A 24 Year-Old Female with Diabetes, Weakness, and Chronic Decubitus Ulcers

Meltem Zeytinoglu, MD

Presents with…

- Generalized weakness
- Multiple skin ulcerations and wounds
- Fevers, chills, and vomiting
- Hyperglycemia (blood glucose 348) and ketones for which Endocrine service is consulted

History of the Present Illness

- Patient developed multiple skin wounds over her left back and hip in the last 3 months. Several hospitalizations for these wounds
- Progressive weakness and decline in mobility with current status of bed-rest
- Discharged from Outside Hospital on the day prior to her admission. She was hospitalized from 8/31-9/5 with similar presentation of fevers, chills, weakness, wound infection
- On arrival home, persistent weakness with c/o fevers, chills, vomiting, and generalized pain
- Uncontrolled blood sugars despite taking her home insulin regimen of Lantus 15 U/day and Novolog 4 U with meals

Past Medical History

- **Diabetes Mellitus – Type 1**
  - Diagnosed age 16
  - Uninsured – 8 Endos in 8 years
  - Recurrent hospitalizations for DKA
  - Complicated by neuropathy
- **Hypothyroidism**
  - Diagnosed during a recent hospitalization
- **Chronic Diarrhea and Weight Loss**
  - Weight 127 kg (12/2011) → 41 kg (9/2013)
- **IgM deficiency**
- **Recurrent Decubitus Ulcers**
  - Surgical drainage of abscess and multiple wound repair
- **Recurrent UTI**
- **Right lower extremity DVT**
- **Eosinophilic Esophagitis**
- **Anxiety and Depression**
- **Polysubstance Abuse**

Family & Social History

- Mother : Possible episodes of hypoglycemia; died in 2009 – cause unknown
- Father: Healthy
- Lives with her father
  - Parents divorced at age 3
  - Father is caregiver
- Last worked in April 2013 as nail technician
- Has been in multiple abusive relationships
- Substance Use
  - Tobacco user: x last 8 years
  - Polysubstance abuse cannabis, opioids

Prior to Admission Medications

- Lantus 15 U qhs
- Novolog 4 U with meals
- Novolog correction 1 U: 50 > 150 + 1:10 g carbohydrate
- Levothyroxine 50 mcg daily (started 3 weeks PTA)
- Levofloxacin
- Vasolex cream
- Remeron 7.5 mg qhs
- Klonipin 0.25 mg bidprn
- Norco prn
- Tramadol prn

Review of Systems

Constitutional:

Fevers, chills, cold intolerance, weakness, fatigue. Marked weight loss.

HEENT: Denies headaches, enlargement or swelling of neck/thyroid.

Recent blurriness of vision.

Cardiovascular: Denies palpitations, syncope.

Chest pain, shortness of breath, light-headedness.

Respiratory: Patient denies cough, wheezing, hemoptysis.

Gastrointestinal: Denies abdominal pain, nausea, vomiting, constipation, dysphagia.

Chronic diarrhea. Very poor appetite.

Genitourinary: Negative for urinary frequency, hematuria.

Skin: Denies diaphoresis.

Multiple pressure ulcers on her left hip and back.

Muskuloskeletal: Patient denies joint swelling.

Diffuse myalgias and arthralgias.

Neurological:

Numbness, tingling in bilateral lower extremities, weakness. Unable to ambulate.

Psychiatric/Behavioral: Denies anxiety/depression.

All other systems reviewed and were unremarkable

Physical Examination

BP 102/78 **P** 115 **T** 35.3 **R** 17 **O2** 96%
HT 165.1 cm **WT** 41.3 **BMI** 15

General: **mild acute distress, cachectic, malnourished and weak-appearing**
HEENT: EOMI, oropharynx clear
Neck: thyroid is symmetric, w/o thyromegaly or palpable nodules
CV: **tachycardic**, regular rhythm, no murmurs or gallops
Resp: Clear to auscultation bilaterally with no wheezes or rales
Abd: Soft, **mild diffuse tenderness**, non-distended, +BS in 4 quadrant
MSK: Moving all extremities. Without edema. 2+ peripheral pulses
Neurological: Sensation intact to light touch. 2+patellar reflexes. **Strength 3/5 in all extremities**
Skin: Warm, dry. **Pallor. Stage IV pressure ulcers on the left lateral low back and left iliac crest, the latter with bone exposure**
Psychiatric: Not agitated. Behavior appropriate.

Diagnostic Evaluation

Glucose	348
Sodium	132
Potassium	4.7
Chloride	107
CO2	12
Anion Gap	13
BUN	40
Creatinine	1.3
GFR	50
Calcium	9.2
Albumin	1.5
Total Protein	4.3
T bili	0.1
Alk Phos	126
AST	12
ALT	10

WBC	12.2 (Diff – 16 bands)
HGB	9.2
HCT	27.7
PLT	179

Phosphate, I	2.8
Magnesium	1.6

Beta-hydroxybutyrate	3.56

TSH	16.99
FT4	0.66
T3	58
Reverse T3	285
TPO Ab	< 0.4
Thyroglobulin Ab	< 0.4

Hemoglobin A1c	8.0

Outside Hospital Labs

No mention of hypercalcemia in assessment/plan

Date	Calcium	Albumin	Serum Glucose
8/31	11.2	1.9	218 (AG 15)
9/1	10.0		161 (AG 16)
9/2	9.8		210 (AG 16)
9/3	9.3		61 (AG 15)
9/4	8.8		205 (AG 16)

Evaluation of Hypercalcemia

PTH (pg/mL) 5

PTH-Mediated

Primary Hyperparathyroidism

Familial
- MEN1 and MEN2A
- Familial hypocalciuric hyperCa
- Familial isolated hyperPTH

PTH-Independent

Hypercalcemia of Malignancy
- PTHrp
- Activation of extrarenal 1 alpha hydroxylase (increased calcitriol)
- Osteolytic bone metastases

