

HYPERCALCEMIA

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Overview

- Hypercalcemia D/D
- Hypercalcemia from Immobilization
 1. Physiology
 2. Literature
- Hypercalcemia from Rhabdomyolysis

Calcium Homeostasis

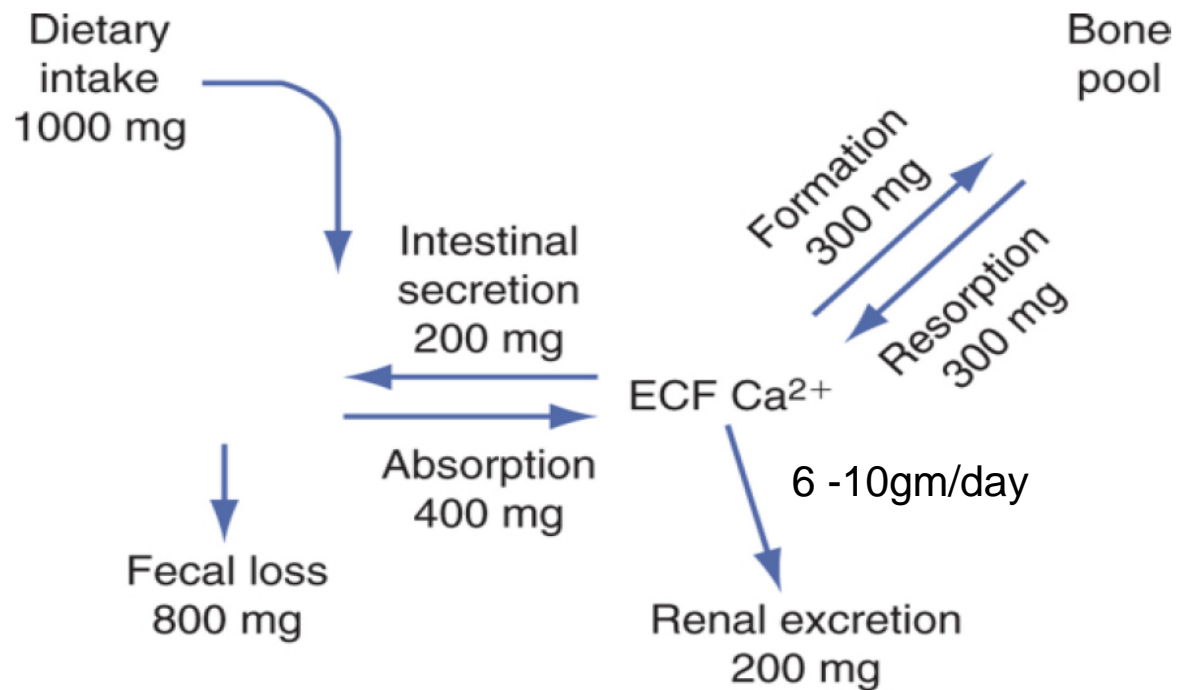
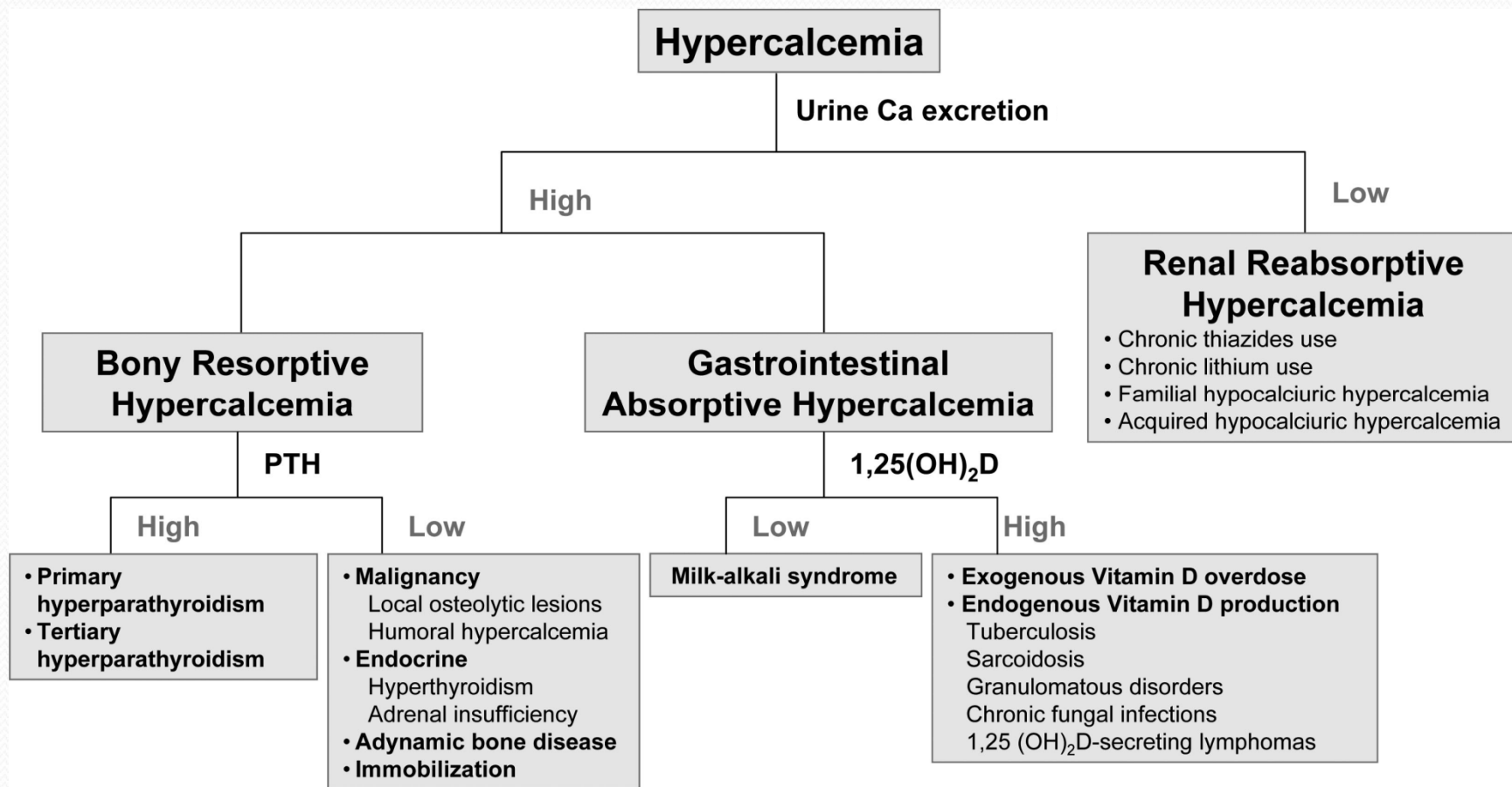


