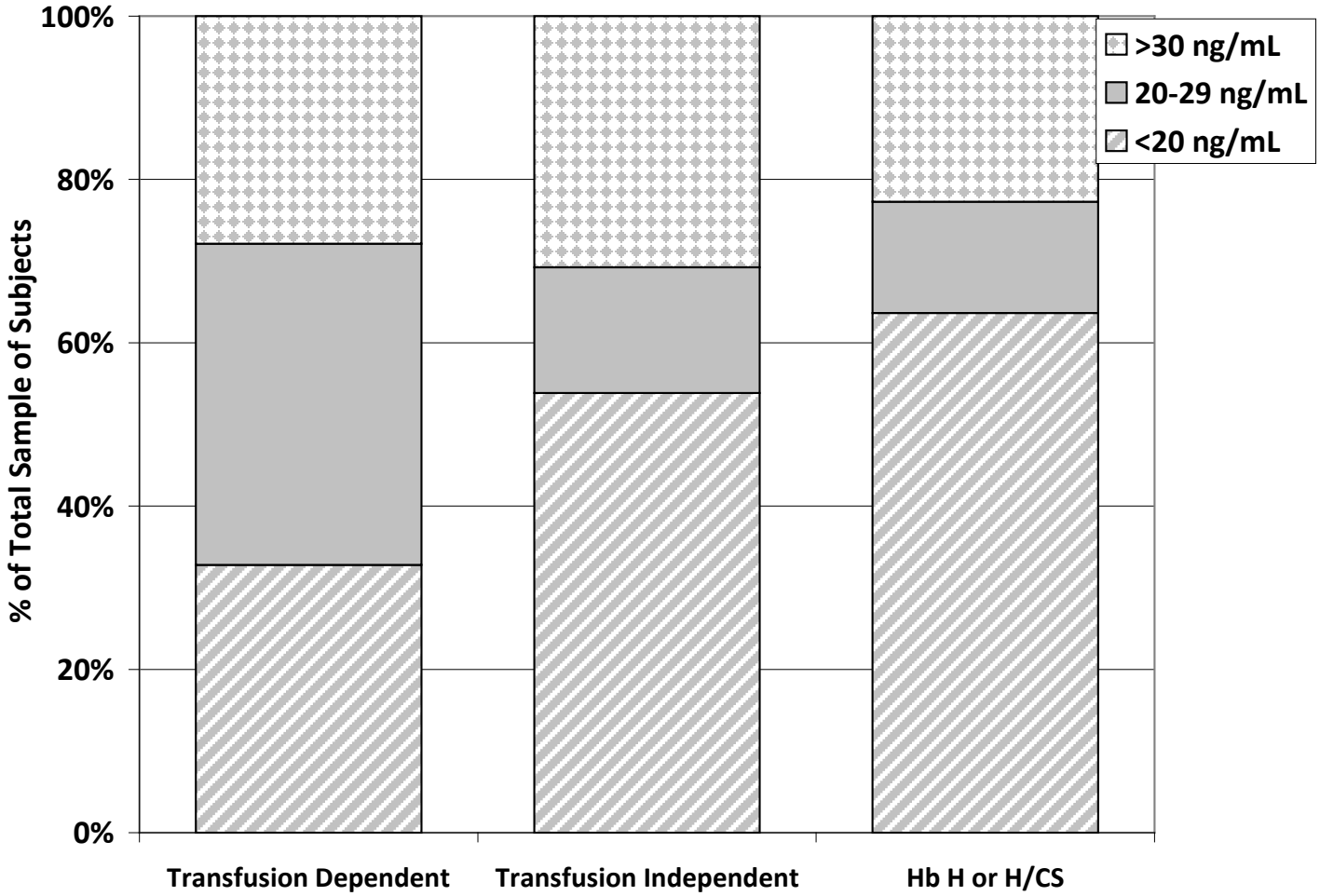
Transfused subjects: transfused iron >>>> dietary iron