PTHrp (pmol/L) 0.6
(ref range < 2.0)

Vitamin D Intoxication

25,OH-D (ngmL) < 5

Chronic Granulomatous disorders

Lymphoma

1,25-OH-D (pg/mL) 8

Medications
- Thiazide diuretics
- Lithium
- Teriparatide
- Excessive Vitamin A
- Theophylline Toxicity

Vitamin A (mcg/dL) 31.6
(ref range 32.5-78.0)

Miscellaneous
- Hyperthyroidism
- Acromegaly
- Pheochromocytoma
- Adrenal Insufficiency
- Immobilization
- Parenteral Nutrition
- Milk Alkali Syndrome

TSH (mcU/mL) 16.99

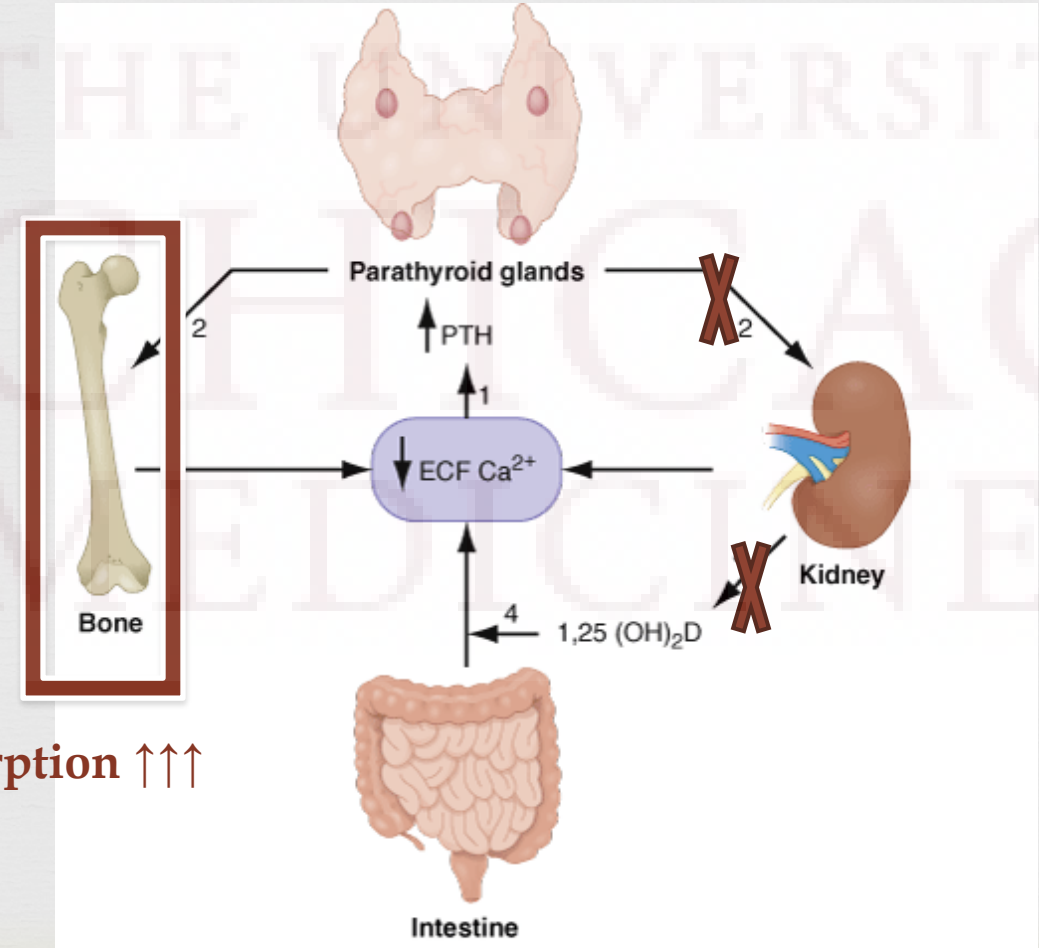
Cortisol (7:47 pm) (mcg/dL) 24.9

Who Gets Immobilization Hypercalcemia?

In general, young patients or those with disorders of accelerated bone turnover

- Poliomyelitis epidemic of 1950's
- Acute spinal cord injuries
- Burn patients
- Post-stroke hemiplegia patients
- Post-bariatric surgery critical illness
- Patient's with Parkinson's disease
- "Weightlessness" induced demineralization in astronauts

Calcium Metabolism in Immobilization



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

1° process:
Bone resorption ↑↑↑

Possible Mechanism

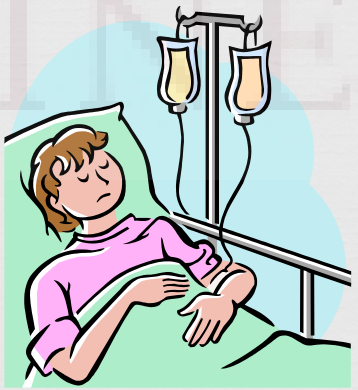
Weight-bearing → mechanical stress → bone remodeling