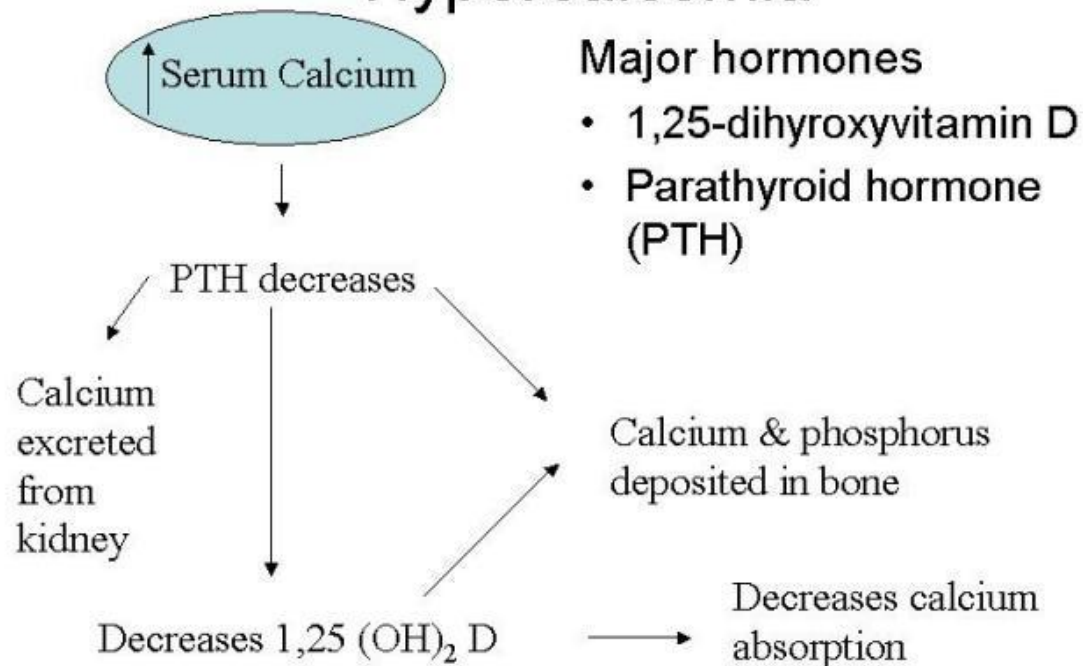
FIGURE 5-26 Typical daily Ca²⁺ intake and output for a normal adult in neutral Ca²⁺ balance (see text for details).

