Parkland Mineral Metabolism Clinic
Evaluation and Follow-up of Common Disorders

Nephrolithiasis

Initial Evaluation:

1. History and Physical including
    a. Stone history...when passed first stone, composition of stone if known, how many in the last 3 years, last stone, how many still left in kidney?
    b. Operative procedures in past for stones/ h/o lithotripsy? Urinary tract abnormalities?
    c. Any history or clinical evidence of gout, urinary tract infection, chronic diarrhea, excess heat exposure, Cushing syndrome?
    d. Dietary habits including how much fluid intake (this can wait until patient returns for results)? How many servings of dairy products (slices of cheese, glasses of milk, yogurt, ice cream, etc.)? Intake of oxalate-rich foods such as nuts, chocolate, tea, spinach? Animal protein?
    e. Medications- especially Diuretics- Triamterene, Steroids, Indinavir, Carbonic anhydrase inhibitors, Topamax
    e. Family history of stones, gout, osteoporosis?
    f. Current stone symptoms

2. Labs/studies
    a. Chem 7, Ca, Mg, Phos, Uric Acid, LFT's, CBC with diff. and PTH
    b. U/A with micro and urine culture
    c. 24 hour urine collection for volume, pH, Na, K, Ca, Mg, creat, uric acid, citrate, oxalate, sulfate (cystine also if age < 30, known FHx or cystine stone, get total protein as well if cystinuric)
    d. KUB, IVP or CT without contrast (if imaging study not recently done)

Follow-Up Evaluation:

1. H&P: Know all of his/her risk factors for stones, number/location of current stones, last imaging studies and labs, other medical problems, meds.
2. Labs
    a. Lytes, Creat (other +/- Ca P, UA, LFT's, CBC, PTH)
    b. 24 hour urine for volume, pH, Na, K, Cr, Ca, UA, citrate and oxalate (sulfate too if history of high UCa) (if cystinuric check urine cystine and total protein as well)

Osteoporosis

Initial Evaluation:

1. History and Physical including
    a. Bone fracture history if any, including h/o trauma and general assessment of fall risk. Symptoms of bone pain? Kyphosis/scoliosis on exam? Blue sclerae?
    b. Other medical conditions including childhood illness, immobilization, menopause, chronic illness.
    c. Medications present or past, especially use of steroids, hormone replacement, anticonvulsants, previous treatment for osteoporosis.
    d. Cigarettes, alcohol use? Physical activity
    e. History of diarrhea (# BM/day)
    f. Intake of dietary calcium and supplemental Ca/vitamin D
    g. Family history stones, osteoporosis, cancer
    h. Physical exam to rule out secondary risk factors

2. Labs/studies
    a. Chem 7, Ca, Mg, Phos, LFT's, CBC with diff., TSH, PTH (+/- ESR and SPEP)
    b. 24 hour urine collection for volume, Na, Ca, Creat, N-telopeptides (+/- cortisol and UPEP)
    c. Strongly consider AP and Lateral of T/L/S-spine (+/- AP pelvis, sites of pain)
    d. BMD (nuclear medicine) DEXA spine and hip (phone 25120)

Follow-Up Evaluation:

1. H&P: Know all the risk factors for osteoporosis, number/location of fractures, last BMD/x-rays, key medical problems and meds
2. Labs
    a. Lytes, Creat, Ca (+/- PTH, AP, TP, albumin)
    b. 24 hour urine Na, Ca, Creat. (+/- N-telopeptide)
    c. BMD q year (initially and then at increasing intervals when stable)

Primary Hyperparathyroidism

1. History and Physical (initial and follow-up)
    a. history or symptoms of stones, abdominal pain, heartburn
    b. history of fractures, bone pain
    c. exposure to neck radiation (get hyperparathyroidism 40 years later)
    d. medication history, steroids, lithium, thiazides, calcium, vitamin D, vitamin A?
    e. family history hypercalcemia, kidney stones, pituitary tumor, thyroid tumor, ulcer disease, abdominal
        tumor, pheochromocytoma, severe hypertension, sudden death?
    f. physical exam—R/O hypertension, Cushingoid/Marfanoid, band keratopathy, neck mass

2. Labs/Studies
    a. Lytes, Creat, Ca, P, Mg, Alk Phos, Albumin, PTH q 6 months (initial and F/U)
    b. 24 hour urine for Na, Ca, Mg, Creat, N-telopeptide initial and selected follow-up
        -R/O pheo if hypertensive
    c. BMD q year (make sure to include the radius)

Paget's Disease

Initial Evaluation:

1. History and Physical focusing on sites involved and related symptoms (bone pain, change in bone shape-especially legs, skull and sites of pain or known involvement (document where involved), hearing loss?). Note any deformity or warmth in sites of involvement.

