Vitamin Deficiencies in Sickle Cell Disease

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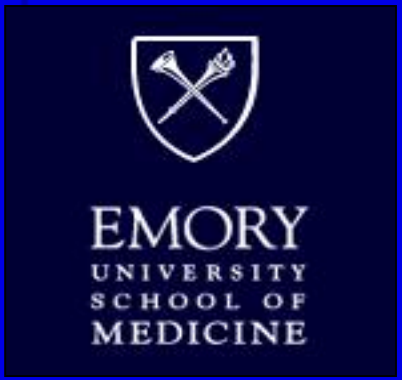
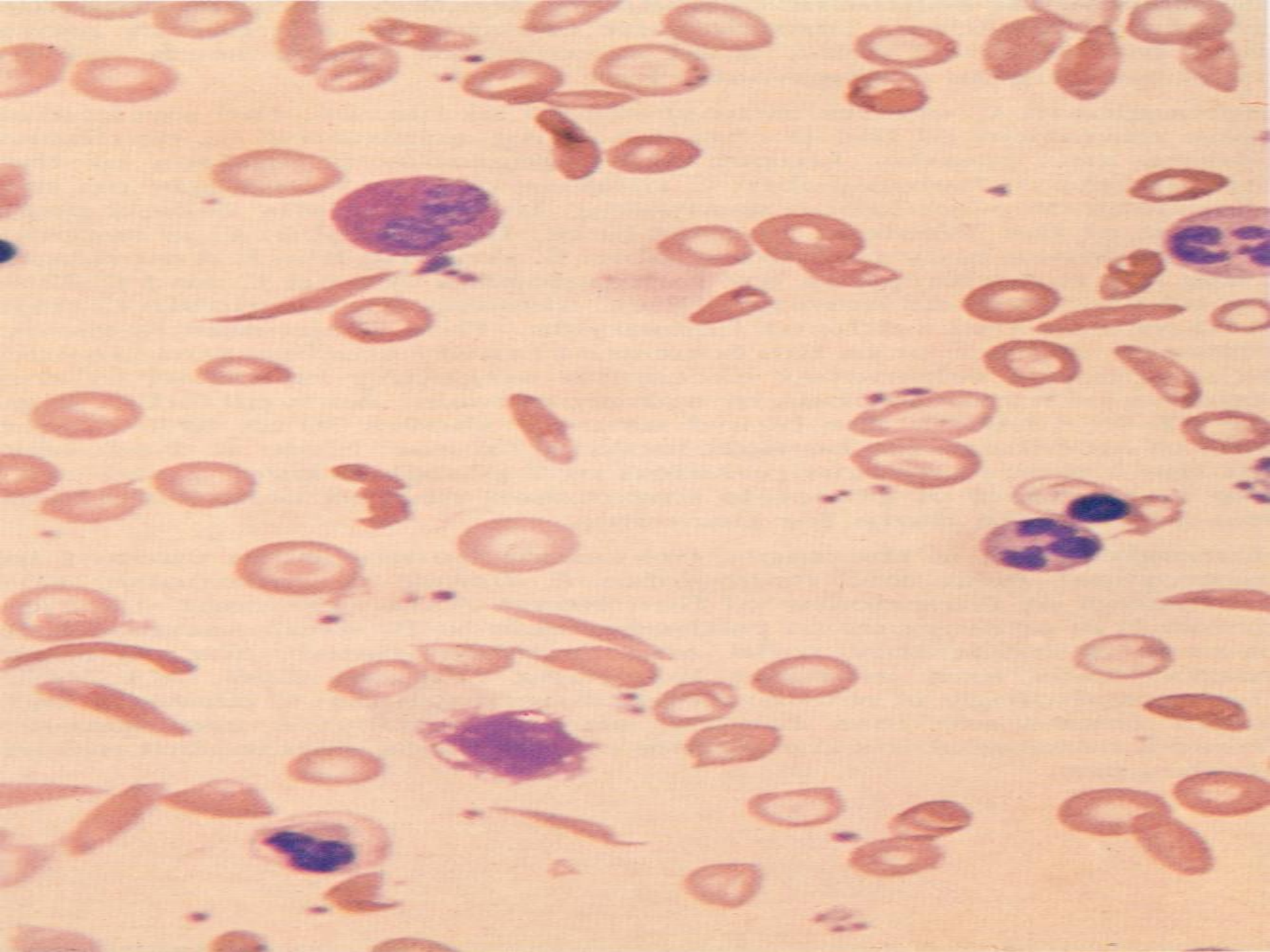


Public Health Webinar on Hemoglobinopathies
Division of Blood Disorders, CDC
Thursday May 26th
2:00pm-3:00pm

Objectives

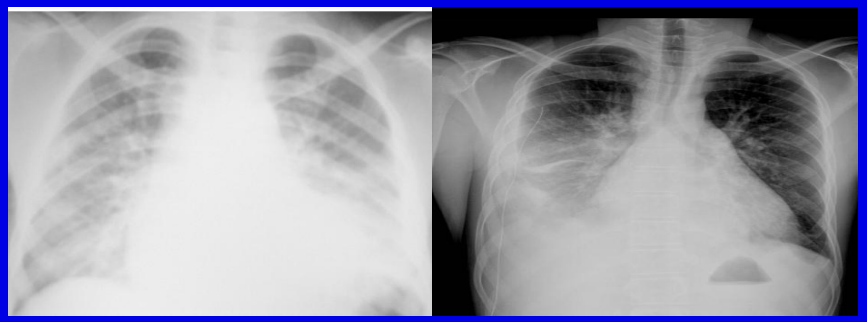
- Brief Overview of SCD Pathophysiology
- Dietary requirements in SCD
  - Total energy expenditure
  - Macronutrients – protein
  - Micronutrients – zinc, vitamin D
- Vitamin D Deficiency in SCD
- Future research