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

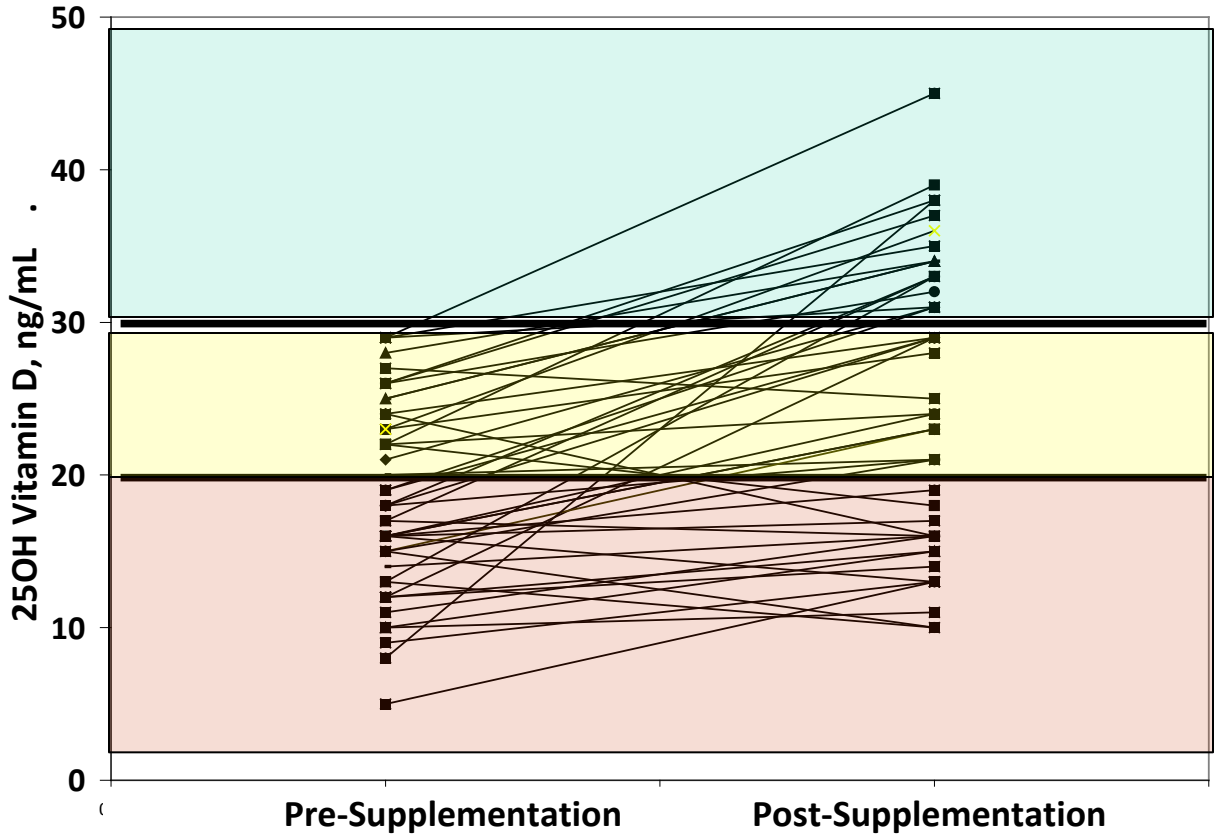


Fung EB et al, Amer J Heme 2011

Vitamin D Supplementation

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

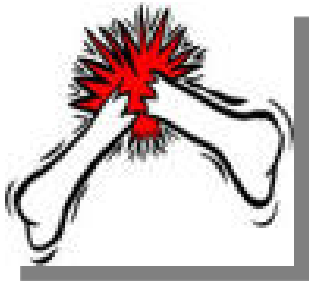
Repeat Vitamin D level
after 6-8 doses



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

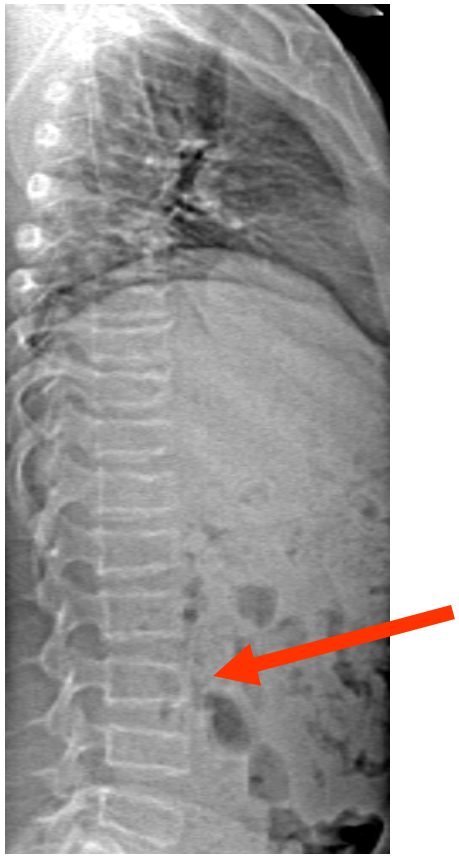


Zinc Supplementation and Bone Metabolism in Thalassemia

What do Bones Look Like in Young Patients with Thalassemia?