2. Labs
    a. Lytes, Creat, Ca, P, UA, PTH, CBC, LFT's (?PSA)
    b. 24 Hour urine for Na, Ca, Creat, N-telopeptide
    c. X-rays and/or bone scan

Follow-Up Evaluation:

1. History (as above)

2. Labs
    a. Creat, Ca, P, Alk Phos q visit (every 3-6 months)
    b. 24 hour urine for Na, Ca, Creat, +/- N-telopeptide q 3-6 months (may not need if AP correlates well)
    c. +/- BMD

GENERAL COMMENTS ABOUT PREVENTING KIDNEY STONES

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Kidney stones are formed when the urine is overly concentrated particularly when there is lack of inhibitors against stone formation. We analyze twenty-four hour urine samples to observe what defects are present, so that appropriate treatment may be started. Below are listed our usual recommendations based on the results of an evaluation. Many of these treatments have been shown to reduce kidney stone recurrence in published studies.

Urine Volume (or TV)

All stone formers should increase fluid intake so that daily urine output is greater than ½ a gallon (about 2 liters) of urine per day. One study found that this reduced stone recurrence rate by about 60%. Usually, about a quart of fluid is lost by the body daily due to sweating, breathing, and going to the bathroom. So, ¾ a gallon (about 3 liters) of fluid intake is probably needed to result in enough urine volume. With increased sweating (due to warm environment, exercise or fever) or other external fluid losses (such as vomiting or diarrhea), even more fluid is needed to replace body losses. An easy way to tell that you are drinking enough fluid is by examining the color of the urine.

If the urine is dark, drink more.
If the urine is almost as clear as water, you' re doing well.

Once the fluid is absorbed into the body, the kidneys quickly filter it. So, it' s important to space out the fluid intake to avoid exposing the kidneys to high concentrations of stone-forming salts. Your goal should be to: drink 16 ounces with each of your three daily meals, 8 oz. between meals, 8 oz. at bedtime, and 4-8 oz. during the middle of the night. The late night fluid is probably the most important in avoiding kidney stones, because the morning urine is usually the most concentrated. If you are not used to having 10 glasses of fluids/day, try to get on the schedule above. First, divide your current number of glasses/day into this schedule. Until you reach your goal intake, add 4 oz. every 5-10 days at a time slot you haven' t yet filled.

If your urine volume is still not high enough on the schedule above, it is best to increase your fluid intake slowly by drinking one more ounce (1 sip) with every glass every 5-10 days until the goal urinary volume is reached. This gradual increase in fluid intake will help your body adjust so you won' t feel bloated. High fluid intake has been proven to reduce kidney stone recurrence in a controlled study, and of course, it is the cheapest treatment and doesn' t cause serious side effects.

Urinary Calcium (or Ca)

If urine calcium is high and the bone density is normal, we cautiously limit dietary calcium. At the moment, recommended dietary calcium intake is controversial, but it seems unwise to completely exclude dairy intake. High calcium intake is known to raise urine calcium. On the other hand, you may have seen news about high calcium intake protecting against stones in those who have not previously had stones. In fact, there is evidence that the higher the urinary calcium in stone-formers, the higher the risk for kidney stones. Unfortunately, the long-term effect of increasing

calcium intake alone has not yet been tested formally in stone-formers, so we do not know for sure if the higher dairy intake protects against stone formation or increases the risk.