Hypercalcemia



Response to Hypercalcemia

Regulation of calcium: Hypercalcemia



Hypercalcemia from Immobilization

- What is considered immobilization?
- Time period of onset?
- Severity?
- Diagnostic Test?
- Treatment

Disclaimer

- Paucity of literature
- Observational study
- Anecdotal and retrospective data

History of Bed Rest/Immobilization

- In the nineteenth century, bed rest was introduced as a medical treatment
- Any adverse consequences of this therapy were attributed to the medical condition that sent one to bed in the first place
- During the polio epidemic of the first half of the twentieth century, this therapy came to question
- Don Whedon and his group (Dietrick et al. 1948) wondered whether the increased excretion of calcium and bone loss in polio victims was due to the disease or the resulting immobilization

History of Bed Rest/Immobilization

- Experiment -30 healthy medical student were put to bed rest
- Result- were similar to polio victims-osteoporosis
- During World War II that men who were made ambulatory soon after surgery ,recovered faster
- Last half of the twentieth century finally saw a gradual reversal of the practice of using bed rest as medical treatment

Hypercalcemia of Immobilization

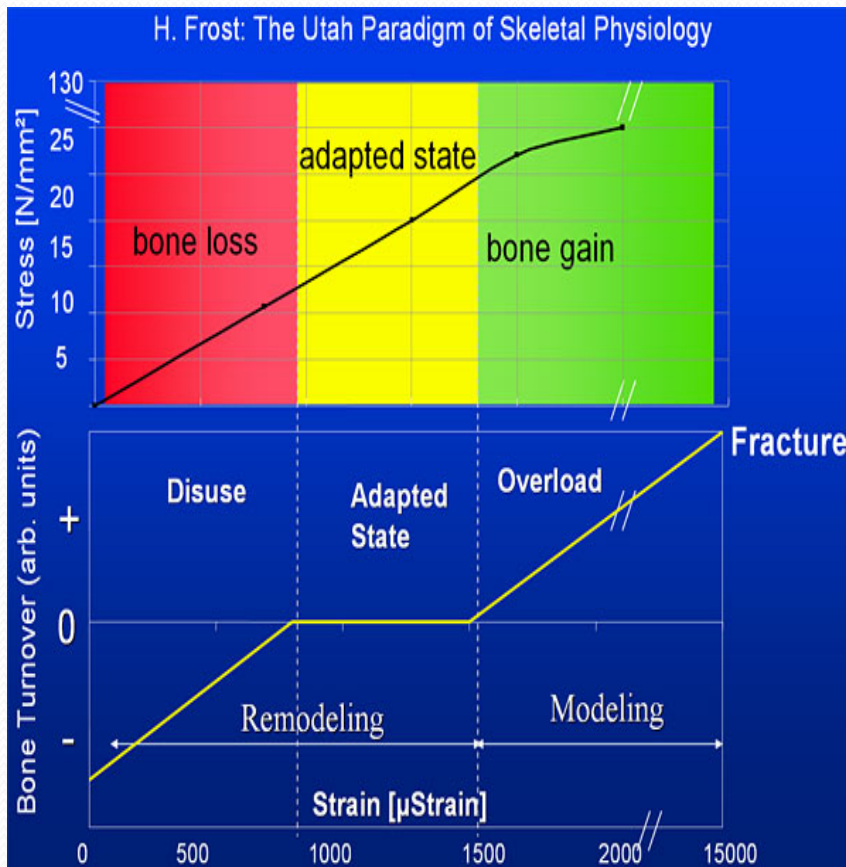
- First described by 1941 by Albright in a teenager with fracture
- Incidence 11-22% in SCI group and 20-30% in immobilized adults sec to fractures in 2 case series
- Usually develops 4-6 weeks post trauma (1 week-16weeks)
- May remain elevated for upto 12 months depending upon mobilization