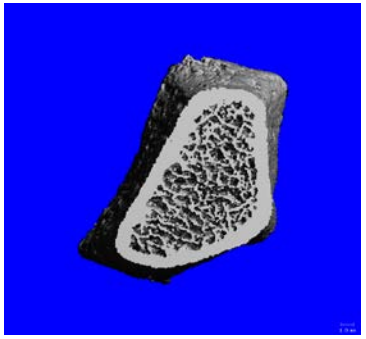
Full Lateral Spine Scans

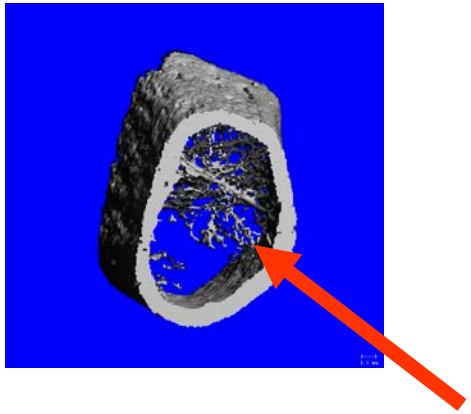
Control



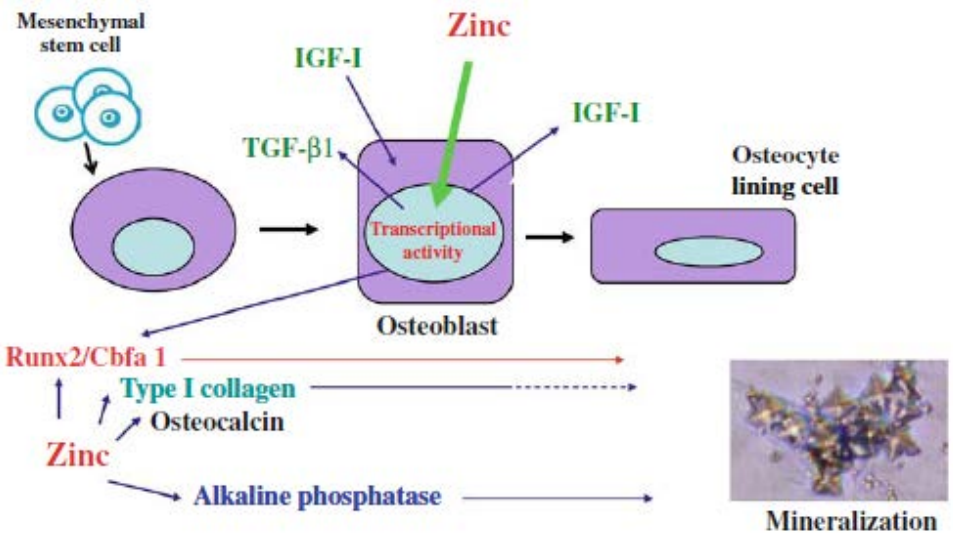
Thalassemia

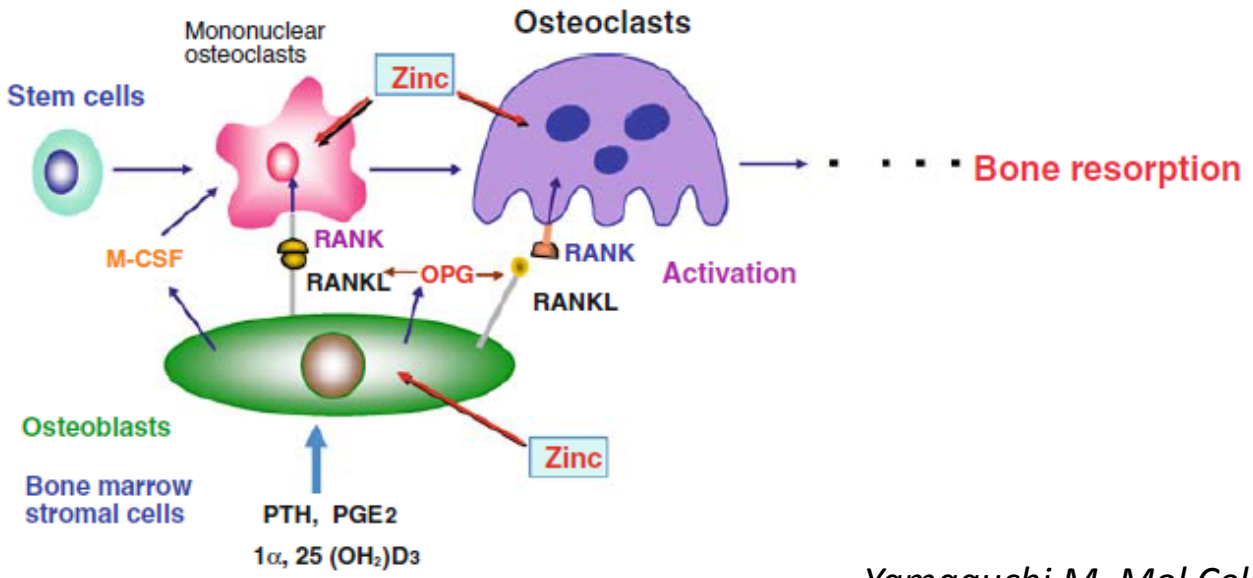
Distal Radius





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

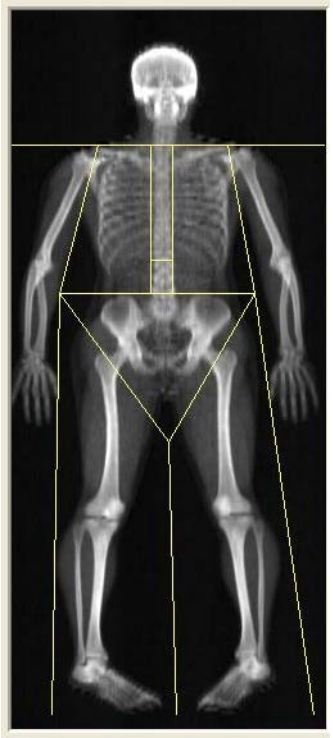
Fung EB et al AJCN 2013

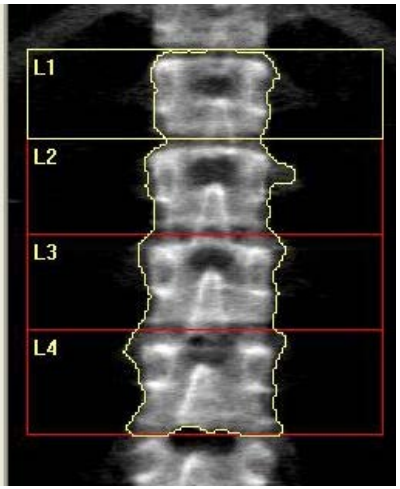
Study Time Line

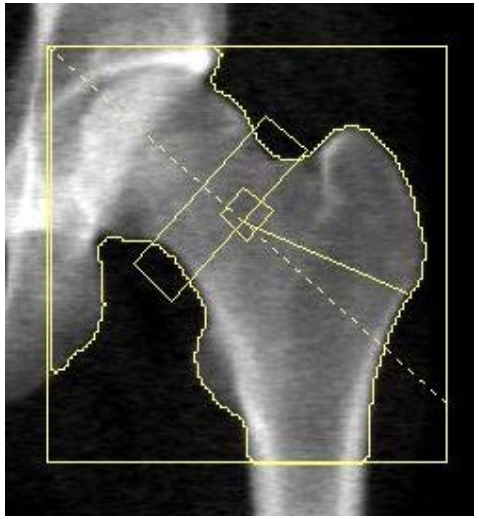
Time (months)	Baseline	3	6	12	18
Zinc/Placebo	→	→	→	→	→
Vit D & Copper	→	→	→	→	→
DXA & pQCT	X			X	X
Bone Age	X				
Puberty	X			X	X
Anthros	X	X	X	X	X
Blood/Urine	X	X	X	X	X
Health ?	X	X	X	X	X
Adherence (pill counts, urinary zinc, calendars)	→	→	→	→	→

Encouragement Tools: Birthday cards, phone calls, reminder emails, pill containers, lunch boxes, pens, magnets, gift certificates

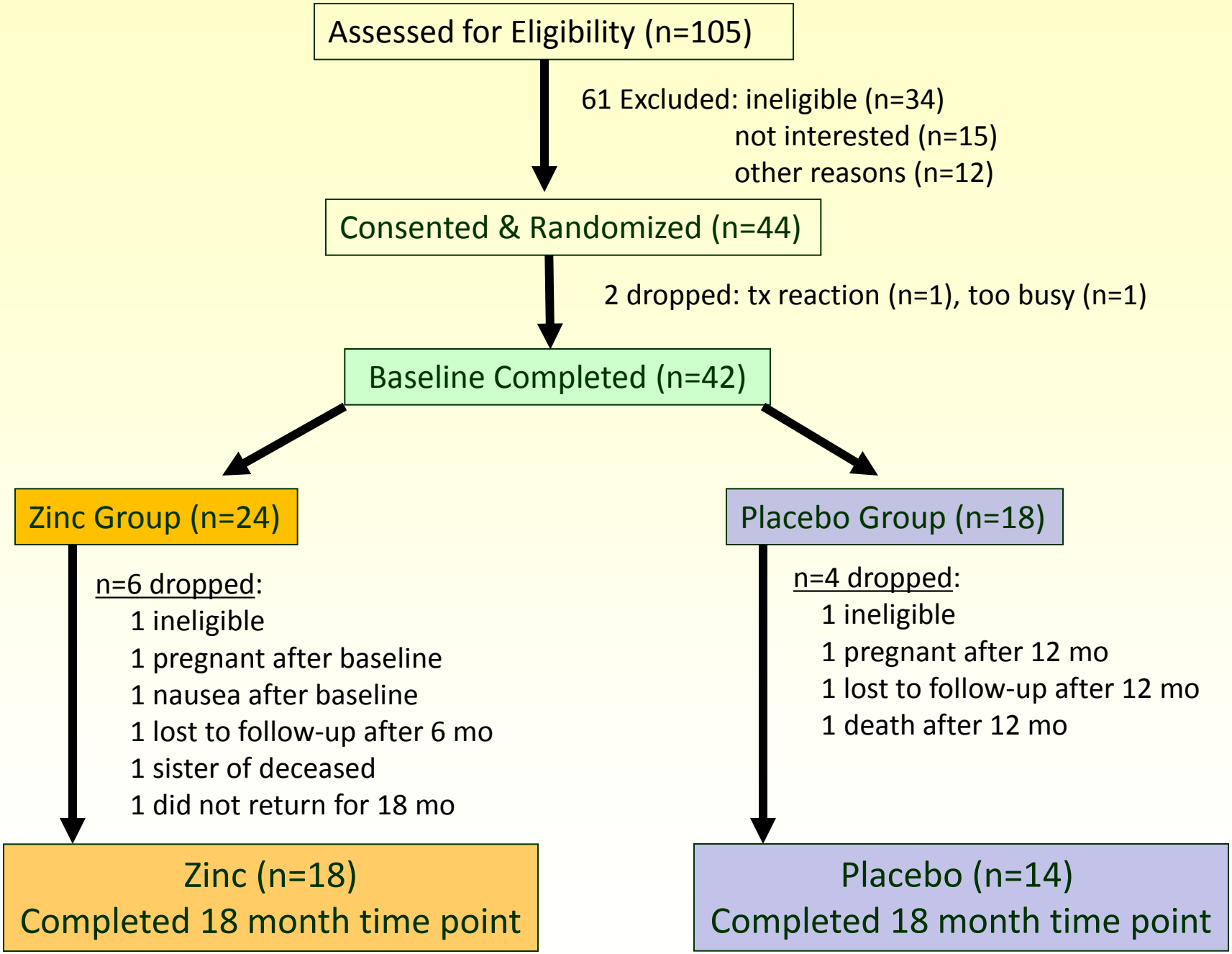
DXA Assessments: Think Zinc Study







BMC:
  Bone Mineral Content
BMD:
  Bone Mineral Density
Z-Score:
  Standard Deviation Score
IVA Analysis:
  Vertebral Fracture



Fung EB et al AJCN 2013.