Triggers of Sickling

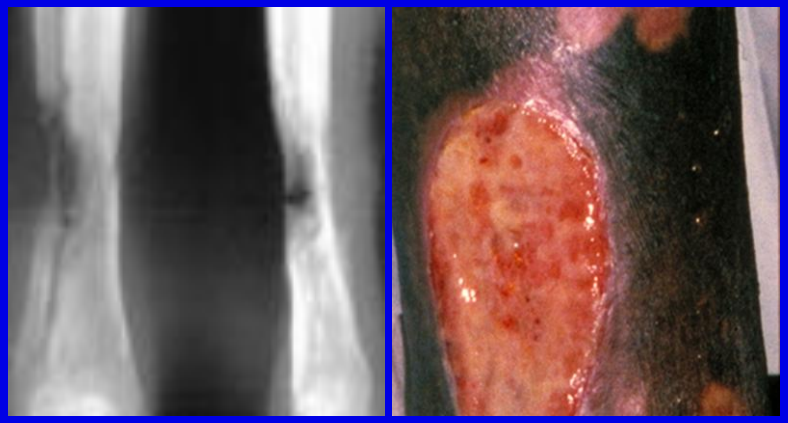
- **Low oxygen levels in blood** (congestion, asthma, large tonsils/adenoids, sleep apnea etc)
- **Fever and Infection**
- **Dehydration**
- **Stress –** physical, emotional
- **Extreme temperatures**
- **High altitudes** due to low oxygen tension