Clinical Rehabilitation 1989; **3**: 243–247

Immobilization

- Orthopedic fractures
- Spinal Cord Injury
- Guillaine Barre Syndrome
- Polio victims
- Astrounauts –Microgravity in space

Pathophysiology



Mechanostat Theory

- Functional adaptability described in 1892 by Julius Wolff.
- 1990 Frost described the mechanostat theory
- How mechanical signals are translated to bone formation and resorption are not clearly defined.

Pathophysiology

Loss of mechanical stress



Increased osteoclastic bone resorption and decreased osteoblastic bone formation



Calcium overload exceeds the normal regulatory mechanism of the body



Hypercalciuria /Hypercalcemia

Five-Year Longitudinal Bone Evaluations in Individuals With Chronic Complete Spinal Cord Injury

BMD changes after SCI is divided into 3 Phases

- 1) **Acute or 'response to injury phase'**- first four months
BMD decreases by 1% /week at knee, 2%/week in LL
Increased bone resorption and osteoclastic response
Begins soon after injury n peaks at 16-24 weeks.
- 2) **Subacute or 'adaption phase'** -4 months to 1 year
Osteoclastic activity starts decreasing
BMD loss decreases to 1%/month
- 3) **Chronic or 'impairment phase'** -1.5 to 2 yrs after injury
Osteoclastic activity returns to baseline
BMD loss 0.5⁰%-1%/year

Risk Factors

- Children /Adoloscent
 - Pagets disease
 - Pre-existing renal impairment are prone to develop immobilization hypercalcemia in a shorter time frame
 - Degree of immobilization? *
- Arch Phys Med Rehabil. 1978 Oct;59(10):443-6.
Hypercalcemia in children with spinal cord injury*
- Acidosis
 - High stores of Vit d ?
 - Genetic predisposition

Immobilization Hypercalcemia Following Spinal Cord Injury

Frederick M. Maynard, MD

Department of PM&R, University of Michigan Hospital, Ann Arbor, MI 48109

Between 1974-1977 , 70 SCI below age 21 were admitted ,11% developed hypercalcemia

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SCI AND IMMOBILIZATION HYPERCALCEMIA, Maynard

Clinical Summary of 10 Cases of IH After SCI

Age	Level and Severity of Injury	Weeks After Injury to Onset	Sx (m: mild s: severe)	Highest SCa (mg/100cc)	Lowest CCr (cc/min/1.73 m ²)
18	C-7 complete	8	m	14.8	68
13	C-2 complete	16	s	15.2	22
14	C-4 complete	9	m	11.3	63
17	C-7 complete	2	s	14.8	22
16	C-4 complete	4	m	12.4	59
7	C-3 complete	10	s	15.8	62
15	C-5 complete	12	o	11.0	101
15	C-2 complete	13	m	12.4	47
21	C-5 complete	8	s	14.2	95
16	C-5 complete	9	s	13.8	55

Immobilization Hypercalcemia Following Spinal Cord Injury

Frederick M. Maynard, MD

Department of PM&R, University of Michigan Hospital, Ann Arbor, MI 48109

- 4 developed mild symptoms- anorexia, nausea and depression
- Severe symptoms included- acute abdomen, constipation and gastric dilatation
- Lab findings- increased calcium, normal phosphorous, normal to increased alkaline phosphatase, hypercalciuria and signs of osteoporosis on Xray
- PTH was low to normal