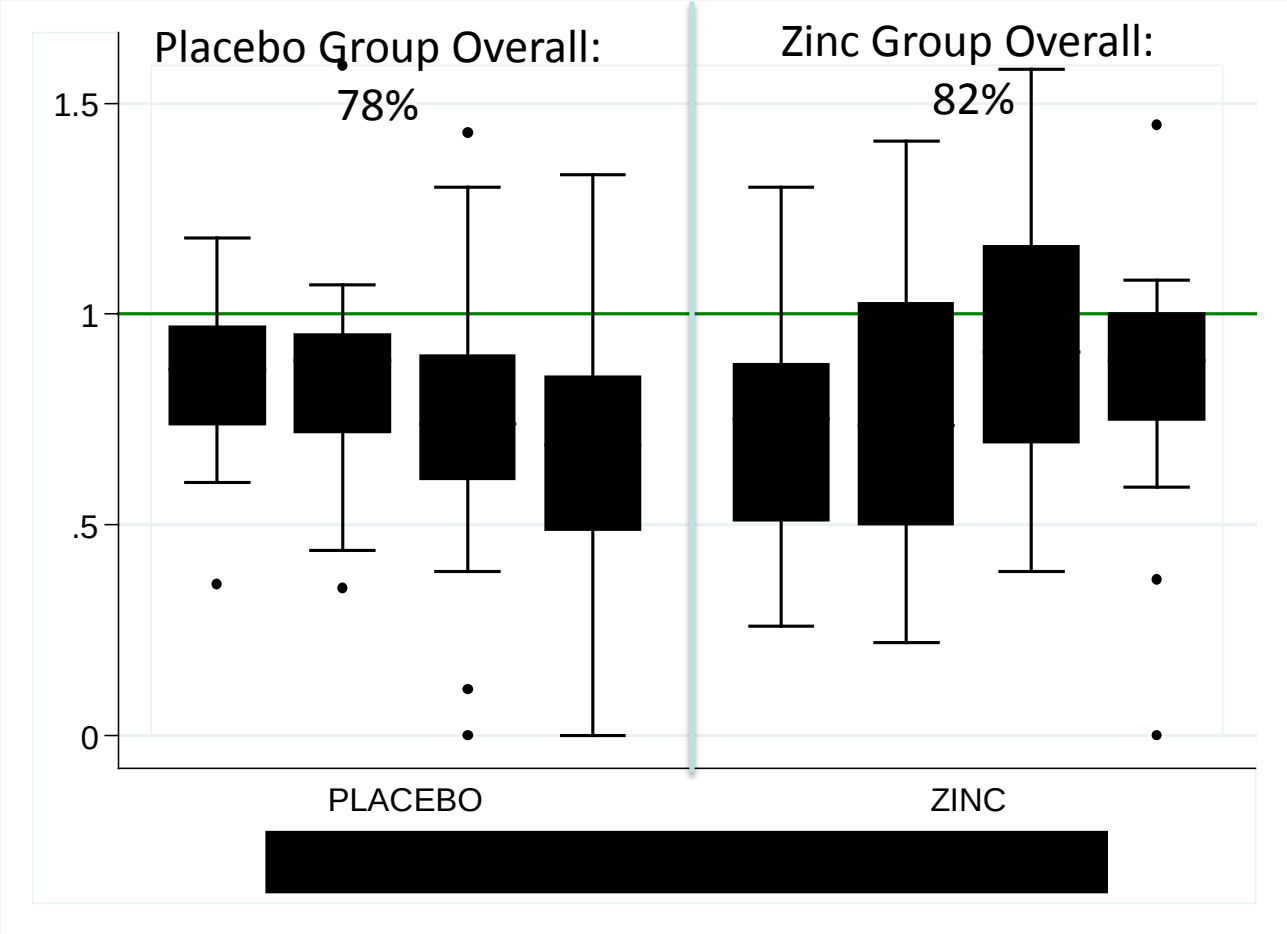
Baseline Subject Characteristics

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

Fung EB et al AJCN 2013

Adherence to Zinc Supplement

by time of study in those who returned supplement bottles

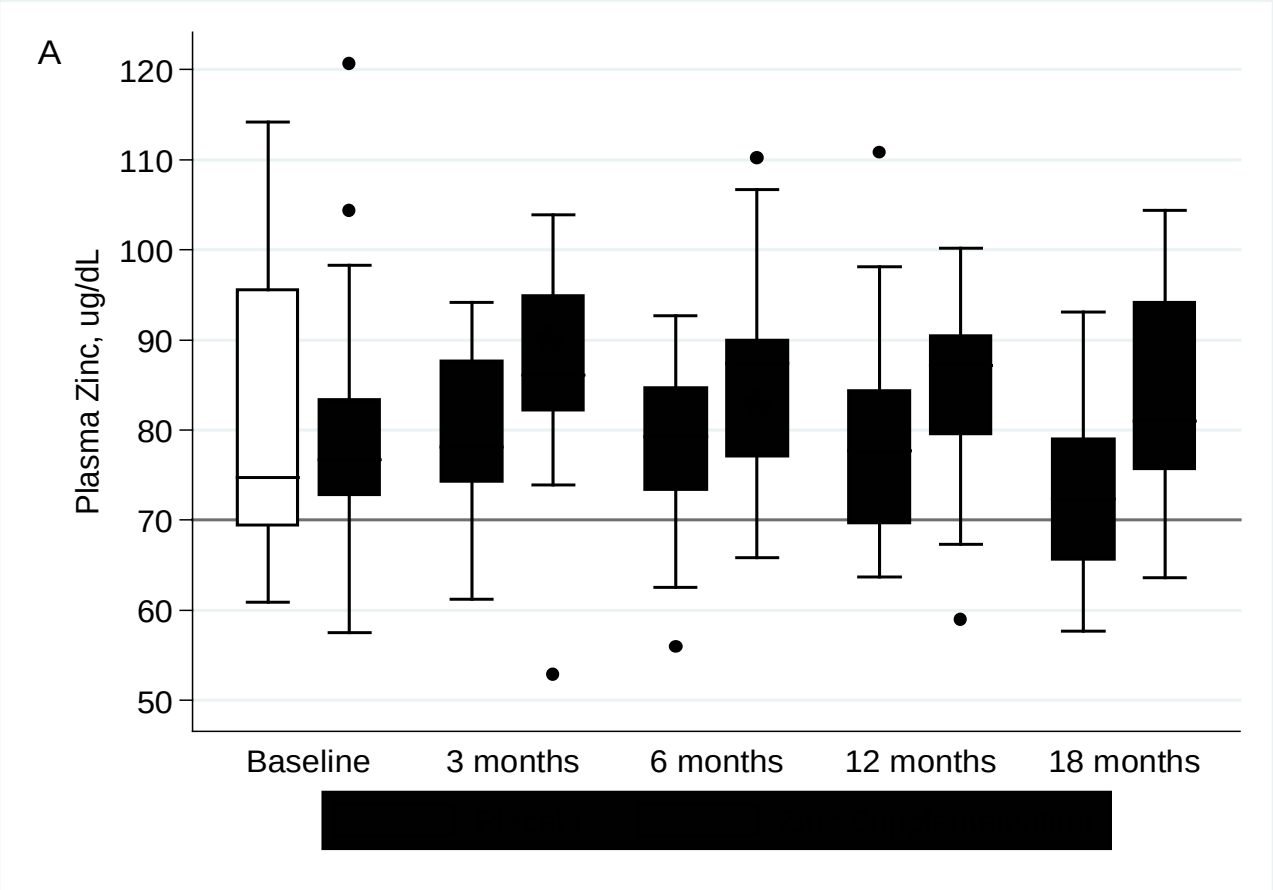


No difference between zinc & placebo groups in % adherence at anytime point