Pathophysiology of SCD



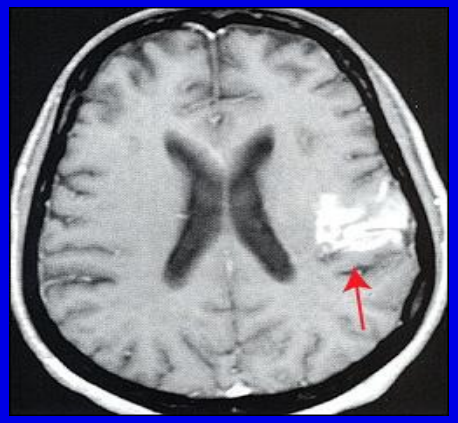
Acute Chest Syndrome

Dactylitis



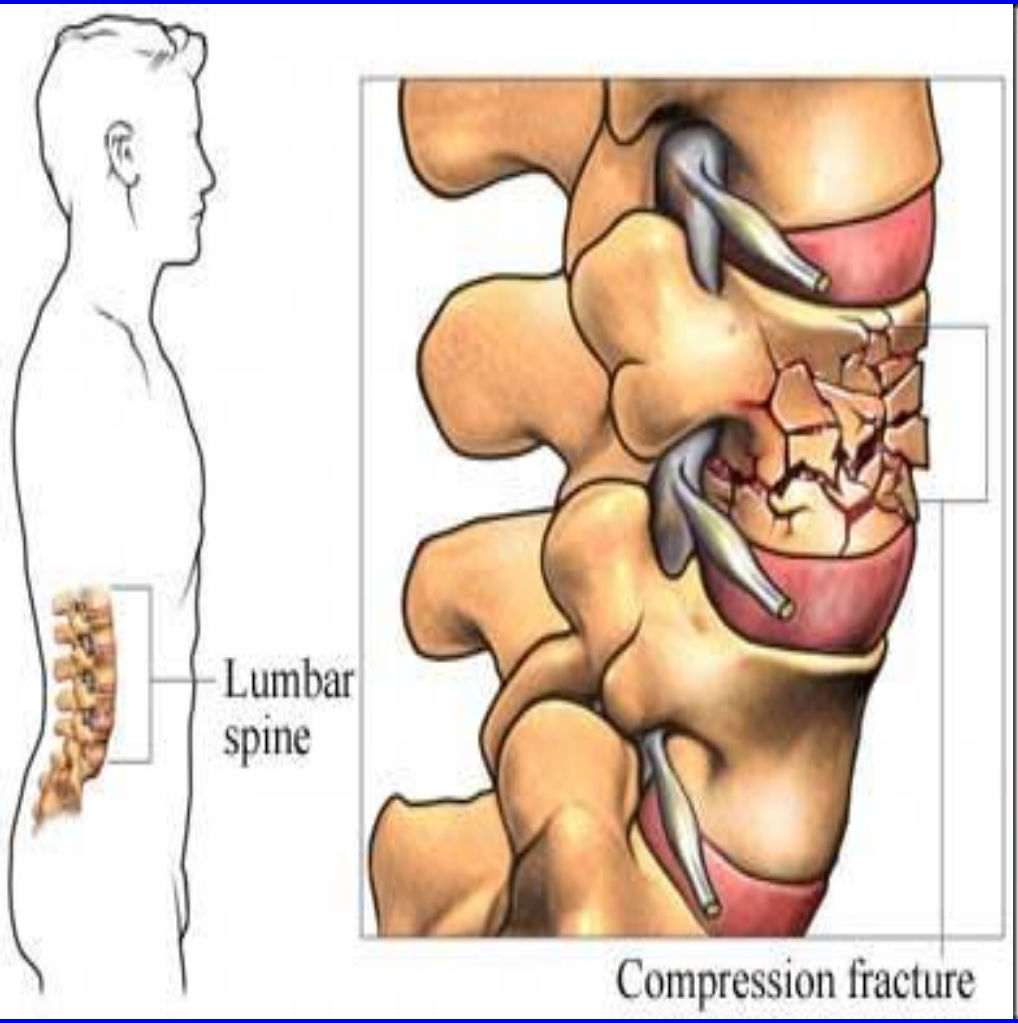
Chronic Osteomyelitis and leg ulcers

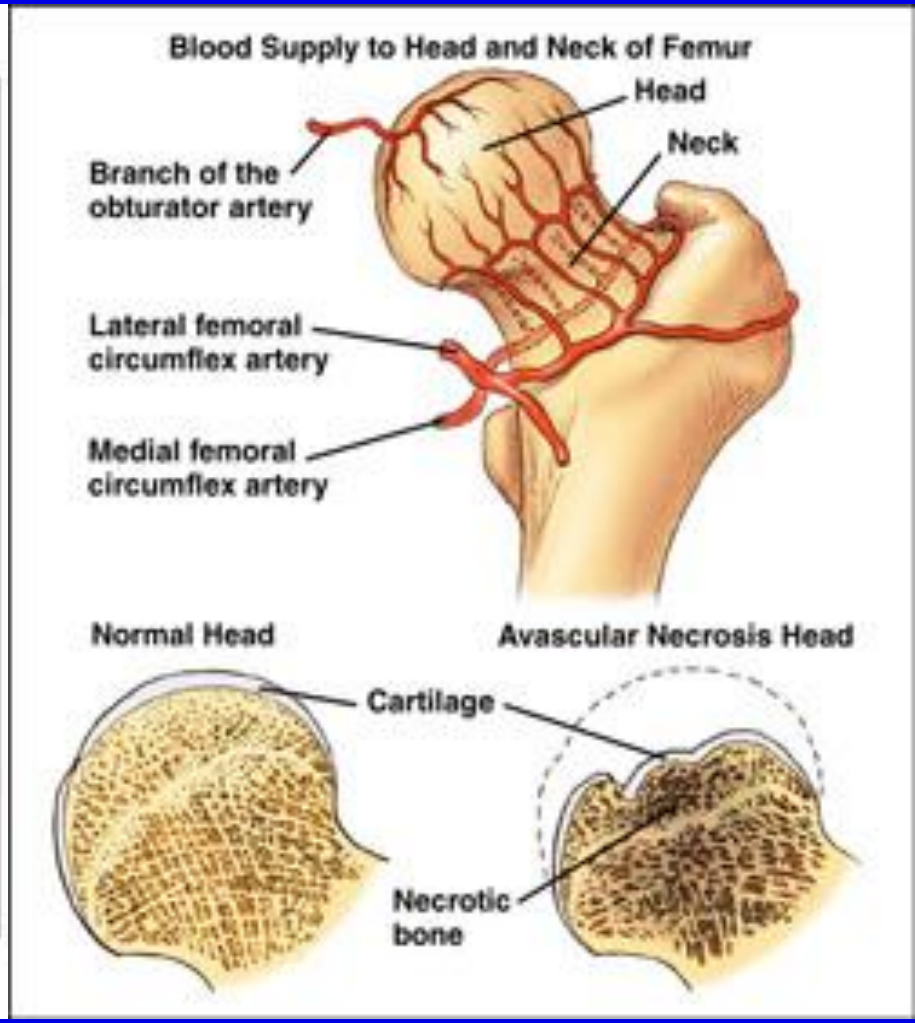
Spine compression



Stroke

Sickle Avascular Necrosis





Nutritional Needs in SCD

- Poor growth, poor nutrition status, delayed bone and sexual maturation is common in SCD
- Increased erythropoeisis → increased metabolic demand for ALL nutrients, protein and energy
- Increased oxidant stress, endothelial dysfunction and antiooxidant depletion exacerbates clinical phenotype
- Socio-economic factors ; Food insecurity
- Cravings such as PICA
- Genetic factors?

Macronutrient needs in SCD

- Hyper metabolism with high protein turnover and increased energy expenditure (Badaloo A; Clin Science 1989; Hibbert J, Eu J Clin Nutr 1992)
- Poor growth and development, delayed puberty documented in SCD in US and around world (Platt OS, NEJM 1984; Serjeant GR Arch Dis Chil 2001; Cox SE, Hematologica 2011; Al-saquladi 20)
- Only **ONE** protein calorie supplementation study in children SCD (Heyman et al 1985, n=5) showed improved growth and clinical status
- Anecdotally, poor nutrition status is associated with more pain and slower recovery in SCD especially during puberty

Macronutrient needs in SCD

Dietary supplement for managing sickle cell disease associated nutritional deficiencies
JM Hibbert, PhD (PI)

Subject	SynHb (g/kg/d)	Protein synthesis (g/kg/d)	Protein breakdown (g/kg/d)	Q
HbAA (n=9)	0.01±0.01	4.3±0.7	3.6±0.8	6.3±0.6
Range	0.001–0.03	2.8–5.2	2.4–4.7	5.1–7.1
HbSS (n=12)	0.2±0.1	7.7±2.0	7.1±1.5	9.6±1.9
Range	0.01–0.39	4.5–12.7	4.4–10.8	6.9–14.5
P	0.0018	0.0004	0.0002	0.0002

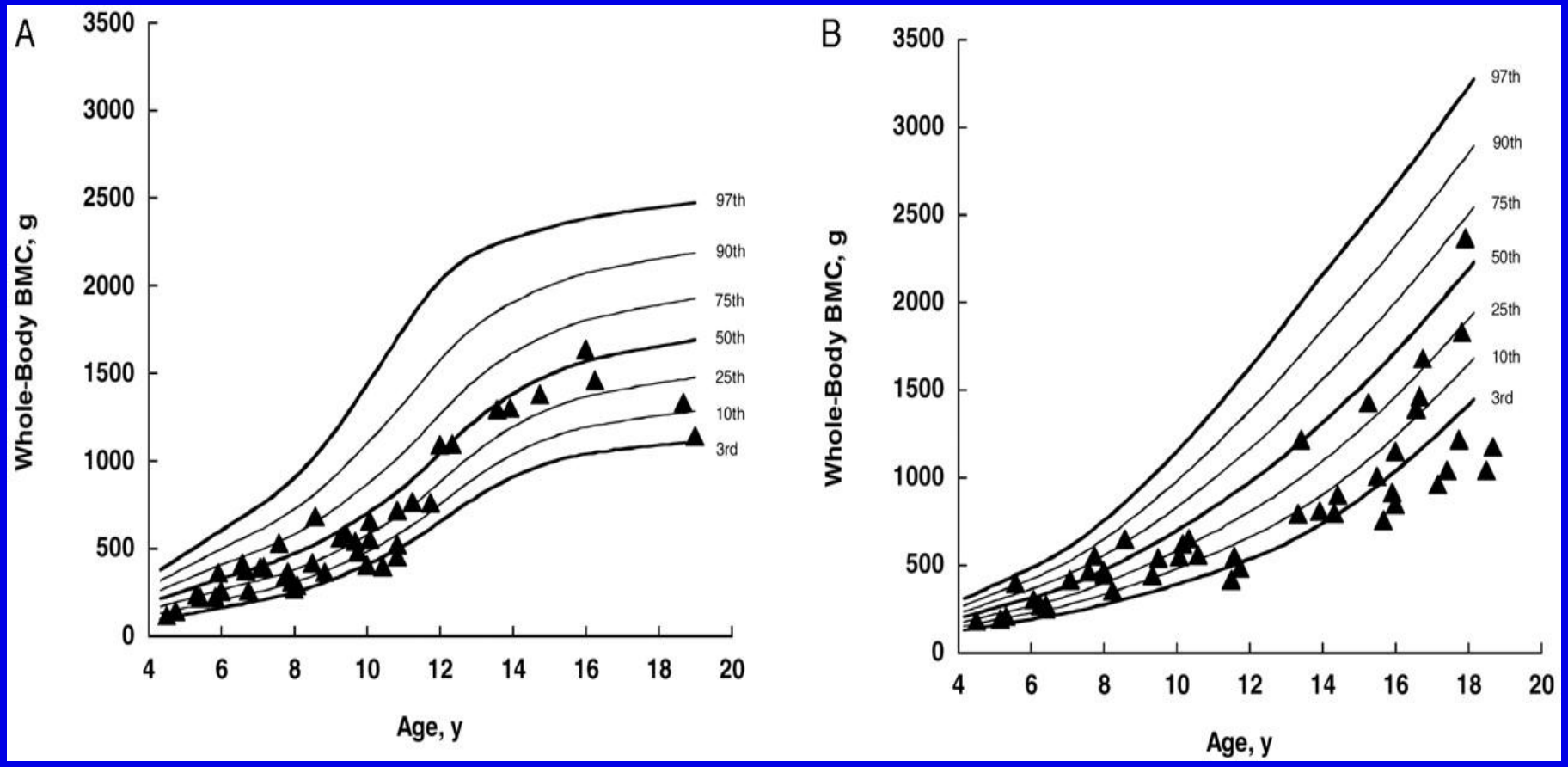
Protein metabolism in HbAA and HbSS children