Immobilization and loss of mechanical stress → uncoupling of bone remodeling →

osteoclast >>> osteoblast activity →

Hypercalciuria within days

Hypercalcemia within weeks*



Mechanisms

RANKL

RANK

Osteoprotegerin

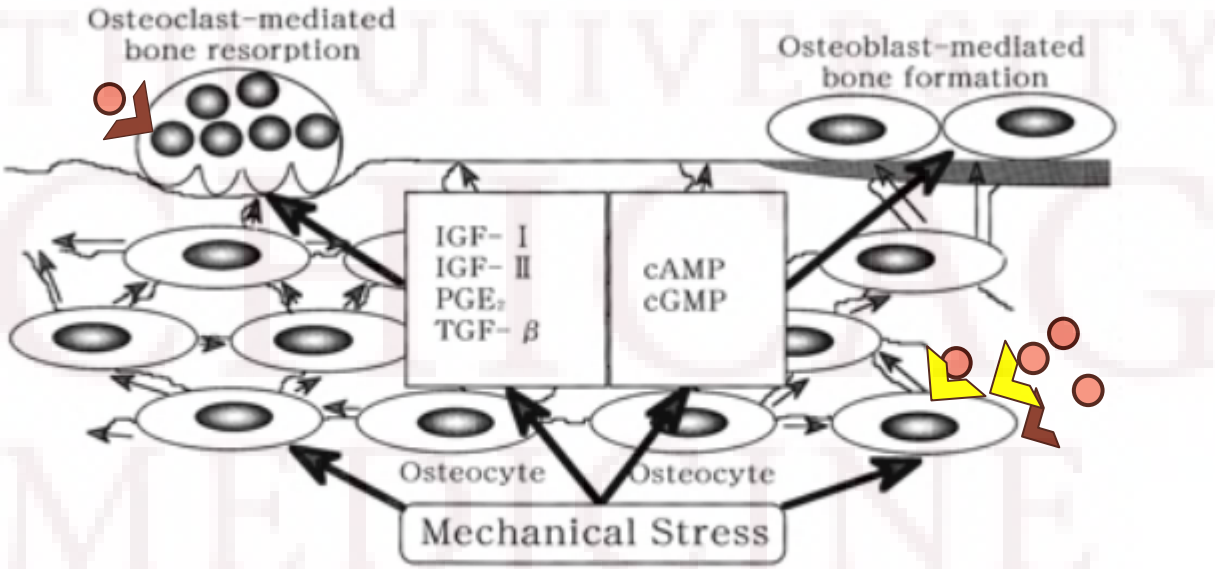


Fig. 1 **Mechanism of transduction of mechanical stress to bone. The gap junction of the long processes of osteocytes plays an important role in transmission of mechanical stress through intracellular signal transmitters (cAMP, cGMP) and extracellular signal transmitters (PGE_2, IGF-I, IGF-II, TGF-β), inducing thereby bone formation by osteoblasts and bone resorption by osteoclasts, or both.**

Takata S, Yasui N. Disuse Osteoporosis. J Med Investig 2001;48:147-56.

Malberti F. Treatment of immobilization-related hypercalcemia with denosumab. Clin Kidney J 2012;5:491-495.

Metabolic Changes in Calcium with Immobilization

Increased osteoclast activity/bone resorption leads to:

1. ↑ 24-hour urine calcium and fractional excretion of Ca^{2+}
2. High-normal or ↑ serum calcium
3. ↓PTH
4. ↑ Phosphorus
5. ↓ 1,25-OH Vitamin D

Stewart, AF, et al. Calcium homeostasis in immobilization: an example of resorptive hypercalciuria. N Engl J Med 1982; 306(19):1136-40.

Metabolic Changes in Calcium with Immobilization

TABLE 4. EFFECT OF 12 WEEKS OF BED REST AND REAMBULATION ON SERUM AND URINARY BIOCHEMICAL MARKERS OF BONE TURNOVER IN 11 NORMAL SUBJECTS

Parameter	*Pre*	*Bed rest phase*			*Reambulation*	*Normal range*
		Weeks 1–4	*Weeks 5–8*	*Weeks 9–12*		
Formation serum						
osteocalcin (μg/L)	7.1 ± 2.5*	7.5 ± 2.0	7.7 ± 2.1	7.4 ± 1.6	7.7 ± 1.9	2.4–11.7
BSAP (U/l)	21 ± 9	19 ± 6	19 ± 5	20 ± 5	21 ± 6	12–40
PICP (μg/l)	117 ± 48	107 ± 29	115 ± 30	110 ± 22	140 ± 36 ($p = 0.013$)†	38–202
Resportion serum						
ICTP (μg/l)	4.9 ± 1.6	6.3 ± 2.0‡	6.1 ± 2.2‡	5.8 ± 2.2	5.5 ± 1.9 ($p = 0.003$)	1.8–5.0
Resorption urine						
OH-proline (μmol/day)	190 ± 61	244 ± 69‡	275 ± 84‡	275 ± 69‡	221 ± 53‡ ($p < 0.0001$)	<198
Dpd (nmol/day)	55 ± 21	61 ± 22	75 ± 27‡	87 ± 28‡	76 ± 26‡ ($p = 0.0001$)	20–144
Ntx (nmol BCE/day)	366 ± 199	476 ± 250‡	553 ± 270‡	547 ± 262‡	421 ± 219 ($p = 0.0002$)	45–803

*All values expressed as mean ± SD.
† p value for repeated measures of analysis to assess differences among the five phases.
‡ Value significantly different from pre–bed rest value by Bonferroni adjusted paired-t test using the $\alpha = 0.0125$ (0.05/4) level of significance.

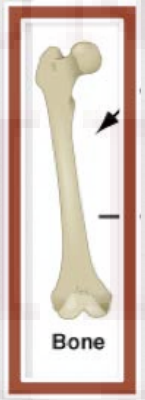
L-spine BMD declined by 2.9%; greater trochanter by 3.8% (p=0.002) , and femoral neck by 1.1%

Zerwekh JE, et al. The effects of twelve weeks of bed rest on bone histology, biochemical markers of bone turnover, and calcium homeostasis in eleven normal subjects. J Bone Miner Res 1998; 13:1594-1601.

Vitamin D Deficiency and Low PTH?