Immobilization Hypercalcemia: SOME NEW ASPECTS OF DIAGNOSIS AND TREATMENT

G. D. LAWRENCE, R. G. LOEFFLER, L. G. MARTIN and T. B. CONNOR
J Bone Joint Surg Am. 1973;55:87-94.

Reference	Subject	Age	Sex	Cause of Immobilization	Ca/P mg per 100 ml	Alkaline Phosphatase	Immobilization Time Before Hypercalcemia Noted (Mos.)	Comments and Therapy	Time to Normocalcemia After Therapy
Albright and associates ¹ , 1941	Active	14	M	Fractured femur, plaster spica	14.6/4.5	4 BU *	3	Negative parathyroid exploration; walking	1 month
Reifenstein and Albright ² , 1944	Paget's disease	58	M	Fractured femur, traction	13.4/4.2	4 BU	1	Intravenous fluids; mobilization	7 days
	Paget's disease	58	F	Fractured femur	13.9/3.6	13 BU	1	Intravenous fluids; mobilization	21 days
Dodd and associates ³ , 1950	Active	12	M	Fractured femur, plaster spica	14.9/3.7	5 BU	2	Negative parathyroid exploration; fluids, walking	8 days
Halvorsen ⁴ , 1954	Active	9	M	Fractured femur, plaster spica	16.4/3.1	3.7 BU	1	Walking	6 weeks
Mason ⁵ , 1957	Active	22	F	Fractured pelvis, paralysis	16/1.9	3 KAU †	1	Negative parathyroid exploration; mobilization, estrogens and androgens	5 weeks
David and associates ⁶ , 1962	Active	13	M	Multiple fractures, plaster spica	13.7/3.5	3 BU	3	Walking	8 days
Winters and associates ⁷ , 1966	Active	13	M	Multiple fractures, plaster spica	16/?	?	1	Fluids, walking, prednisone	5 days
Present report	Active	12½	M	Fractured femur, plaster spica	15/3.3	6 KAU	1	Fluids, walking, prednisone	10 days

* Bodansky units

† King-Armstrong units

Symptoms

- Renal -polyuria, polydipsia, stones
- Intestinal symptoms -nausea, vomiting, constipation
- Mimicks acute abdomen
- Neurologic symptoms -weakness, headache, depression, altered mental status
- Cardiac symptoms -tachycardia, hypertension

Treatment

- Self limiting until new equilibrium is reached between bone formation and resorption
- A passive mobility or weight-bearing rehabilitative program
- Saline \pm lasix
- Calcitonin
- Pamidronate
- Steroids
- Anabolic Steroids

Successful Treatment of Immobilization Hypercalcemia Using Calcitonin and Etidronate

Case/Sex/Age	Diagnosis	Initial Serum Calcium (mg/dL)	Initial Serum Albumin (mg/dL)	Follow-up Serum Calcium (mg/dL)	Follow-up Serum Albumin (mg/dL)	Initial 24 Hour Urine Calcium (mg/day)	Follow-up 24 Hour Urine Calcium (mg/day)
1/F/46	SCI	14.7	4.5	9.5	4.0	790	—
2/M/26	SCI	11.0	4.0	9.4	3.6	527	—
3/F/44	SCI	12.6	3.1	10.2	3.2	854	440
4/M/28	SCI	11.6	4.1	9.7	3.9	509	—
5/F/24	Multiple fractures	12.3	3.6	8.9	3.0	—	—
6/M/17	SCI	11.4	3.5	9.5	3.5	598	388

- Retrospective case study
- Calcitonin for initial 4-5 days
- Etidronate BID for 14 days and then q daily for 2-3 months depending on mobilization

Immobilization Hypercalcemia Treatment With Pamidronate Disodium After Spinal Cord Injury

- Retrospective case study
- 9 patients (19-51yrs) with HCI after SCI btw 1994-1998
- Hypercalcemia developed btw 3-18 weeks of immobilization
- 7 patients received one dose of pamidronate ,that resolved hypercalcemia
- 2 Patients req additional doses

Hypercalcemia From Immobilization

- What is considered immobilization?
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Hypercalciuria in Astronauts

- As of October 2001 there had been 15 US crewmembers in whom renal stones developed and Russian Space Program reported 3 cases.
- Renal stone in a cosmonaut necessitated the termination of the space flight.
- Bedrest immobilization model, has been used to study biochemical and skeletal changes during space flight.