Fung EB et al AJCN 2013

Plasma Zinc With Time of Study

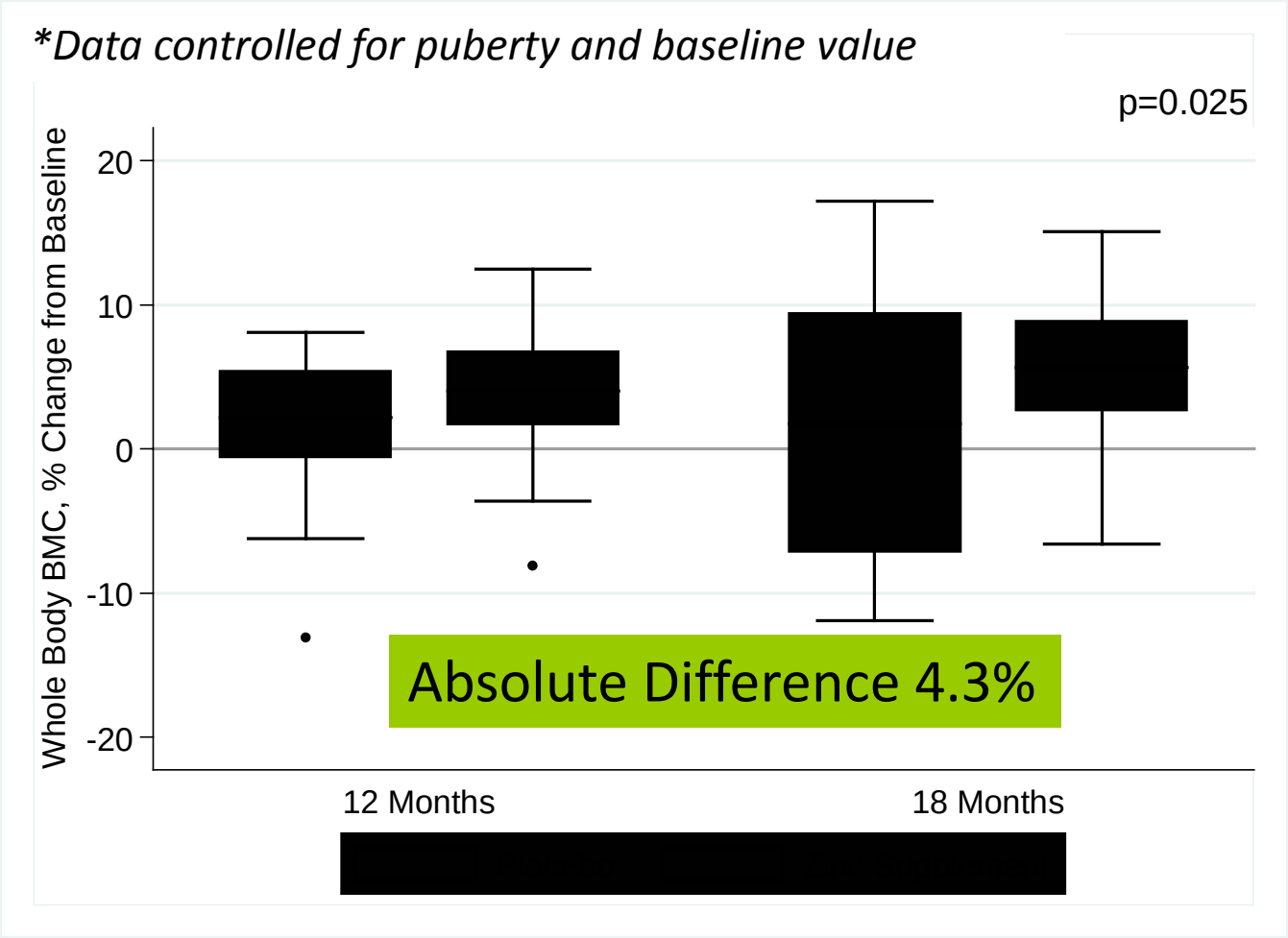
Placebo vs. Zn Supplementation in Patients with Thalassemia



Fung EB et al AJCN 2013

% Change in Whole Body Bone Mineral Content

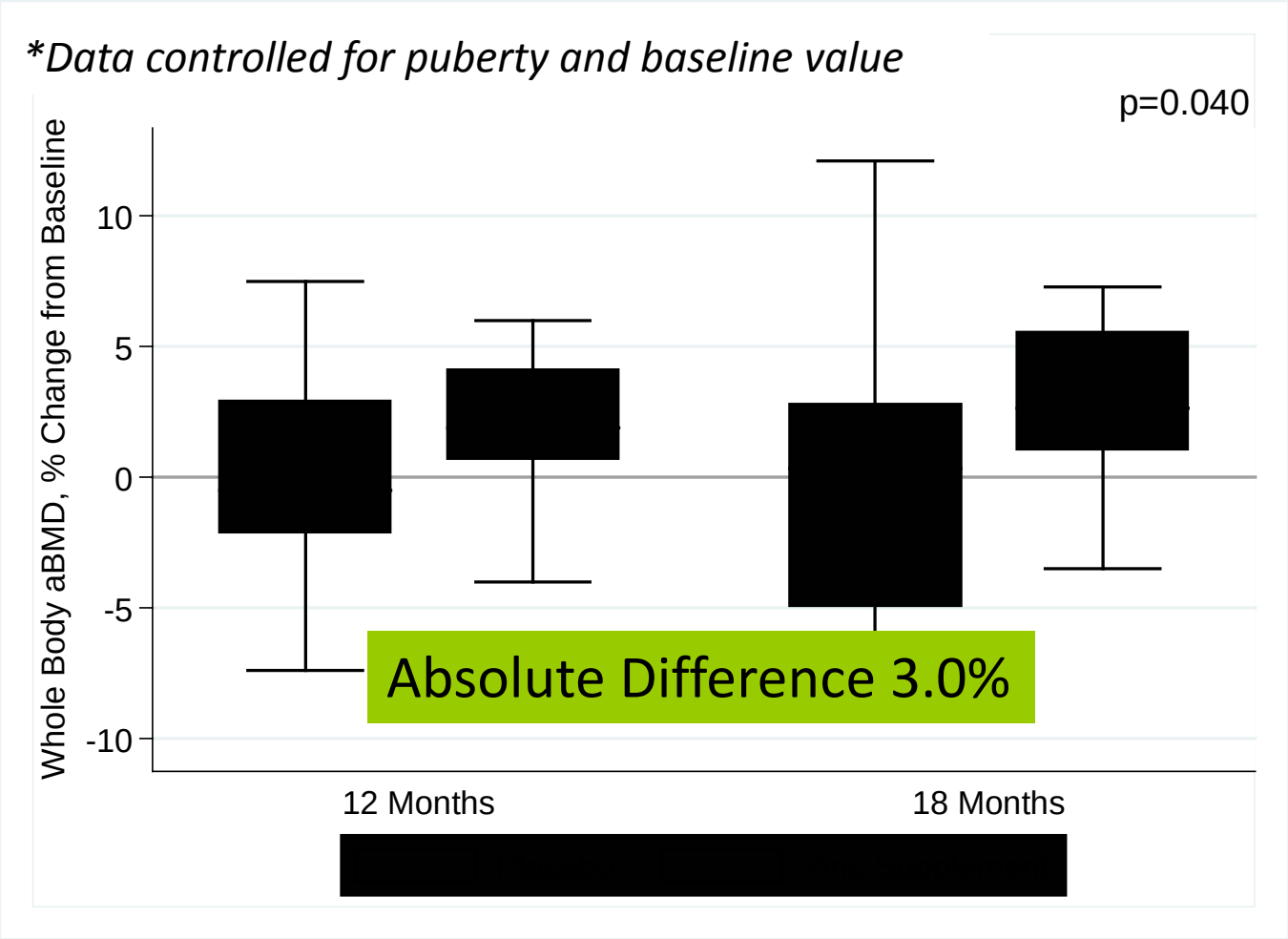
compared to baseline value in Placebo vs. Zinc Groups*