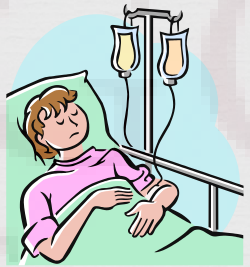
Vitamin D Deficiency

2º Hyper PTH



Elevated PTH primes bones for resorption to maintain normal Ca

Mechanical stress (activity) promotes osteoblast activity limiting rise of Ca and counteracting rise of PTH



Bones primed to release Ca by high PTH lose mechanical stress resulting in uncoupling of bone activity. Osteoclasts predominate. Ca released and rises

↑ Calcium suppresses PTH and overrides Vitamin D regulation

What is the Optimal Management of Immobilization Hypercalcemia?

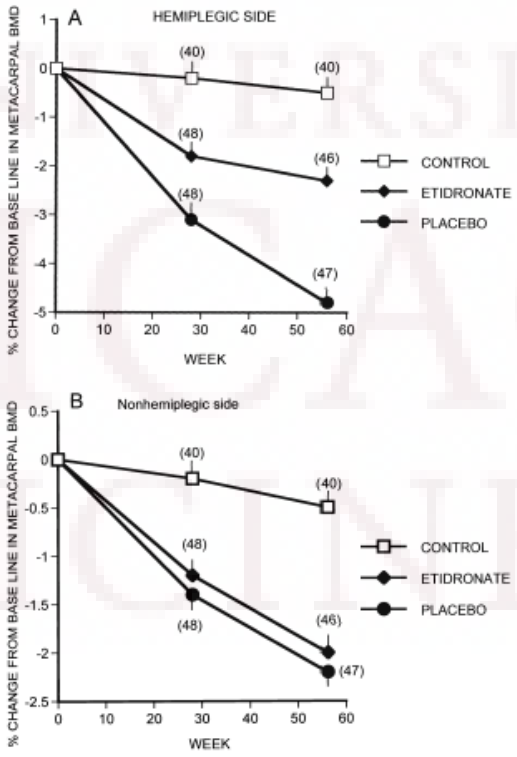
- Mobilization
- Mobilization
- Mobilization
- Bisphosphonate therapy
- Denosumab
- Dietary calcium reduction → not recommended

Bisphosphonate Therapy

TABLE 2. SELECTED CHANGES AFTER 56 WEEKS IN THE 93 SUBJECTS WHO COMPLETED THE STUDY

	Percent change after 56 weeks follow-up (values at 56 weeks)		
	Placebo (n = 47)	*Etidronate (n = 46)*	p *Value**
BI	+33.0 ± 6.7	+30.1 ± 4.7	0.66
Degree of hemiplegia			
Hand	+29.9 ± 8.3	+26.8 ± 8.4	0.94
Leg	+36.7 ± 10.2	+42.7 ± 10.2	0.93
BMI (kg/m^2)	−2.3 ± 1.1	−1.9 ± 1.1	0.53
Ionized calcium (mEq/liter)	+0.6 ± 0.2	−3.2 ± 0.3	<0.0001
Intact PTH (pmol/liter)	−10.6 ± 4.2	+102.2 ± 12.1	<0.0001
Intact BGP (ng/mL)	+54.7 ± 14.4	+72.0 ± 10.0	0.0033
ICTP (ng/mL)	+74.0 ± 13.1	−38.8 ± 3.8	<0.0001
25(OH)D (ng/mL)	−26.6 ± 4.4	−32.1 ± 2.1	0.73
$1,25(OH)_2D$ (pg/mL)	−12.4 ± 4.0	+62.2 ± 7.7	<0.0001

Values are the mean ± SEM.
*Wilcoxon rank sum test.



Sato Y, et al. Beneficial effect of intermittent cyclical etidronate therapy in hemiplegic patients following an acute stroke. J Bone Min Research 2000;15(12):2487-2494.

Questions Remain

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 20, Number 1, 2005
Published online on October 18, 2004; doi: 10.1359/JBMR.041010

Long-Term Disuse Osteoporosis Seems Less Sensitive to Bisphosphonate Treatment Than Other Osteoporosis

Chao Yang Li, Christopher Price, Kemesha Delisser, Philip Nasser, Damien Laudier, Mariza Clement, Karl J Jepsen, and Mitchell B Schaffler

ABSTRACT: We sought to determine whether risedronate can preserve cortical bone mass and mechanical properties during long-term disuse in dogs, assessed by histomorphometry and biomechanics on metacarpal diaphyses. Risedronate slowed cortical thinning and partially preserved mechanical properties, but it was unable to suppress bone loss to the degree seen in other osteoporoses.