Space and bed rest

	Space	Bed rest (HDBR)
Height	↑ ± 1.3 cm	↑ ± 1.0 cm
Body mass/weight	↓ 3–4%	↓ 2–4%
Maximal aerobic capacity	Not measured	↓ 25%
Plasma volume	↓ 10–15%	↓ 10–15%
Urinary calcium	↑	↑
Bone density	↓ 1.6%/month	↓ 0.5–1%/month
Absorption of Ca from Gut	↓	↓
Renal stone risk	↑	↑
Muscle mass	↓	↓
Muscle strength	↓	↓
Insulin resistance	↑	↑
Nausea/sickness/vertigo	None 35% Severe 7% Moderate 23% Mild 35%	Vertigo 10% Nausea rarely present

Alendronate and potassium citrate have been studied to prevent stone formation

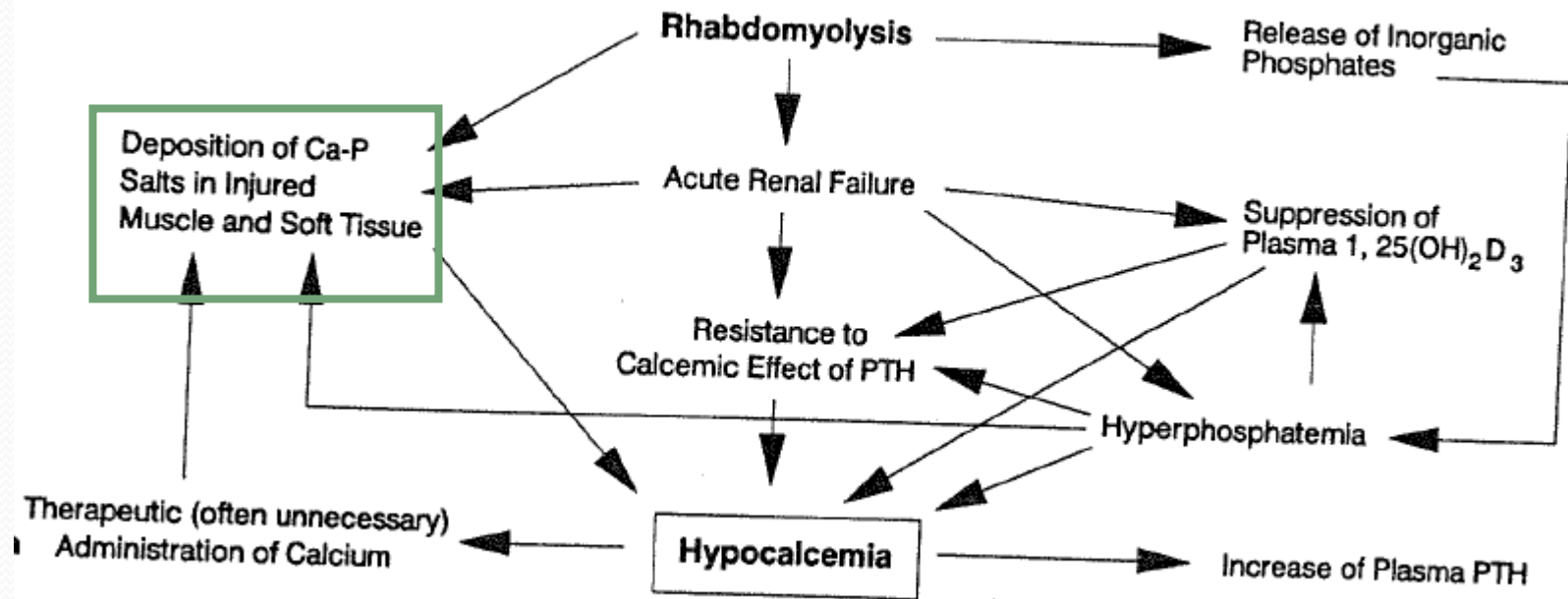