Fung EB et al AJCN 2013

% Change in Whole Body Bone Mineral Density

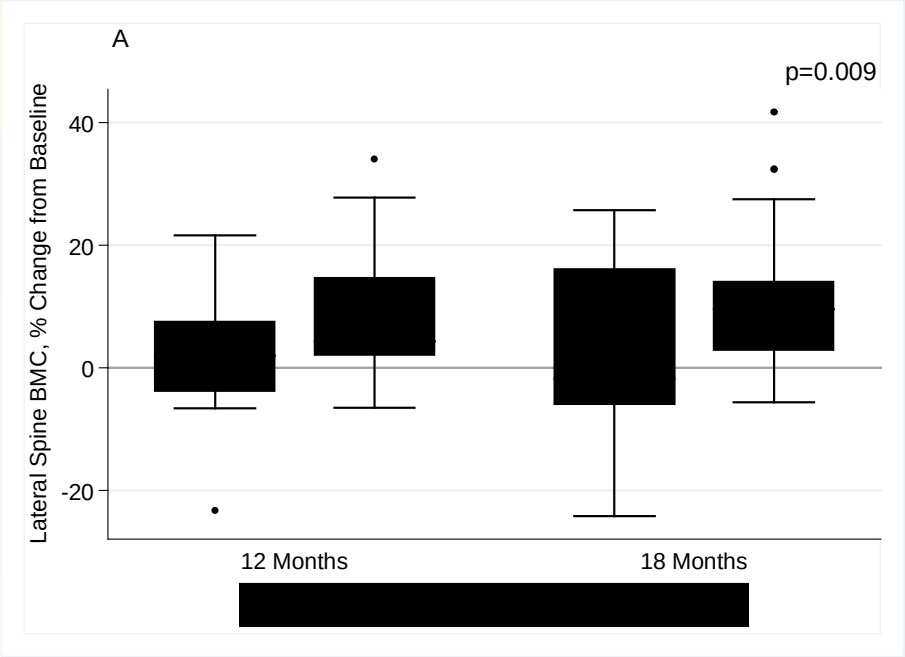
compared to baseline value in Placebo vs. Zinc Groups*

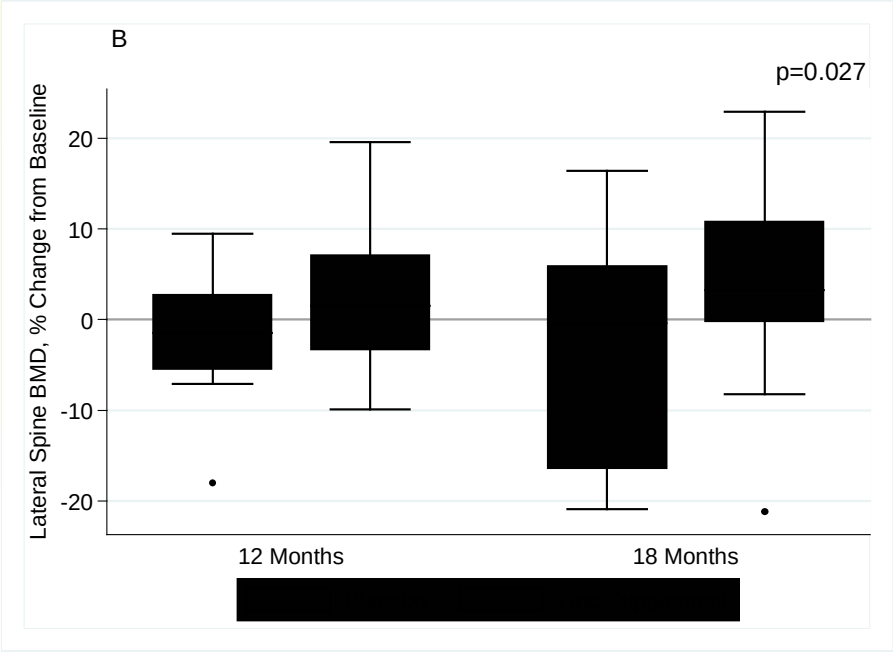


Fung EB et al AJCN 2013

% Change in Lateral Spine BMC & BMD

compared to baseline value in Placebo vs. Zinc Groups





Absolute Difference 9.6%

Absolute Difference 5.9%

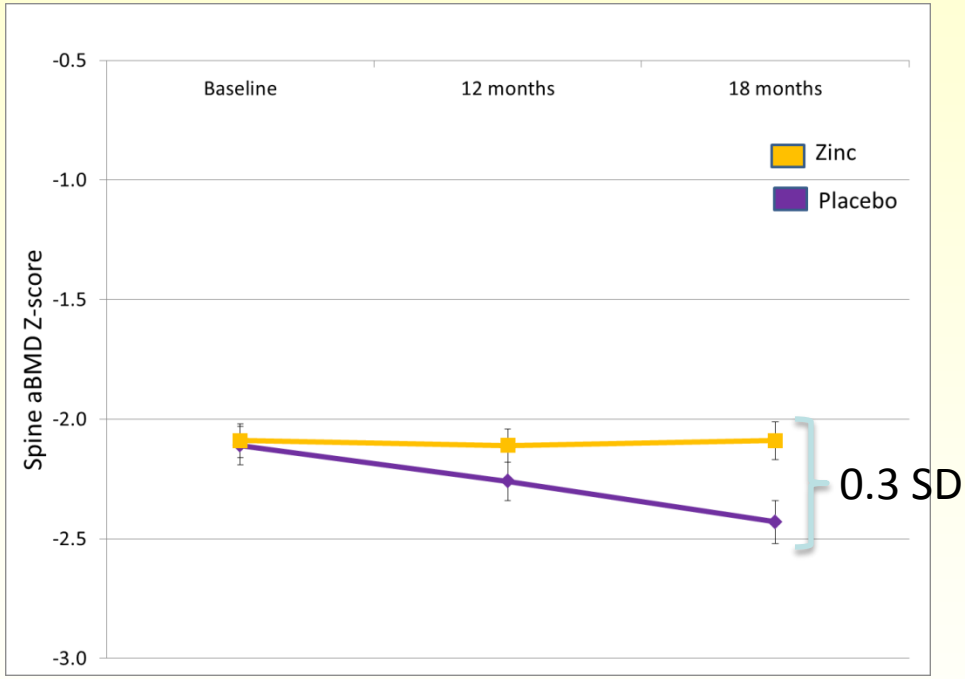
**Data controlled for pubertal development and baseline BMC value*