ELSEVIER

Bone 37 (2005) 287 – 295

BONE

www.elsevier.com/locate/bone

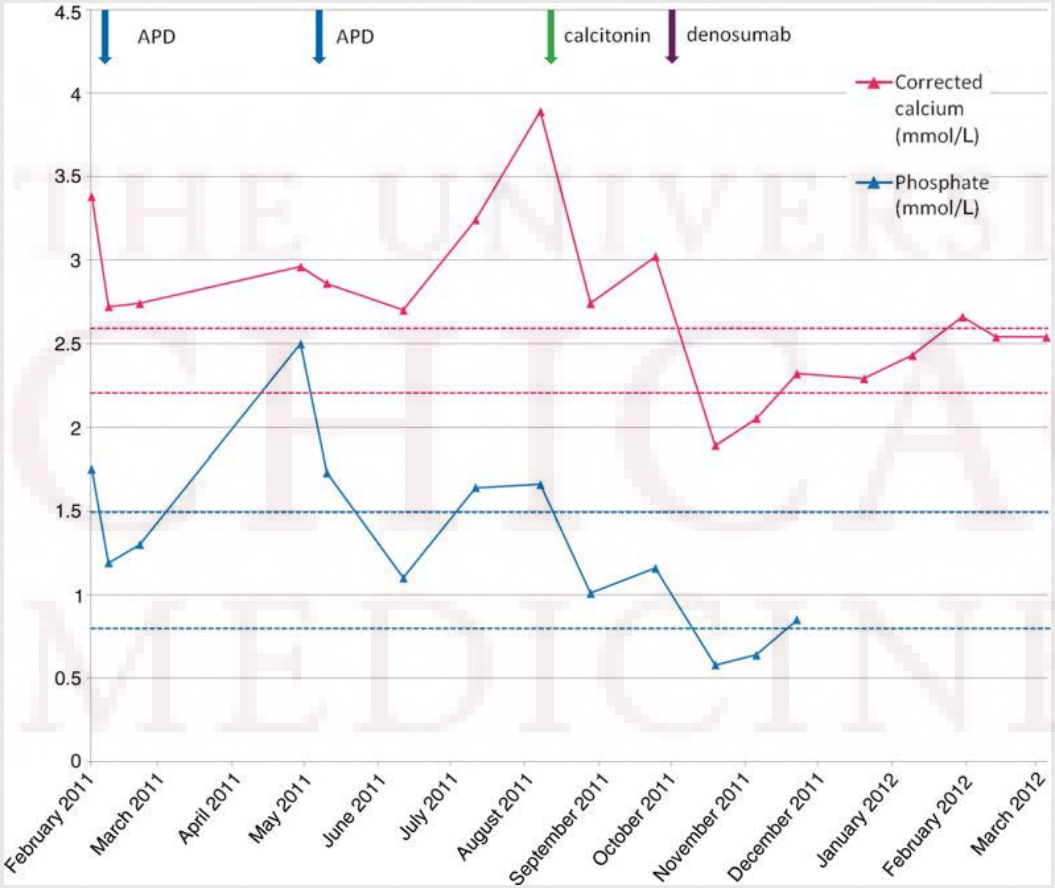
High-dose risedronate treatment partially preserves cancellous bone mass and microarchitecture during long-term disuse

Chao Yang Li[a], Robert J. Majeska[a], Damien M. Laudier[a], Richard Mann[b], Mitchell B. Schaffler[a,*]

[a]*Leni and Peter W. May Department of Orthopaedics, Mount Sinai School of Medicine, Box 1188, One Gustave L. Levy Place, New York, NY 10029, USA*
[b]*Bronx VAMC, New York, NY 10468, USA*

Received 13 October 2004; revised 5 April 2005; accepted 13 April 2005
Available online 11 July 2005

Denosumab Therapy



De Beus E, Boer WH. Denosumab for treatment of immobilization-related hypercalcaemia in a patient with advanced renal failure. Clin Kidney J 2012;5:566-71.

Malberti F. Treatment of immobilization-related hypercalcemia with denosumab. Clin Kidney J 2012;5:491-495.

Complicated Hospital Course

Pulmonary
Pulmonary edema
ARDS 2/2 aspiration and sepsis
Mechanical ventilation x 2
Exudative pleural fluid growing yeast

Cardiovascular
Hypotension requiring pressors

Infectious Disease
Sepsis suspected secondary to:
Gastric perf: ascitic fluid with VRE and Candida sp.
PNA: Pleural fluid with yeast after abx therapy
Osteomyelitis: Klebsiella, Enterococcal sp., E. coli

Endocrine
Diabetic ketoacidosis
Hypothyroidism
Hypercalcemia

Gastrointestinal
Diarrhea
Gastric perforation requiring wedge resection/repair

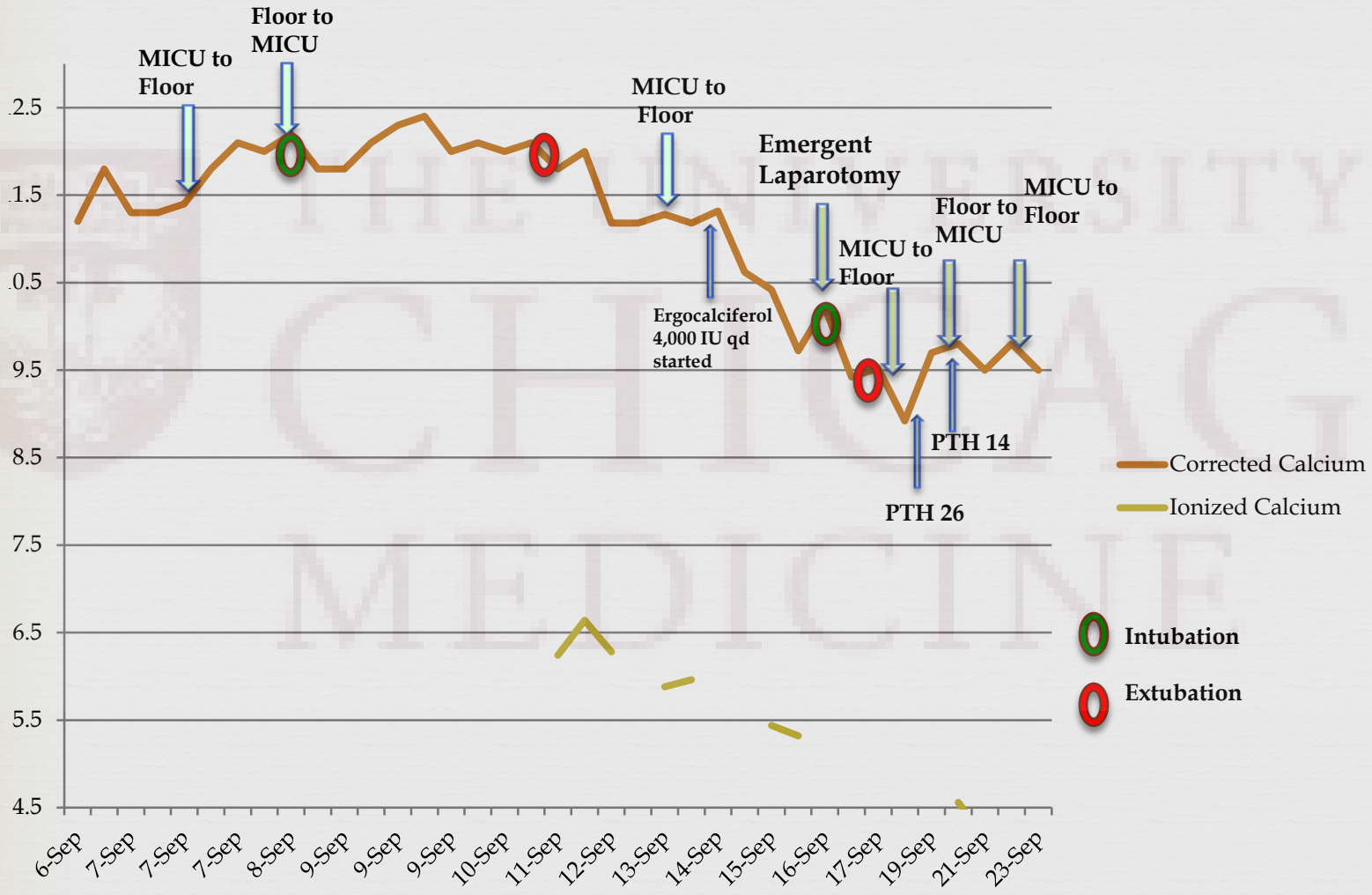
Nutrition
Severe protein calorie malnutrition
Zinc, Vitamin A, Vitamin D deficiencies
IgM deficiency
J- tube insertion w/enteral nutrition started