Most of dietary calcium is in dairy products (skim products have slightly more calcium), so we limit them to one serving per day (8 oz. milk or breakfast yogurt or calcium fortified orange juice; 1 ½ thin slices of cheese; or about 12 oz. of ice cream, frozen yogurt or cottage cheese) in patients with high urinary calcium. This restriction is gradually relaxed each follow-up visit if possible base on urinary calcium. Salt, demonstrated by urinary sodium (or Na), and acid load (from animal protein), estimated by urinary sulfate or (SO_4), may increase urinary calcium and reduce the effectiveness of dietary and/or medication therapy. For these reasons, salt should be avoided and animal protein intake should be limited (goal urine values of Na < 150 meq/d; SO_4 < 25). A good website for dietary options on a low salt diet is www.saltfreelife.com. I believe it costs $5.00 to become a member.

We often test urine calcium after an overnight fast and after a 1gram oral calcium load. If the 2 hour fasting urinary calcium is increased (> 0.11mg/mg creatinine), we are suspicious of too much loss of calcium from the bone or kidney. If the 4-hour postload urinary calcium is increased (> 0.20mg/mg creatinine), we are suspicious of excessive intestinal calcium absorption. In contrast, if the 4 hour postload urinary calcium is < 0.10mg/mg creatinine, we are worried about in adequate calcium absorption. This latter finding may require follow-up by your primary care physician to make sure that there is no underlying intestinal disease.

If the urine calcium remains high, a thiazide diuretic or Indapamide have been shown to decrease the risk of further kidney stones and to protect against bone loss. Do not take any diuretic containing triamterene, which may actually cause kidney stones. It is important to avoid potassium loss usually caused by thiazides, so potassium citrate is usually added. This potassium supplement is preferred over potassium chloride because studies show that potassium citrate also prevents kidney stones. Urinary calcium should be monitored while on treatment because the drug often loses effectiveness (usually after > 2 years of treatment). If this happens, effectiveness is restored by changing medication (for example: hydrochlorothiazide to Indapamide). The bone density should be followed periodically to make sure that mild dietary calcium restriction or the predisposition to high urinary calcium does not result in loss of bone mass. Whenever urine calcium is found to be very high (> 300mg/day) or very low (< 100mg/day), it is important to be evaluated by a physician to rule out underlying disease such as primary hyperparathyroidism (high urinary calcium) or vitamin D insufficiency (low urinary calcium).

Urinary uric acid (or UA)

If urinary uric acid is very high, there is increased risk of calcium and uric acid stones. Animal protein from the diet (beef, chicken, fish, etc) is metabolized into uric acid. When we measure a high sulfate (SO_4) levels in the urine, it tells us that your animal protein intake is high. So, the first treatment option is reducing animal protein intake to about <8oz. per day. Allopurinol, which lowers uric acid production and decreases the risk of kidney stones, is added if necessary. If the urine is acidic (pH ≤ 5.5), there is additional risk of uric acid and calcium stones, so potassium citrate is added to raise pH to the 6 to 6.5 range. Potassium citrate has been shown to reduce recurrent stones in this group.

Urinary oxalate (or Ox)

If urinary oxalate is high, dietary oxalate restriction is very important. Food with high oxalate content include nuts (and peanut butter), green leafy vegetables (such as spinach), brewed tea, chocolate, and rhubarb. Vitamin C should not be taken in excess (> 500mg/day) since it can be metabolized to oxalate. It is important to have evaluation by your doctor if your urine oxalate is high because it may represent other important underlying conditions (diarrhea, primary metabolic disorder and vitamin B6 deficiency). Calcium binds oxalate in the intestine and thereby may lower urine oxalate by 10 to 20%. Calcium administration will only help if given during the meal and if urinary calcium remains well-controlled. Sometimes, vitamin B6 decreases urine oxalate very effectively.

Our basin approach is to limit 2 to 3 foods common in your diet that are the most likely cause of elevated urinary oxalate (we have a more detailed oxalate content handout). If repeat urinary oxalate is high, further dietary restriction is added and medical treatment with vitamin B6 (50 to 100mg twice daily) or calcium is considered. This treatment is done not only for those with high urinary oxalate, but also for those with high normal urinary oxalate combined with high or high normal urinary calcium.

Urinary citrate (or Cit)

Citrate is a known inhibitor of calcium stones, so low urinary citrate is a risk factor for kidney stones. The average urinary citrate is about 640mg/day. The lower limit of normal urinary citrate is 320mg/day. First line treatment is to avoid environmental causes of low citrate such as diarrhea, urinary tract infection, excessive exercise, and high intake of animal protein or salt.