Hypercalcemia From Rhabdomyolysis

- Develops in 20-23% of pt in diuretic phase

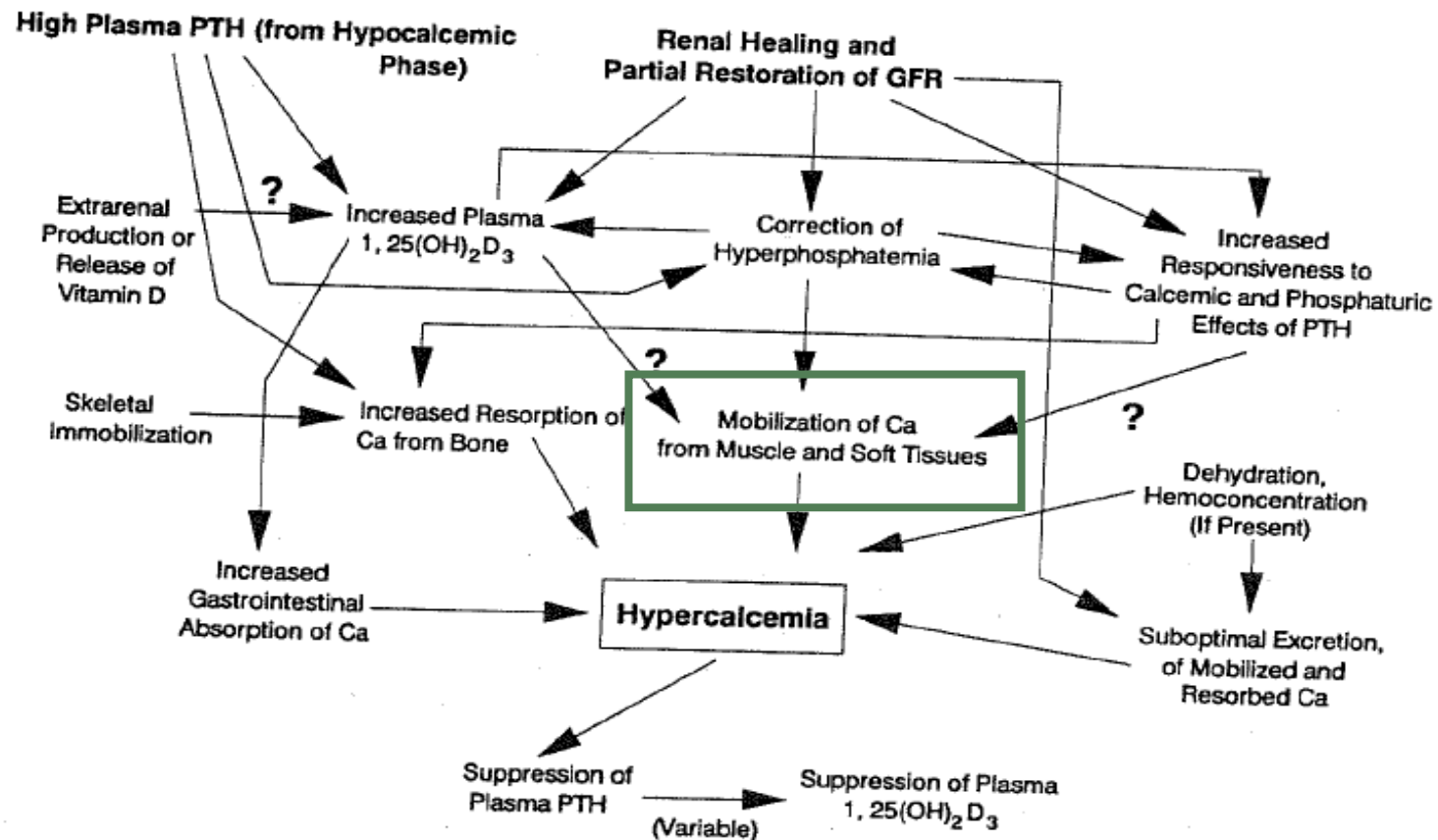
Table 5. Frequency of hypercalcemia in patients with R/ARF

Investigators	Year	Frequency	Percent
Fortner et al. [9]	1971	1/11	9.1
Mautalen et al. [14]	1973	4/7	57.1
Grossman et al. [18]	1974	3/15	20
Koffler et al. [22]	1976	5/21	23.8
Fuss et al. [28]	1978	1/5	20
Chugh et al. [31]	1979	10/17	58.8
MacSearraigh et al. [32]	1979	1/9	11.1
Patel et al. [33]	1980	2/8	25
Thomas and Ibels [43]	1985	2/11	18.2
Akmal et al. [47]	1986	4/7	57.1
Totals		33/111	29.7