Musculoskeletal
Osteomoyelitis
Critical Illness Myopathy

Hematologic
Anemia requiring PRBC transfusion
Sub-acute DVT

Psychiatric
Anxiety, PTSD 2/2 illness
Psychiatric service on consult

Calcium and Clinical Course



Move It or Lose It!

- Mechanism of immobilization hypercalcemia is thought to be due to increased bone resorption, uncoupling of bone remodeling and increased osteoclast activity
- Limited data on bisphosphonate therapy suggests that it may be helpful, but that benefits may not last as long as with other types of osteoporosis
- There may be a role for denosumab therapy, however, mobilization is the mainstay of treatment
- As little as OOB to chair twice daily for 30 minutes has been shown to prevent hypercalciuria in immobilized patients

Comments/Questions?

Bisphosphonates for Treatment of Childhood Hypercalcemia

ABSTRACT. Most clinicians only have a limited experience in treating childhood hypercalcemia with bisphosphonates. We report our experience in the use of intravenous and oral bisphosphonates in a 5-year-old with hypercalcemia secondary to acute lymphocytic leukemia, a 16-year-old with immobilization hypercalcemia, and a 14-year-old with chronic hypercalcemia of unknown cause. Single infusions of 0.5 mg/kg and 1 mg/kg of intravenous pamidronate were administered over 4 hours. No adverse reactions were observed except for hypocalcemia. A dose between 10 and 20 mg of oral alendronate was successfully used to maintain normocalcemia in the patient with chronic hypercalcemia. In our experience, the administration of bisphosphonates has enabled us to achieve normocalcemia in all cases, and in all cases there were no significant side effects. Long-term potential side effects from their use in children during the active phase of growth remain unknown. *Pediatrics* 1998;102:990–993; *hypercalcemia, pamidronate, alendronate, side effects.*

When Healthy Individuals Become Immobile

Zerwekh JE, et al. The effects of twelve weeks of bed rest on bone histology, biochemical markers of bone turnover, and calcium homeostasis in eleven normal subjects. J Bone Miner Res 1998; 13:1594-1601.

- 11 normal subjects studied on 12 weeks of bed-rest
  - L-spine BMD declined by 2.9%; greater trochanter by 3.8% (p=0.002) , and femoral neck by 1.1%

Yusuf, MB, et al. Comparison of serum and urinary calcium profile of immobilized and ambulant trauma patients. Bone; 2003. http://dx.doi.org/10.1016/j.bone21013.09.001..

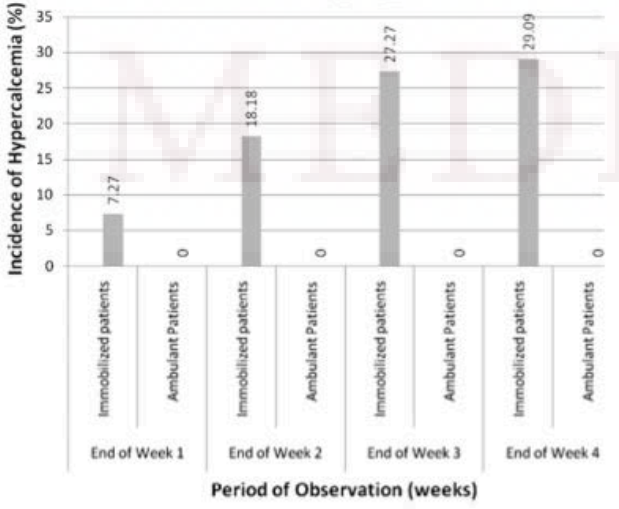


Fig. 3. Chart showing the incidence of hypercalcemia with period of observation in the immobilized and ambulant trauma patients.