Growth status of children with SCD vs. controls

	SCD-SS	Controls	*P*
No. of subjects	90	198	–
Body composition*			
Lean body mass, kg	23.5 ± 10.5	24.9 ± 11.2	.32
Lean body mass-for-height *z* score	−0.36 ± 0.90	−0.01 ± 1.00	<.01
Fat mass, kg	5.6 ± 5.0	9.6 ± 9.0	<.01
Fat mass-for height *z* score	−0.66 ± 0.86	0.05 ± 1.02	<.01
Bone measures*			
WBBA, cm^2	942 ± 428	1072 ± 493	.03
WBBMC, g	686 ± 446	830 ± 560	.03

Buison A M et al. Pediatrics 2005;116:943-949

WBBMC age for children with SCD-SS compared with reference percentiles from healthy children.



Buison A M et al. Pediatrics 2005;116:943-949

Summary of nutritional research in SCD

- **Al-Saquladi et al (2008) reviewed 46 studies on SCD and nutrition**
- Most studies were observational with wide variations in sample size and selection of reference growth data, which limited comparability.
- **There was a consistent pattern of growth failure among affected children from all geographic areas, with good evidence linking growth failure to endocrine dysfunction, metabolic derangement and specific nutrient deficiencies.**

Micronutrient deficiency in SCD

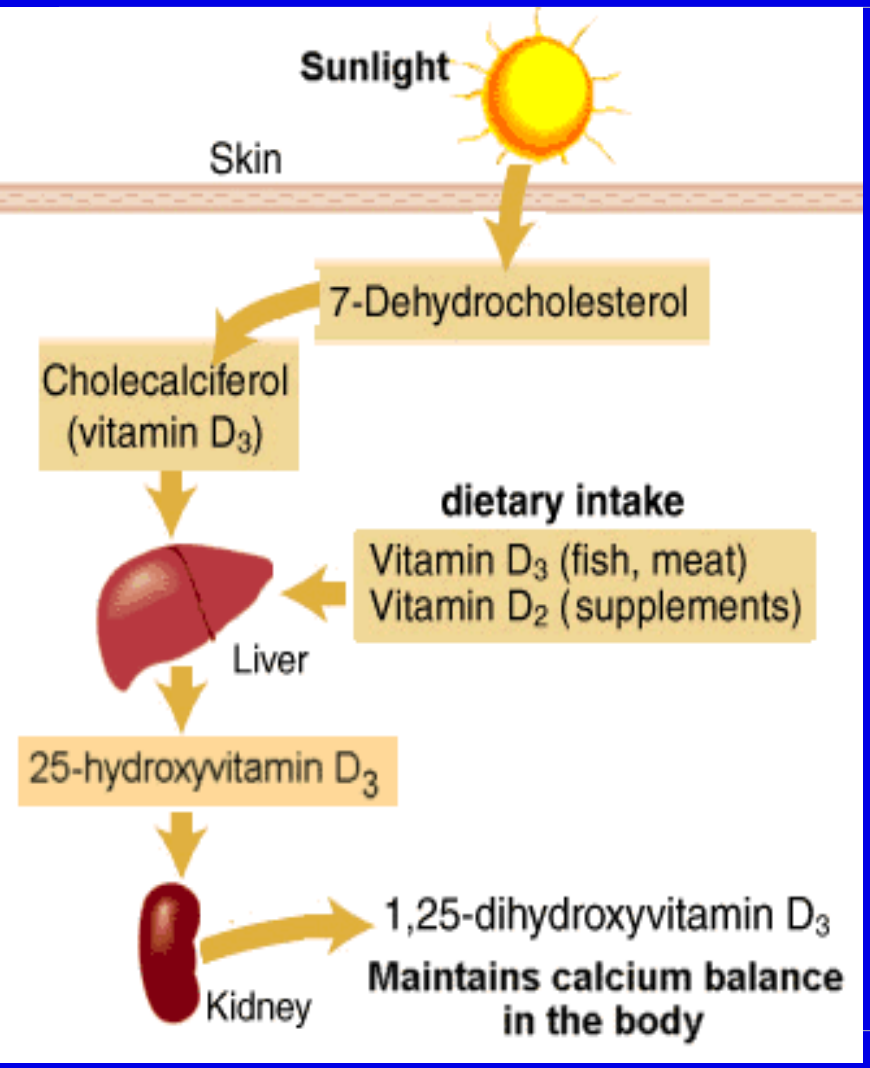
Nutrient	References	Effect
Folic Acid	Lindenbaum et al, NEJM 1961	Megaloblastic anemia, rbc survival
Riboflavin (vitamin B2)	Virma et al, Am J Clin Nutr 1986	Low NADPH, reduced rbc survival
Vitamin B6	Nelson et al JPHO 2002	Amino acid metabolism, cold sores, neuropathy
Vitamin A	Schall et al, JPed 2004 Hasanato Ann Saud Med 2006	Immune function, bone metabolism, vision, rbc , skin
Vitamin E	Natta and Machlin, AJ Clin Nut 1980	Reduce ISC, reduce hemolysis
Vitamin D	Osunkwo et al, BJH 2011	Bone metabolism, immune function, lungs , cardiovascular health
Zinc	Prasad et al, *Am Col Nutr* 2009	Immunity, taste, cognition, leg ulcers
Cobalamine (B12)	Kamineni P et al; 2006	Fatigue, depression, psychosis