Although dietary measures may raise citrate (lemonade, citrus drinks, high intake of fruits/vegetables, low intake of animal protein), additional medication will be necessary for most people. We use potassium citrate, which has been shown to reduce recurrent kidney stones. Urocit-K is the only slow-release tablet form of potassium citrate available. A wax remnant (the carrier) in the stool should be expected and is not a sign of poor absorption on the medication. There are several liquid preparations but due to their immediate release, they must be taken more frequently and they have more side effects. In subjects with chronic diarrhea, the liquid preparations are preferred due to rapid intestinal transit. Treatment with potassium citrate has been shown to reduce kidney stone recurrence. Other available medications that will raise medication include sodium citrate, potassium bicarbonate, and sodium bicarbonate. We prefer to avoid sodium-based therapies due to the hypothetical concerns that they will raise urinary calcium and reduce the citrate raising effects.

Urinary pH

If the urine is acidic (pH ≤ 5.5), there is increased risk of calcium or uric acid stones. Potassium citrate corrects this problem by raising the pH towards normal. Low urinary pH is common in those who suffer from gout. Low urinary pH is the easiest stone risk factor to treat. If the measurement of urine pH, on the other hand, is very high (> 7.0), there is increased risk of calcium phosphate stones and urinary tract infection should be ruled out.

So, our goal pH is about 6 to 6.5 to avoid either extreme. This can be accomplished by diet or medical treatment. High animal protein intake (acid load) and strenuous exercise (only during exercise) may lower urine pH while fruit and vegetable intake may raise it. Potassium citrate, which provides alkali load, is used to raise urinary pH. At the present, we do not give medication to lower pH > 7, but potassium citrate and other alkali should be avoided in this setting.

Urinary Magnesium (or Mg)

Magnesium, when given with food, is believed to inhibit stone formation by binding oxalate. Initial controlled studies with magnesium have shown benefit; however, later, controlled studies showed no benefit over placebo (sugar pill). The latter studies were not done on magnesium deficient patients, so it is still possible that magnesium supplementation would be useful in that setting to avoid kidney stones. In about 6% of our patients, the only detectable physiologic defect is urinary magnesium less than 60mg/day. In these patients, we would consider treatment with magnesium supplements such as magnesium oxide or gluconate (often 2 pills three or four times a day are needed) or milk of magnesium (2.5ml two to three times per day). The problem with magnesium supplements is that they often cause diarrhea, which would increase stone risk by at least four ways-lower urinary volume, pH and citrate and higher urinary oxalate.

Infection stones

Sometimes, kidney stones result directly from urinary tract infection. Certain bacterial organisms create very alkaline urine (pH often > 8.0) and produce ammonia, a combination that predisposes to infection stones such as struvite (magnesium ammonium phosphate) and carbonate apatite. Infection may also complicate existing calcium stones. When kidney stones are caused by recurrent urinary tract infections, surgery and antibiotics are almost always necessary. Lithostat, a medication that lowers the urine pH by inhibiting production of ammonia, has been shown to be effective additional medical therapy to help reduce recurrent stone formation in these patients. Since it has possible toxic side effects, it should be used carefully.

Other tests

Parathyroid hormone (PTH) is an important hormone that maintains our blood calcium level. Sometimes, an abnormal gland or glands make too much of this hormone and too much calcium is taken out of the bone, absorbed from the intestine and excreted into the urine. If your PTH is > 65pg/ml, you may have an overactive parathyroid gland that is causing your kidney stones.

You may have had a bone mineral density test since the bone mass if often low in stone-formers. Bone mineral densitometry is the most sensitive tool we have to estimate bone mass and predict future risk of fracture. The two types of bone (trabecular and cortical) are distributed differently at specific skeletal areas, so we measure the density in three different sites. In the lumbar spine, mostly trabecular or spongy bone is found. At this site, bone mass preferentially declines after the loss of male or female sex hormones or with glucocorticoid treatment. Arthritis in the spine and calcification of the aorta (very common in individuals older than 60 years) falsely elevates this measurement. The long bones (legs and arms) have primarily compact or cortical bone, which is primarily lost with conditions of excess parathyroid hormone. We use the distal radius of the arm as an indicator of cortical bone. The femoral neck of the hip has a mixture of both types of bone. This is an important site to measure because it is the best predictor for the most serious complication of low bone mass, hip fracture.