Fung EB et al AJCN 2013

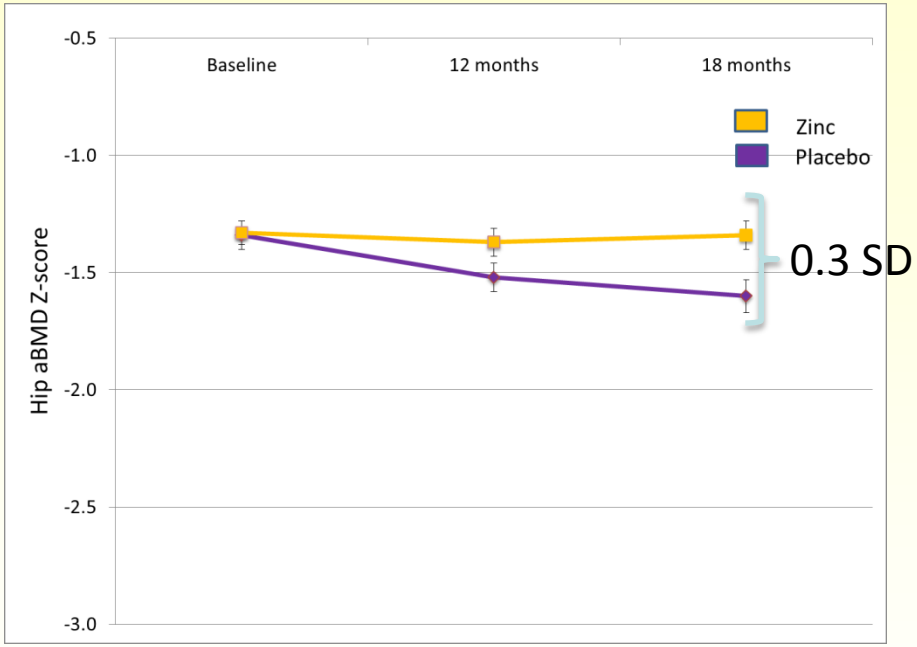
Longitudinal Change in Spine & Hip BMD Z-score

Placebo vs. Zinc Groups

p=0.041



p=0.036



Adjusted spine & hip BMD Z-scores were 0.3 SDs lower in placebo compared to zinc group by the 18 month time point

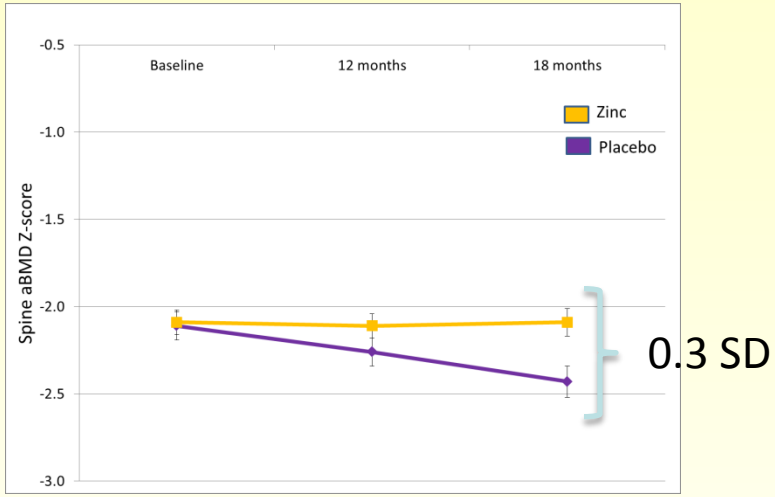
*BMD Z-scores adjusted for baseline BMD value and pubertal stage

Fung EB et al AJCN 2013

Relevance to Other Bone Mineral Density Treatment Options in Patients with Thalassemia

<u>Current Study (Fung et al AJCN):</u>

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

<u>Voskaridou E (Br J Haematol 2003):</u>

Time period: 12 months
Pamidronate
Spine change: 4%

<u>Mamtani M (Osteoporosis Int 2010):</u>

Time period: 2 years
Zoledronate
Spine change: 10%
Spine BMD Z-score: +0.69 SD

*Voskaridou E et al Br J Haematol 2003; Mamtani M et al Osteoporos Int 2010.

Fung EB et al AJCN 2013

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

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

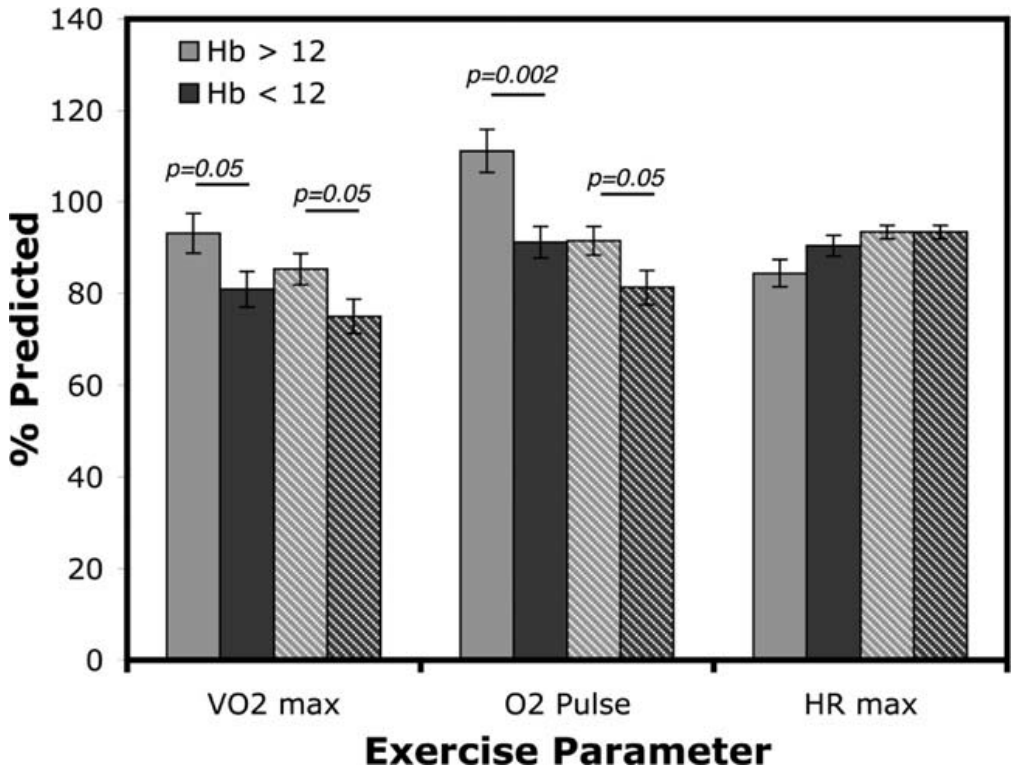
60 min of exercise each day!