Public Health Cost of Sickle Complications

- Recurrent acute pain that progresses to almost daily persistent/chronic pain
- Higher mortality rate with increasing pain episodes/yr
- High morbidity and disability
  - Lost work/school days
  - Lung disease
  - Frequent Infections, more severe
  - Depression / anxiety/learning disabilities *
- High health care cost (conservative)
  - Direct cost/admit $8-30,000 monthly; increase with age
  - $475 million/yr (1994), now est. > $1 billion/yr (AJH 2009)

Vitamin D and Sickle Cell Disease

Vitamin D



- D2 (ergocalciferol) & D3 (cholecalciferol)

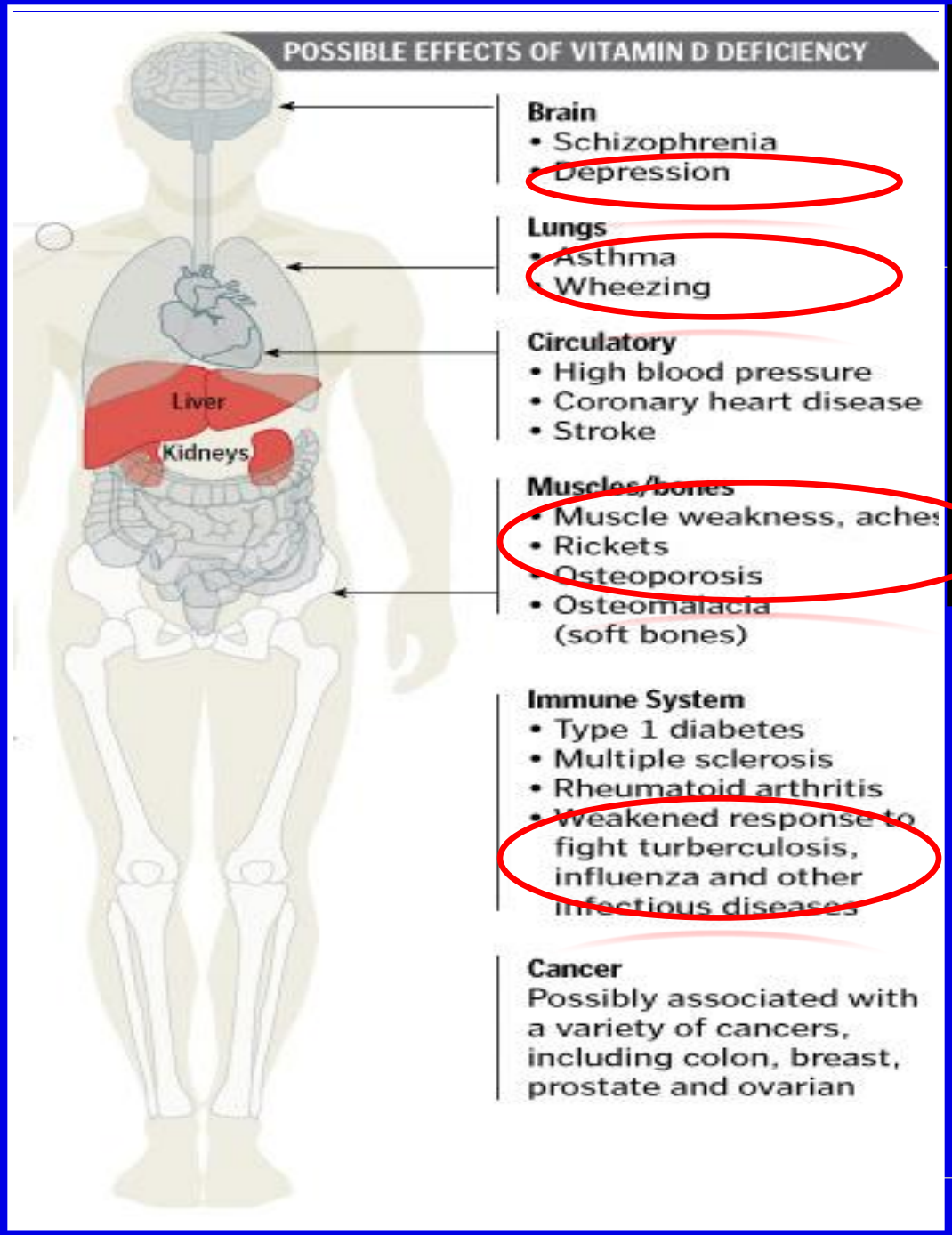
Vitamin D3

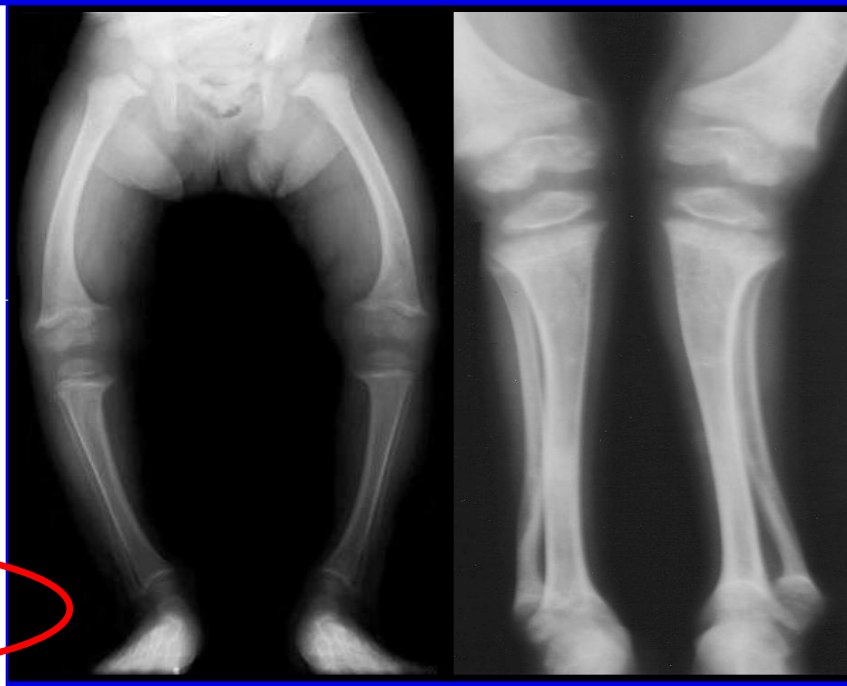
- 90% made in skin (UV radiation)
- Oily fish, egg yolks, fortified milk /cereal
- Breast milk has only 10% of D3 in fortified cow's milk