Osteoporosis Evaluation and Treatment

I. **Scope of Problem** – 40% of women and 13 % of men suffer osteoporotic fracture/yr; 1.5 million osteoporotic fractures/yr (700,000 vertebral, 300,000 hip) at a cost of 10-20 billion; fracture may result in death, disability and loss of independence (180,000 nursing home admissions/year)

II. **Definition** – loss of bone mass and disturbance of skeletal architecture that predisposes to fracture. Remaining bone is normally mineralized.

III. **Background**

A. **Bone Composition and Types:**

1. Composition – mineral (hydroxyapatite crystals – $Ca_{10}PO_4(OH)_2$) and protein (> 90% collagen), 70-80% of the body' s bicarbonate
2. Type of bone
   a. **Cortical** – 80% of skeleton, 20% of surface area, mechanical function, 4% turnover/year
   b. **Trabecular** – 80% of surface area, metabolic function (99% calcium, 70-80% HCO_3), 20% turnover/year

B. **Bone Remodeling Unit –** organelle composed of osteoclasts and osteoblasts responsible for remodeling the bone. Multiple units are active at any one time. An individual unit is active for a few months. Osteoclasts start the process by removing the old or damaged bone. Then, osteoblasts lay down and organize new bone.

C. **Bone acquisition pattern**- rapid bone acquisition occurs in puberty and peak bone mass is reached. Then, bone mass is stable for 2 to 3 decades. In women, rapid loss occurs with menopause lasting 3 to5 years. In both sexes, gradual loss (0.5-1%/year) occurs after age 40 or 50.

IV. **Make the diagnosis** with Bone Mineral Density (BMD)

A. **Indications**- postmenopausal (especially age > 65), osteopenia by x-ray, key risk factors (personal history of
l ow trauma fracture, family history of fracture, hyperparathyroidism, steroids), monitoring on treatment.

B. **Types** of densitometers

1. DEXA (dual energy x-ray absorptiometry)- gold standard
2. QCT (quantitative computed tomography)- less precise, better for spine in elderly
3. Ultrasound- cheaper, no radiation

C. **Interpretation**-

1. **T-score**- compared to peak bone mass; by W.H.O. criteria, normal within 1 standard deviation, osteopenia- loss of 1 to 2.5 S.D., osteoporosis- loss of >2.5 S.D. Every loss of 1 S.D. doubles the risk of fracture. This is relative risk, so the risk may still be low in young patients.

2. **Z-Score**-matched for age and sex; loss >2 S.D. suggests secondary bone loss; yet, those with secondary risk factors may certainly have Z-score loss of smaller magnitude.

3. **Artifact**- carefully match positioning, arthritic changes, scoliosis, fracture

4. **Site**- spine- trabecular (loss with hypogonadism, steroids); radius- cortical (loss with Ca deficiency or hyperparathyroidism); femoral neck- mixture of cortical and trabecular bone. This is now the preferred site to measure since it correlates best with risk of hip fracture (-1 S.D.= RR 2.6)

5. **Frequency**- Generally, follow patients every 2 or more years (acceptable to insurance companies). If new patient with low BMD or monitoring treatment, recheck in 1 year. In a very high risk patient (especially with new glucocorticoid treatment). Consider rechecking in 6 months. Increase intervals between BMD when stable.

V. Establish risk factors and rule out secondary causes of osteoporosis if density is low (pneumonic: **The Medic**) by history, physical and labs (V). Rule out osteomalacia.

A. Tumor – multiple myeloma, mastocytosis, mestastases

B. Hereditary – family hx of fracture (hip), hip geometry, race, size, osteogenesis imperfecta, homocystinuria, Marfan's disease, Ehlers Danlos, Gaucher's

C. Endocrine – menopause, male hypogonadism (mumps), timing of puberty, hyperthyroidism, hyperparathyroidism, Cushing's syndrome.