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 sendentary 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)*

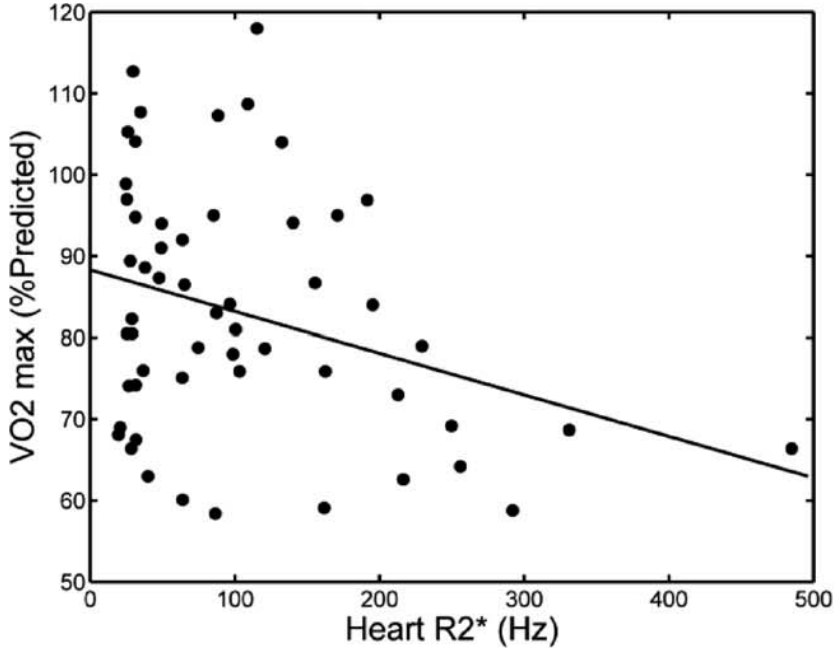
Relationship between Hemoglobin, VO_2Max & Heart Rate

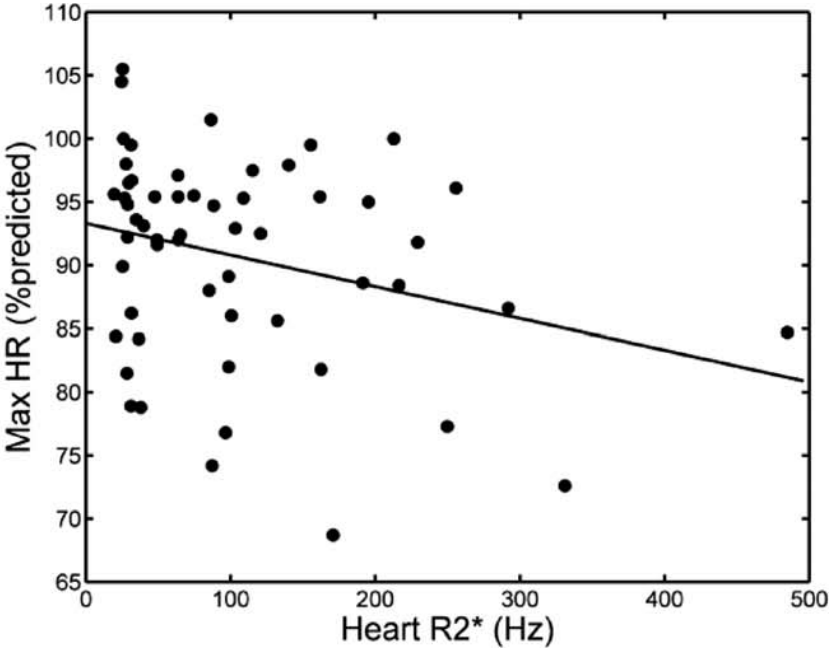


Females= solid bars, Males= cross-hashed bars

Sohn EY et al AJH 2013

Relationship between Cardiac Iron and VO_2 Max and Heart Rate



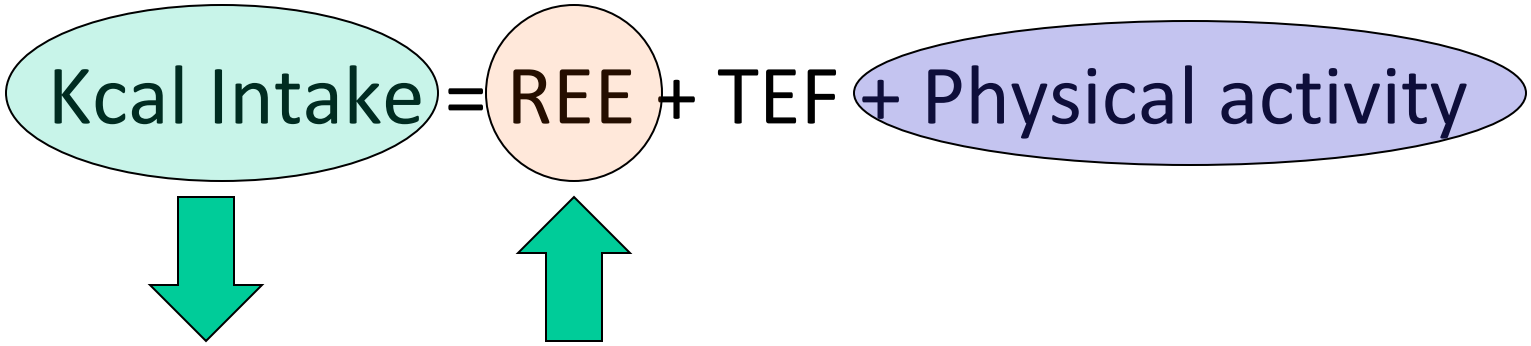


more iron overloaded = worse exercise tolerance

Sohn EY et al AJH 2013

Energy Balance Equation

Energy In = Energy Out



REE: Resting Energy Expenditure
TEF: Thermic Effect of Food

Describing Physical Activity Patterns in Thalassemia

GT3x+ Actigraph to Assess Physical Activity

n=50 Thal

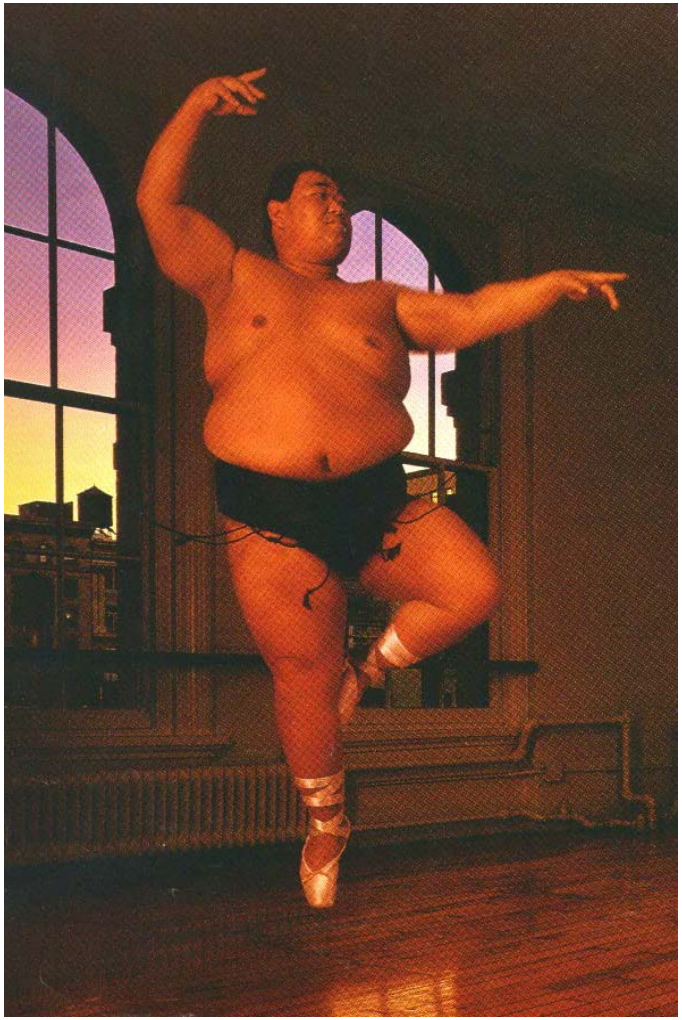
50% Tx

50% Non-Tx

n=30 Controls

Ongoing Study, CHRCO 2014
Results are Unpublished

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…

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