Vit D deficiency impairs bone mineralization, and contributes to osteoporosis, myopathy and fractures

Vitamin D Actions

Organ	Action
BONE	Promotes bone health by maintaining adequate Ca and PO_4 concentrations; muscle strength
IMMUNE SYSTEM	Enhances immunogenic and antitumor activity Decreases risk of autoimmune disorders
INTESTINE	Enhance Ca / PO_4 absorption
KIDNEY	Enhance Ca reabsorbtion by tubules
PARATHYROID	Inhibits PTH secretion
PANCREASE	Stimulates insulin production





Multi-system complications of vitamin D deficiency

Vitamin D Deficiency- Epidemiology

- ↑ VDD in Afro Americans
  - 42.4% have severe VDD (25OHD <15ng/ml)
- Causes soft bones from defective mineralization
- Risk factors:
  - Lactose intolerance
  - Poor sun exposure
  - Hyper- melanosis
  - Hyper- metabolic state
- Consequences
  - Osteopenia
  - Osteoporosis
  - Chronic bone pain
  - Myopathy
  - Waddling gait
  - ↑ fracture risk
  - Poor immune function
  - Increased asthma risk

VDD in Sickle Cell Disease - Epidemiology

Author/yr	Results	Comments
Lal et al Ped Blood Cancer 2006	74% 25OHD ≤20ng/dl 64% low BMD	N=25 Severe SCD Median age 12.4y
Buison et al J Pediatr 2004	65% 25OHD ≤11ng/dl	N=65 Hgb SS, 5-18y
Van der Djis et al Ann Clin Biochem 1997	25OHD levels adequate	N= 18 w 18 controls
Padmos et al Annals Saudi Med 1995	No difference in Vit D levels or DEXA with or without AVN	N=118
Mohammed et al Ann Clin Biochem 1993	12% with low 25OHD	N=99

VDD in Sickle Cell Disease - Epidemiology

Author/yr	Results	Comments
Adewoye et al Am J Heam 2008	100% VDD (11.6±4ng/dl) Good response to 12mo treatment ⇧25OHD, ⇧ BMD	N=14 No change in bone turnover
Rovner et al J Am Diet Assoc 2008	25OHD 15ng/dl vs. 21ng/dl VDD 33% vs. 9% (25OHD ≤11ng/dl) 90% v 17% insufficient (≤30ng/dl)	N=61 C=89 Age 8-14
Chapelon et al Eur J Heam 2009	25OHD ≤12ng/dl 76%	N=53
Goodman et al 2010 J Nathl Med Assoc	25OHD ≤10ng/dl 60% 25OHD ≤30ng/dl 98%	n-=142

Consequences of VDD

- Increased risk of non vertebral fractures; reduced by 20% with vitamin D replacement
- 26% higher risk of death if in lowest 25OHD quartile (n-13000)
- Rates of type I Diabetes drop 88% with 2000IU/d from infancy (Finland)
- Cardiovascular mortality linked to low 25OHD (Framingham Offspring study)
- Chronic Pain, often misdiagnosed as Fibromyalgia
  - Tenderness elicited on palpation of bone

Holick 2005, J of Nutr

Previous studies VDD & Pain

- Plotnikoff et al (n=150) chronic pain
  - 28% 25OHD <8ng/ml
  - 93% 25OHD <20ng/ml
- Faraj & Mutairi (n=299) chronic low back pain
  - Mean 25OHD <11ng/ml
  - Pain resolved completely in 2.9 months with Vit D
- Farat B et al (n=33) asylum females with chronic pain
  - 100% median 25OHD <4.5ng/ml
  - 67% complete resolution of pain by 2.8 months
- Lee et al 2007- case report pseudo Fx treated with vit D

VDD supplementation in SCD
Adewoye et al (n=14, adults)

Test	Pre	Post	P value
25(OH)D	**11.6 4**	**34.6 11**	**< 0.001**
PTH	22.4 5.1	25.6 10.6	0.19
Osteocalcin	12.3 3.7	10.7 4.3	0.1
Z score FN	**-1.36 0.84**	**-1.14 0.75**	**0.02**
Z score LS	**-2.63 0.71**	**-2.31 0.75**	**0.04**

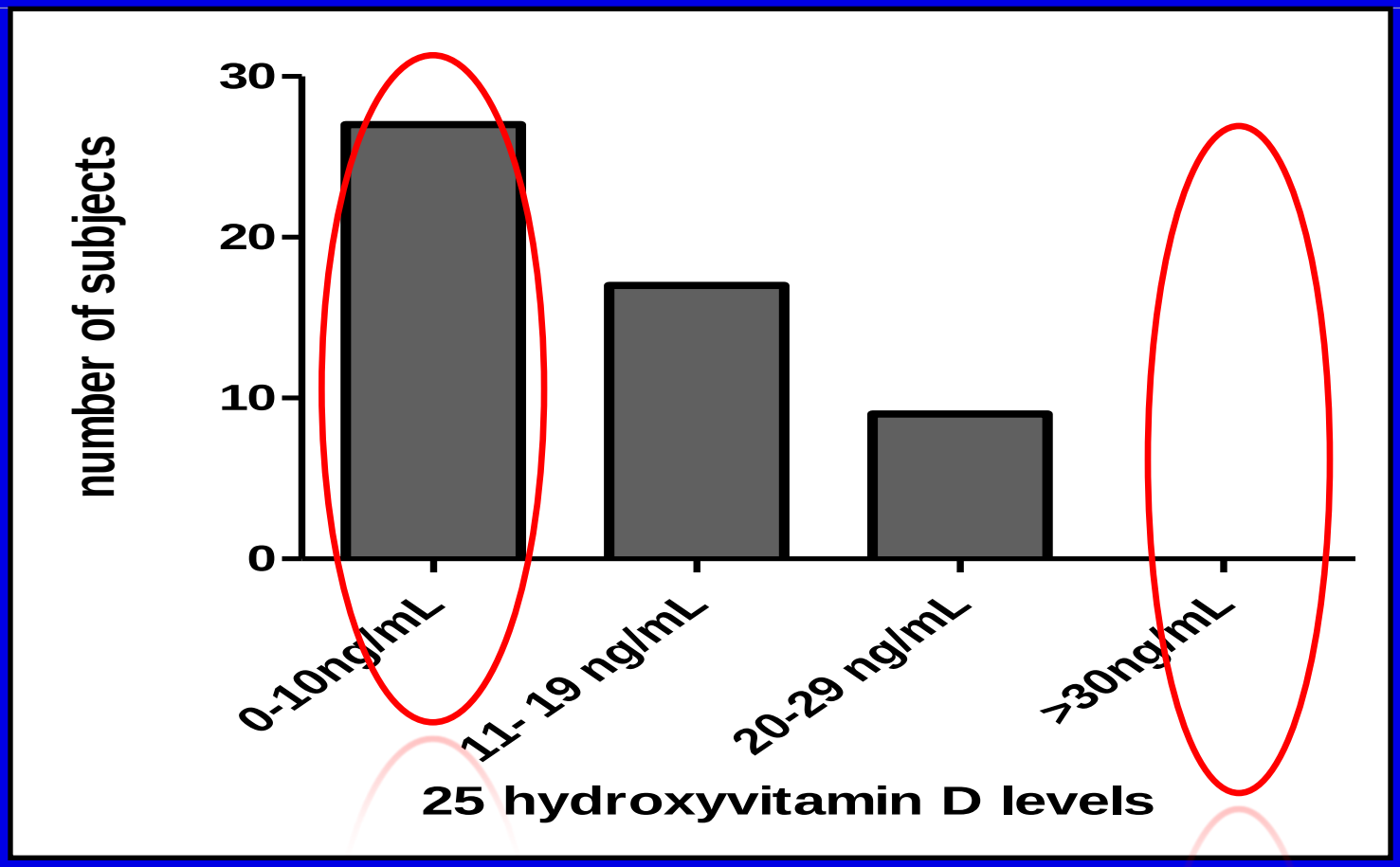
Improved 25OHD levels and BMD following 8 weeks of vitamin D supplementation