D. Medications – steroids, heparin, anticonvulsants (Phenobarbital, dilantin), aromatase inhibitors, PPIs

E. Environmental – diet (calcium, salt, protein), vitamin D (sunlight), cigarettes, alcohol

F. Diarrhea – (malabsorption)

G. Immobilization – bedrest, sedentary lifestyle

H. Chronic disease – heart, kidney, liver, rheumatic disease, infection, severe illness during childhood, prevalent fractures

VI. Work-up

A. Blood – SMA, CBC, TSH, PTH (± ESR, 25-D, SPEP)

B. Urine – Na, Ca, Cr (± UPEP, cortisol, bone turnover markers)

C. X-rays – spine (interpret density, asymptomatic fractures) and painful areas

D. Other – consider biopsy of the bone or skin, stool fat, etc., in selected cases

VII. Treatment

A. **Calcium** – 1200-1500mg/d (including diet) if > 65 years or untreated postmenopausal; otherwise 1000mg/d; protects against bone loss and fracture (particularly when given with vitamin D). Dietary calcium is mainly from dairy (300 mg per 8 oz. milk or yogurt, 1 ½ oz. cheese, 12-16 oz. cottage cheese, frozen yogurt or ice cream). Risks: constipation, bloating. Consider adding magnesium to combat constipation side effects.

B. **Vitamin D** – 600 to 800IU/day; Pharmacologic doses if UCa < 50-100mg/d. Risks – hypercalcemia.

C. **Thiazide/Lozol** – if UCa > 300 mg/d; protects against bone loss

D. **Estrogen** - ↑ density over 3 years by 5-10% at spine, 2-5% at femoral neck and 0-2% at arm. ↓ fracture 30-60%. Other benefits: improved cholesterol (↓ LDL, ↑ HDL). Other potential benefits: improvement in vasomotor function, in atrophy of the mucosa of vagina and outer 1/3 of urethra, prevention of tooth loss and wrinkling. Risks: Women's health initiative: (oral Premarin/Provera) found higher risk of heart attack, stroke, dementia, thromboembolism and breast cancer with decreased colon cancer and fracture: (Premarin) higher risk stroke and lower risk fracture. Other risks: vaginal bleeding, mastalgia, breast cancer, uterine

cancer (negated by progestins), hypertriglyceridemia, gallstones. Indication: hot flashes and prevention of osteoporosis in postmenopausal women (indication will likely be more limited soon; dose 0.3 to 0.625 mg/d conjugated; 50 to 100 mcg transdermal).

E. **Raloxifene** - ↑ density at spine and hip by 1-2% over 2 years. ↓ fracture risk at spine by 30%. Other benefits - ↓ LDL, may reduce breast cancer risk; Risks: thromboembolism. Indication: treatment/prevention at 60mg/day.

F. **Alendronate** - ↑ density over 3 years by 6-10% at spine, 3-6% at femoral neck and 0-1% at arm. ↓ fracture by 50% spine, hip and 30-50% peripherally. Other benefits – apoptosis of cancer cells?; Risks: esophagitis, hypocalcemia, accumulation in renal failure (< 35cc/min), slight increase in atypical femoral shaft fractures with long-term use. Indication – treatment 10 mg/d or 70 mg/wk; prevention 5 mg/d or 35 mg/wk.

G **Risedronate** – bisphosphonate class like alendronate. ↑ density over 3 years by 5.4% at spine, 2-3% at femoral neck and 0-1% at arm. ↓ fracture by 40-50% spine and hip and 30-40% peripherally. Risks: same as alendronate. Indication – treatment/prevention 5mg/d or 35mg/wk or 150 mg/month.

H. **Other Bisphosphonates** – ibandronate has been approved for osteoporosis in daily or monthly oral dose (similar risks and benefit but hip fracture efficacy not yet demonstrated). Intermittent intravenous therapy with zoledronic acid (Reclast) improves bone mineral density and reduces fracture risk. 5 mg IV once a year.

I. **Calcitonin** - ↑ density at the spine by 0-2%. No apparent protection at the hip or arm. ↓ risk of spine fracture by 33%. Other benefits – central analgesia, no severe risks; Risks: (nasal spray) – nasal ulcer, coryza, ± nausea. Indications – treatment 200IU puff daily (alternate nostrils).

J. **Teriparatide** (PTH 1-34) - ↑ density over 18 months by 9.7% at spine, 2.8% at femoral neck and ↓ 2.1 at radial shaft. ↓ vertebral fracture by 65% and nonvertebral fracture by 53%. Risks: osteogenic sarcoma?, orthostatic hypotension, leg cramps, hypercalcemia. Indication – treatment of " severe" osteoporosis. 20mcg/d sq (approved for 24 months in specific patients).