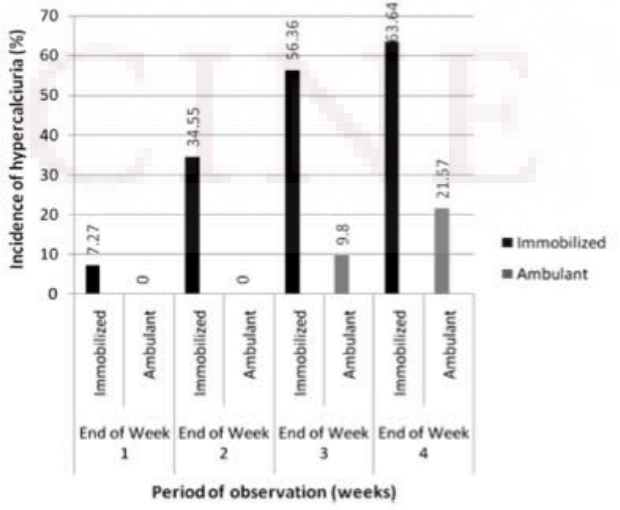
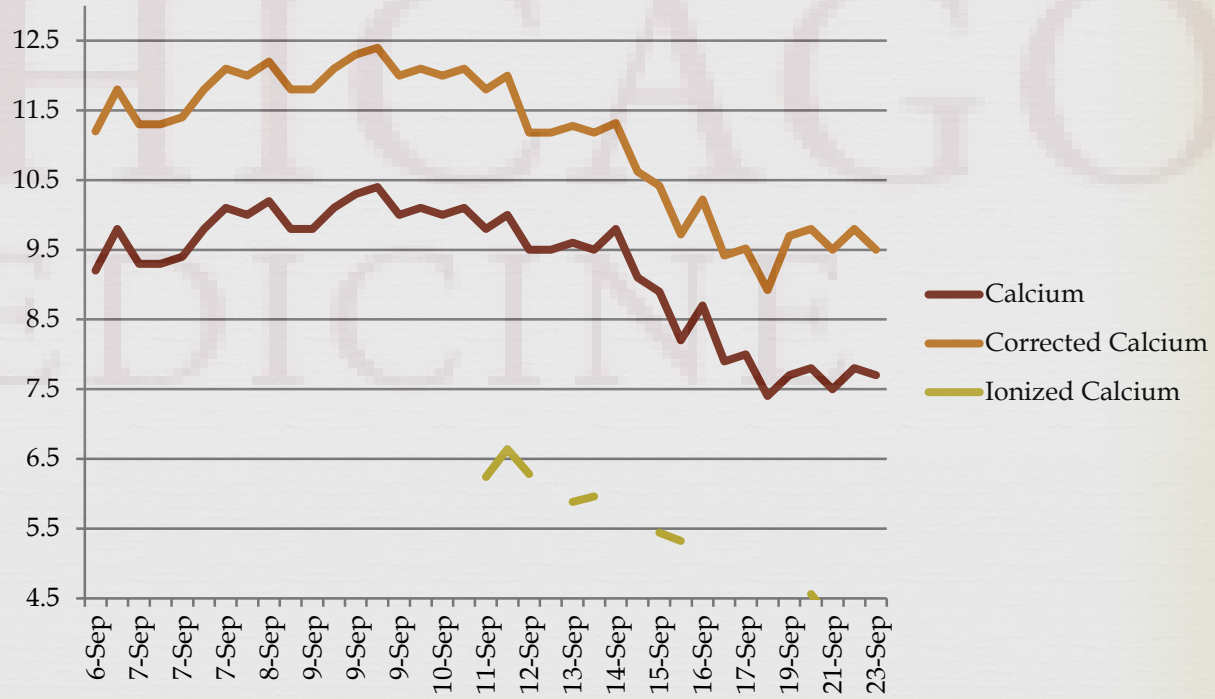


Fig. 4. Chart showing the incidence of hypercalciuria with period of observation in the immobilized and ambulant trauma patients.

Date	Cortisol (Time)	
9/2	14.0 (05:00)	
9/3	15.9 (05:00)	

Complicated Hospital Course

Date	PTH	1,25-OH-D
9/8	5	
9/14		<8
9/20	26	
9/21	14	16



Date	Calcium	Albumin	Ionized Calcium
9/6	9.2	1.5	
9/6	9.8		
9/7	9.3		
9/7	9.3		
9/7	9.4		
9/7	9.8		
9/7	10.1		
9/8	10.0	1.5	
9/8	10.2		
9/8			6.92
9/8	9.8		
9/9	9.8		
9/9	10.1		
9/9	10.3		
9/9	10.4		
9/9	10.0		
9/10	10.1		
9/10	10.0		
9/10	10.1		
9/10			6.26
9/11	9.8		6.24
9/11	10.0		6.64
9/12	9.5		6.28
9/12	9.5		6.21
9/13	9.6	1.9	5.88
9/13	9.5		5.96
9/14	9.8	2.1	
9/14	9.1		
9/15	8.9		5.44
9/16	8.2		5.32
9/16	8.7		
9/16	7.9		
9/17	8.0		
9/18	7.4		
9/19	7.7		