Osunkwo et al, Case Report

- 16y F SS, FTT, delayed puberty, + AVN
- Chronic pain syndrome (legs, arms and abdomen), poor response to narcotics, NSAIDS
- Severe Migraine HA
- Increased intracranial pressure by LP
- 25OHD <8 DEXA WB -4.3 LS -3.2 (osteoporosis)
- Treated with 2 courses of Ergocalciferol 600,000IU over 6 weeks
- Complete resolution of pain by week 12
- No acute care visits x 3 years!

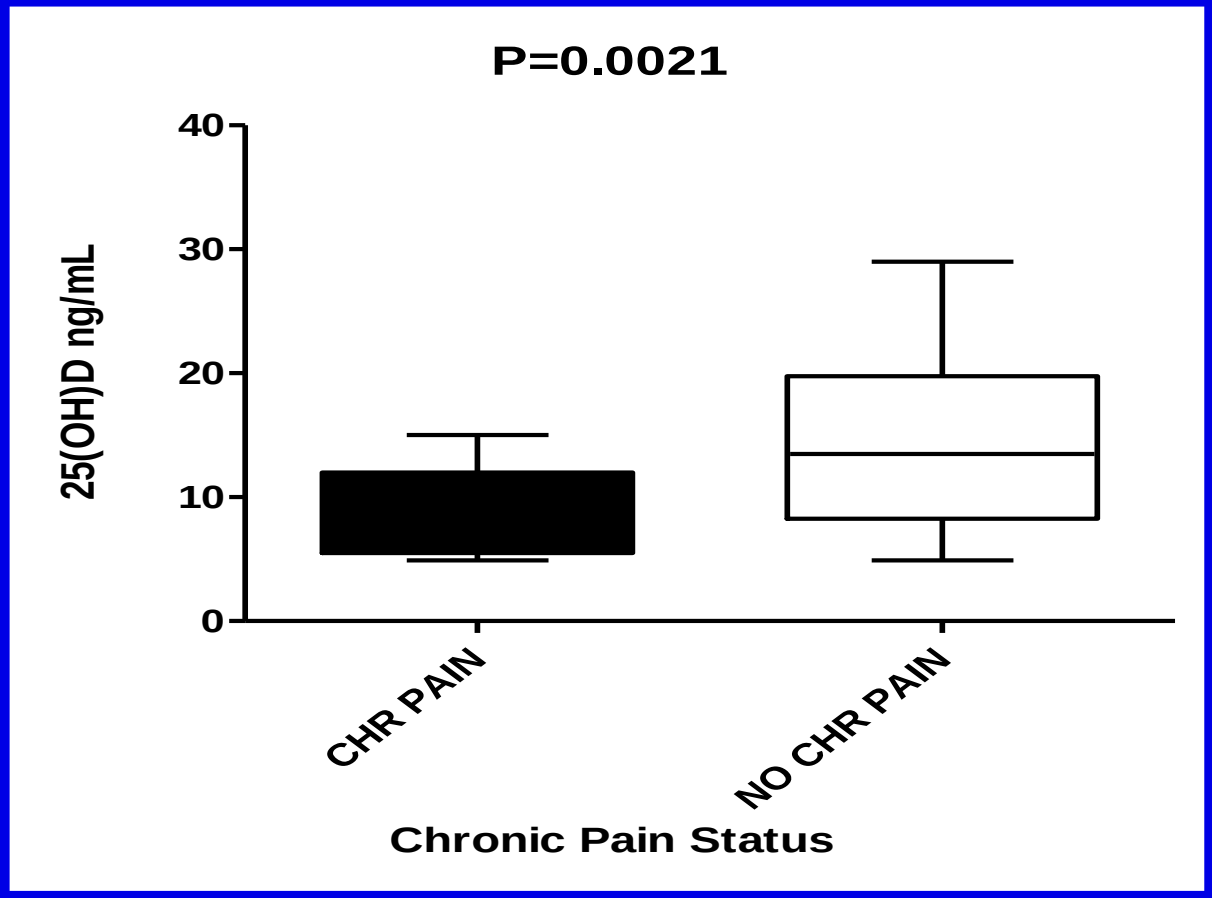
JPHO 2011, in press

VDD prevalent in SCD, Osunkwo et al BJH 2011



25OHD levels among study participants.