K. **Denosumab.** Monoclonal antibody against RANKL. Given as 60 mg SQ injection every 6 months. Powerful anti-resorptive agent with proven fracture efficacy. Reversible mechanism of action.

L. **Exercise/Hip protectors** – exercise mainly prevents bone loss. Walkin 30 minutes 3x/week is effective. Active exercise may raise bone mass up to 3%. More importantly, by improving strength and balance, exercise may prevent fall and fracture. Hip protectors may reduce hip fracture > 50% (studies are mixed). Evaluate balance and consider evaluation by physiatrist and visit by occupational therapist to reduce fracture risk.

VIII. **Six risk factors for fracture**

A. Bone Density	Double the risk for every loss of 1 S.D. from peak
B. Age	Double the risk for every 5 to 10 years over 50
C. Fracture	Synergistic with bone density
D. Tendency to Fall	Poor balance, visual perception, weakness, flexibility; drugs
E. Bone Turnover	Synergistic with bone density
F. Family hx of hip fracture	Double the risk of hip fracture

IX. Suggested Readings

A. Rubin C, Grand Rounds, UT Southwestern, June 18, 1998.

B. Hui SL, et al. Age and bone mass as predictors of fracture in a prospective study. J Clin Invest 1988; 81: 1804

C. Dawson-Hughes, B. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997; 337: 670

D. Lufkin EG, et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med 1992; 117: 1.

E. Ettinger B, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3 year randomized clinical trial. JAMA 1999; 282: 637.

F. Chesnutt CH, et al. A randomized trial of nasal spray salmon Calcitonin in postmenopausal women with established osteoporosis: The prevent recurrence of osteoporotic fractures study. Am J Med 2000; 109: 267-76.

G. Black, DM et al. Randomized trial of effect of alendronate on risk of fracture of women with existing vertebral fractures. Lancet 1996; 348: 1535.

H. Cummings SR, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fracture. JAMA 1998; 280: 2077.

I. Harris ST, et al. Effects of risedronate treatment on vertebral and non vertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. JAMA 1999; 282: 1344.

J. Kannis P, et al. Prevention of hip fracture in elderly people with use of a hip protector. N Engl J Med 2000; 343: 1506.

K. Risks and benefits of estrogen plus progestin in postmenopausal women: Principle results from the women' s health initiative randomized control trial. JAMA 2002; 288: 321

L. Neer RM, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001; 344; 1434.

Key Risks benefits of Anti-Osteoporotic Medications and Hip Protectors

Mineral Clinic

If you are started on any new medication, you should contact your physician for new persistent symptoms.

1) **Bisphosphonates: Alendronate (Fosamax)/Risedronate (Actonel)** – both protect against fracture of the hip, spine and peripheral bones. They are as effective as estrogen for bone gain. Most bone gain occurs within 3 years (usually 5-10% at the spine and 2-5% at the femoral neck). Thereafter, bone mass is stable (may gain 4% over the next 7 years). They reduce the risk of fracture at the spine by 50%. They likely reduce fracture at the hip and arms by 30-50%. Both drugs are approved for the prevention and treatment of postmenopausal osteoporosis. They are also approved for treatment of steroid induced osteoporosis (risedronate for prevention also). Alendronate is approved for osteoporosis in men. Key side effects include heartburn, pain in the chest or abdomen, trouble swallowing, and bone pain. Both of them may be given daily or once/week. Your must take medication as noted on our bisphosphonate handout. A new drug, Ibandronate (Boniva), is given by mouth only once/month. It has similar effect on bone gain and has been shown to prevent fracture at the spine.

2) **Other Bisphosphonates:** Occasionally, patients are unable to tolerate any oral medication, and Calcitonin is not effective for them. Intravenous bisphosphonates such as pamidronate (Aredia) or zoledronic acid (Zometa) may be useful. They have been shown to raise bone mass and have similar action to alendronate and risenodrate. However, antifracture efficacy is, as yet, untested or weakly reported.