Hypocalcemia during Oliguric Phase of Rhabdomyolysis



Hypercalcemia during Diuretic Phase of Rhabdomyolysis



Resolution of Muscle Calcification in Rhabdomyolysis and Acute Renal Failure

- 4 patients with nontraumatic Rabdo were studied
- Diagnosis established by
 - visible damage to muscle(tenderness n swelling)
 - CPK in thousands
 - Hyperphosphatemia (6.5-10mg/dl), Hypocalcemia(5.4-7.1)
- Regular radiography, electron radiography and Tc DP scan
- Marked calcification noted during first 2 weeks of oliguric AKI
- Resolution or normal uptake in 1 month in 2 pt and 4 months in 2pts. Rpt scan at 5,7, 11 month were normal

Hypercalcemia from Rhabdomyolysis

Hypercalcemia in association with ARF and rhabdomyolysis

Mineral electrolyte Metab 1993

- Reviewed 86 cases of hypercalcemia associated with AKI
- 67 cases were sec to rabdo, other were probable /indeterminate
- Summarized the data reported

Hypercalcemia in association with ARF and rhabdomyolysis

Mineral electrolyte Metab 1993

- Renal failure was severe and reqd RRT (BUN 150-200)
- 86% pt hypercalcemia occurred during diuretic phase
10 \pm 2.4 days
- Average calcium peak was 13.5 \pm 0.2mg/dl
- Average duration of hypercalcemia was 14.7 \pm 3.1 days
- S. Phosphate had decreased to 7.1 \pm 0.5mg/dl
- PTH, 1-25 Vitd have been normal to low
- 25 Vitd levels reported in 13 pt(n -9, l-2, h-2)

Hypercalcemia in association with ARF and rhabdomyolysis

Mineral electrolyte Metab 1993

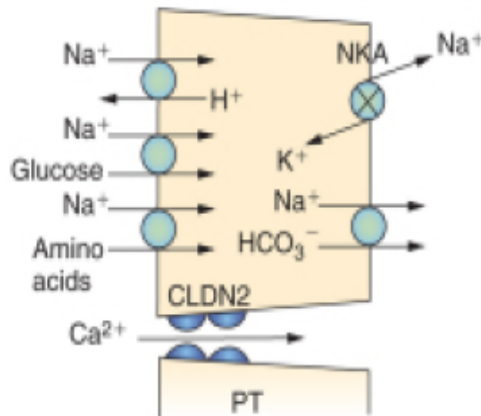
- Ectopic calcification was reported in 22 pts
- 4 pts had hypercalcemia after 4 weeks of diuretic phase and there was suspicion of immobilization hypercalcemia
- Asymptomatic or mild symptoms
- Treatment –saline, calcitonin, bisphosphonates steroids

Thank you!

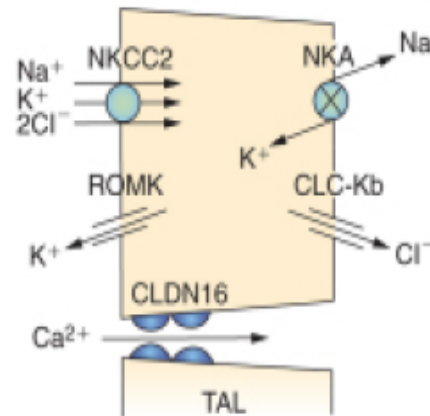


Calcium Absorption in Kidneys

	Lumen	Cell	Blood
$[Ca^{2+}]$:	1 mM	0.1 μ M	1 mM
ψ :	+3 mV	-70 mV	0 mV



	Lumen	Cell	Blood
$[Ca^{2+}]$:	2 mM	0.1 μ M	1 mM
ψ :	+10 mV	-70 mV	0 mV



	Lumen	Cell	Blood
$[Ca^{2+}]$:	0.5 mM	0.1 μ M	1 mM
ψ :	-10 mV	-70 mV	0 mV