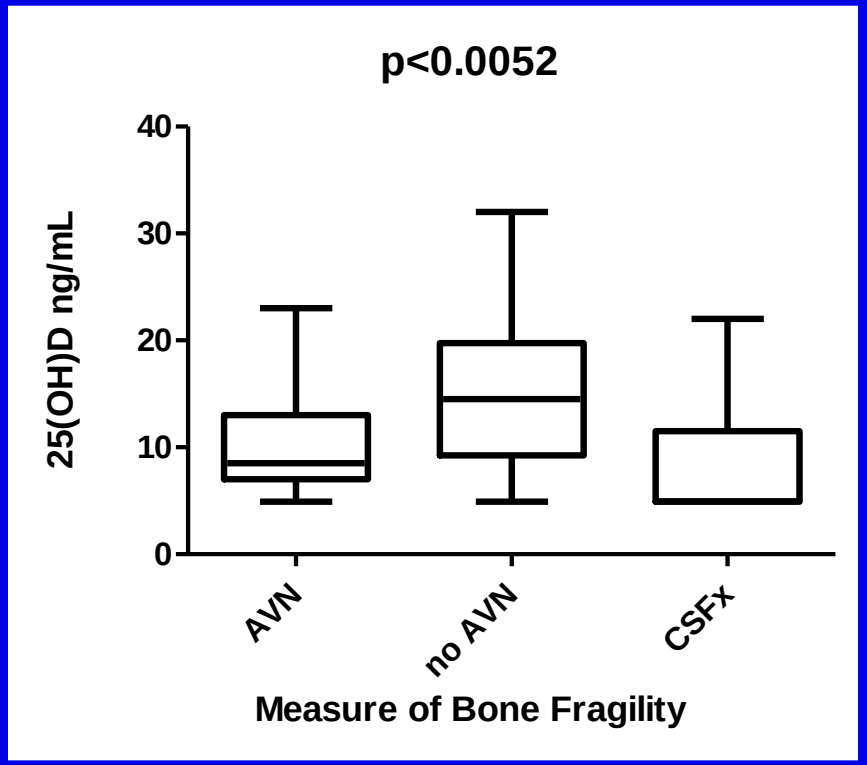
VDD associated with chronic pain in SCD

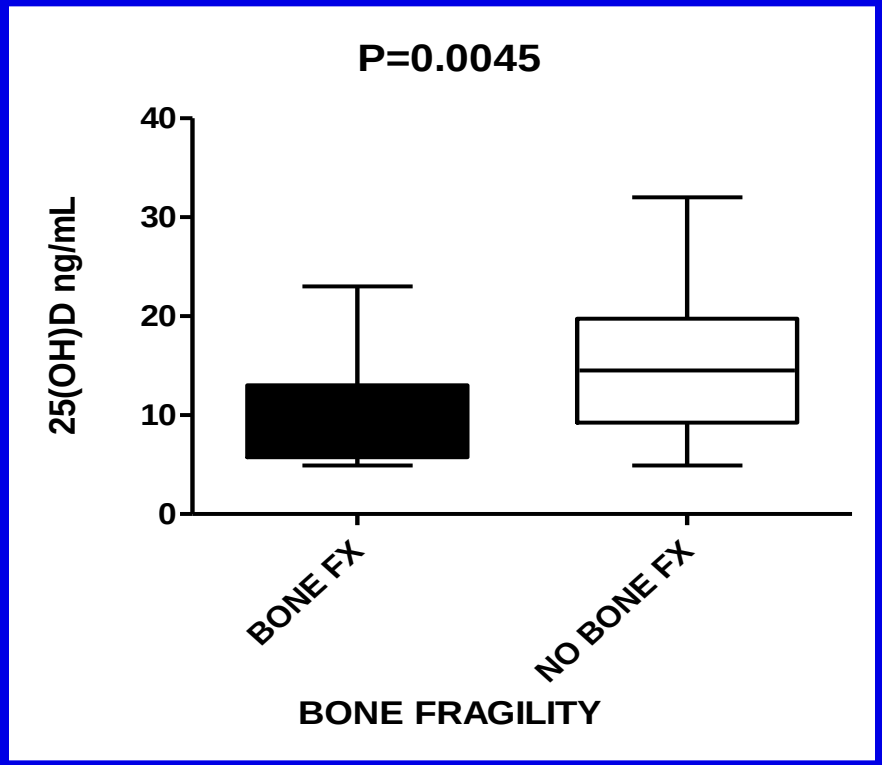


Chronic pain status inversely correlated with 25OHD levels

Osunkwo et al, BJH 2011

VDD associated with AVN and Spine compression in SCD





Bone fragility status inversely correlated with 25OHD levels

Osunkwo et al, BJH 2011

Prospective study of vitamin D to ameliorate SCD chronic

Hypothesis: High dose vitamin D will ameliorate sickle cell chronic pain

Specific Aims: To demonstrate that

a. high dose vitamin D will correct VDD in SCD
b. High dose vitamin D will improve chronic pain and bone health SCD

Vitamin D to ameliorate SCD chronic pain

- Randomized double blind placebo controlled trial
- Aged 7-21; chronic pain defined as pain on 50% or more days per month; SS/SBothal only
- Study closed to accrual. Enrollment target of 30 chronic pain and 30 non chronic pain was not reached; Study concluded with **27 non pain and 11** pain
- Data analysis on clinical correlates associated with high dose vitamin d supplementation are pending.

Plasma response to high dose vitamin D – interim results

- n= 17 subjects randomized (6 CP; 11 non CP),
- Mean age 14.2y (8-19y).
- Mean 25OHD at baseline was 17.1 ng/dL and 17.4ng/dL for subjects randomized to drug and placebo respectively.

Group	Baseline	Week 8	Week 16	Week 24
Drug	**17.1**	**52.3 (10-115)**	**24.2 (20-34)**	--
Placebo	17.4	19.4	17.8	--

- After 6 week course of high dose vitamin D, 25OHD levels trended back down despite daily RDA calcium/vitamin D

Vitamin D to ameliorate SCD chronic pain - summary

- Prevalence of VDD is high world wide – clinical rickets more common in 3rd world countries
- Profound VDD is associated with chronic pain and AVN in SCD
- Our results support screening for and treatment of VDD in SCD.
- Longitudinal and randomized intervention studies are needed to better delineate the role of VDD in the evolution of SCD bone disease
- Other clinical correlates of VDD need to be evaluated systematically. – lung, CNS, immune function

Public health implications

- All children are created equal- do not accept growth abnormalities in SCD as status quo
- Clinical importance of micronutrient deficiencies in SCD needs to be appreciated.
- Guidelines for micro/macro-nutrient supplementation in SCD are sorely needed.
- Is it time for a Sickle Cell Multivitamin?
- Research into genetic / disease specific risk factors of mico/macronutrient deficits in SCD; RCT trials with quantitative end points.

Thank you!

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