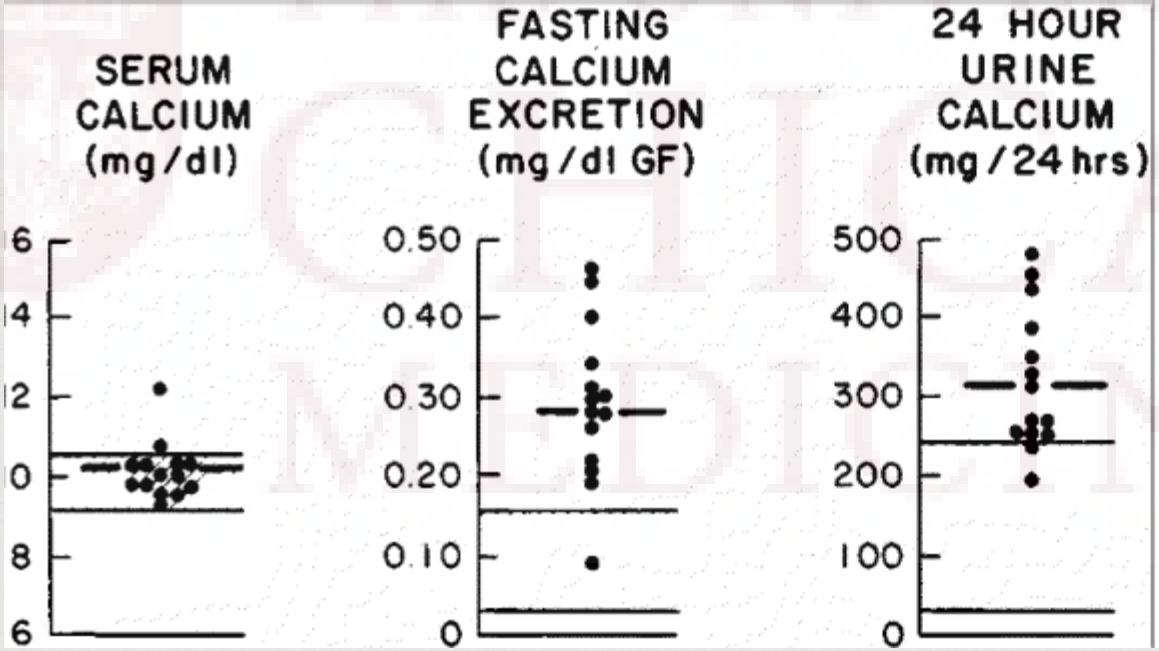


Figure 1. Serum Calcium Levels and Urinary Calcium Excretion in 14 Immobilized Patients.

The mean value is denoted by the horizontal line, and the normal range by the hatched area. GF denotes glomerular filtrate. The mean (±S.D.) ionized serum calcium was 4.28±0.56 mg per deciliter (normal, 4.28±0.20 mg per deciliter[20]); the fractional calcium excretion was 0.068±0.020 (normal, 0.029±0.018[17]). To convert milligrams of calcium to millimoles, multiply by 0.02495.
Although the mean serum calcium level was normal, marked hypercalciuria was present, suggesting a reduced effect of parathyroid hormone on the distal nephron.

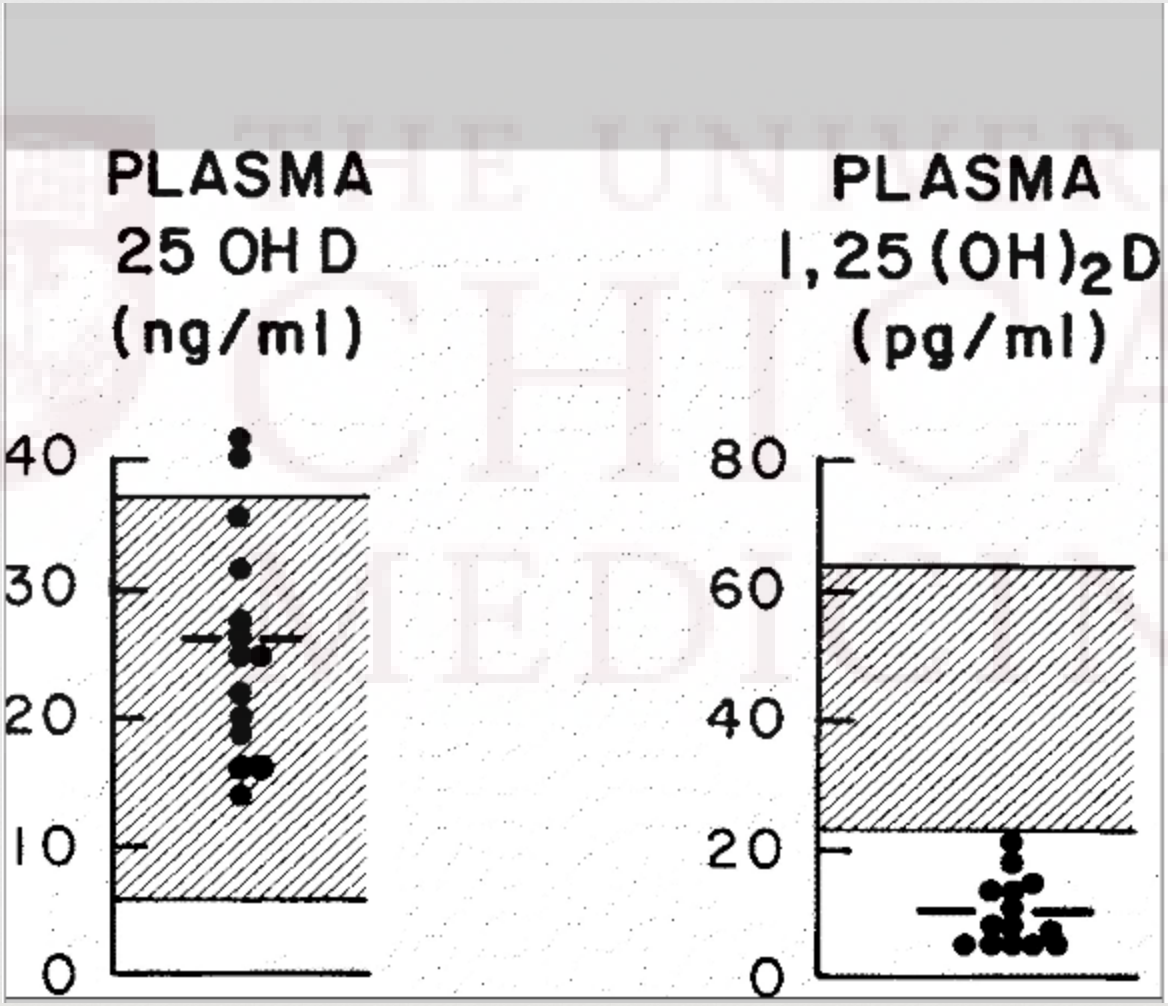


Figure 3. Plasma Levels of 25-Hydroxyvitamin D (25 OH D) and 1,25-Dihydroxyvitamin D ($1,25(OH)_2D$).

Despite normal plasma 25 OH D values, $1,25\ (OH)_2D$ values were reduced, suggesting a reduction in circulating parathyroid hormone levels.