3) **Estrogen** – Raises bone density at the hip and spine similar to the above drugs. Decreases fracture at the spine and hip in women with osteopenia or osteoporosis. It is approved for the prevention of osteoporosis. Key side effects include vaginal bleeding, breast pain. The most worrisome risk factors when estrogen is given progesterone are breast cancer, ovarian cancer, increased risk of cardiovascular disease (nonfatal heart attack, blood clots and strokes) and dementia, but it decreased colon cancer risk. The global relative risk (critical bad – minus good outcomes) is about 0.2%/year. The key risk noted when estrogen was given without progesterone was increased risk on nonfatal stroke (3/1000per year). Despite these risks, treatment with estrogen +/- progesterone did not demonstrate increased death. Potential benefits of estrogen treatment include decreased hot flashes, correction of withering of the vagina and outer urethra (tube to empty urine from bladder; source of discomfort during urination in the absence of estrogen), decreased wrinkling, decreased tooth loss, decreased LDL cholesterol, increased HDL and decreased colon cancer (this last effect was noted when progesterone was also given). Estrogen is continued lifelong if started because bone is rapidly lost when it is stopped. Given recent studies, it is now unclear which patients are more likely to benefit from estrogen but two long-term studies are ongoing.

4) **Raloxifene (Evista)** – Protects against fracture at the spine in patients with osteopenia or osteoporosis. Prevents bone loss, but it does not raise bone mass (2-3% at spine; 1-2% at hip) as much as estrogen or the above group. It is approved for prevention and treatment of osteoporosis in women. It decreases risk of fracture by 30-40%. It does not stimulate the breast or uterus. In fact, it may reduce breast cancer risk by 40-80%. Key risk is doubling or tripling of the risk of clotting (same as estrogen); however, this side effect is fairly uncommon. Some women complain of increased hot flashes.

5) **Nasal Calcitonin (Miacalcin/Calcimar)** – Protects against fracture of the spine. Has the least effect of all approved agents on bone density. Approved for the treatment of osteoporosis in women. Key benefits are: no severe side effects (mainly runny nose, or transient nasal ulcer) and it may decrease bone pain.

6) **Teriparatide (Forteo)** – Synthetic analogue of parathyroid hormone that is given by daily injection. Protects against fracture at the spine (65% fewer fractures) and other areas (>50% fewer fractures). Increases bone mass except at the arm (At 18 months; 9.7% at spine, 2.8% at hip and ↓ 2.1% at arm). Approved for up to 2 years of treatment of " severe" osteoporosis. Main symptoms are local reaction to injections, dizziness upon standing, leg cramps and high blood calcium. Although it has been shown to cause bone cancer in animals when given lifelong at very high dose, this complication has never been seen in humans.

7) **Testosterone** – If blood testosterone concentrations are low in a man, further testing is needed to determine whether the cause is from inadequate production by the testes or by inadequate guidance by the master gland within the skull (sometimes due to absence of guiding hormones or due to a noncancerous tumor). In men with low blood testosterone concentrations, the male hormone, replacement therapy is known to increase the bone mass by > 5% even if they are treated with glucocorticoids such as prednisone. Although this increase in bone mass is believed to prevent fracture, no study has yet tried to prove that testosterone treatment decreases fractures. Testosterone may be given by injection every 2 to 3 weeks, by daily tablet applied to the inside lining of the mouth, by daily transdermal patch or by gel rubbed into the skin daily. Some patients prefer to use injection due to the infrequent dosing, but blood levels are not as well maintained (both too high and too low). The other three formulations make it easier for your physician to keep the blood testosterone concentrations in the normal range. Testosterone increases prostate growth – especially if the dose is too high. In men whose prostates are already large, further growth may cause symptoms such as difficulty starting urination, decreased force of urinary stream, or worsened dribbling. If prostate cancer is present, testosterone will increase the rate of its growth. Other side effects include swelling of the breasts, acne, worsening of sleep apnea or high red blood cell count. Skin irritation or rash may occur with the patch or gel (more with the patch). If the gel is chosen, there is a theoretical risk that the hormone may be transferred to a sexual partner. However, one study found this does not happen. Testosterone is available as a pill to swallow, but this should generally be avoided since it may cause liver disease or even liver cancer. At this time, we do not recommend the use of testosterone in women or in men with normal testosterone levels because the effect on the bone mass is small to absent despite risks. In women, the risks includes permanent enlargement of the clitoris, deepening of the voice and baldness.

8) **Calcium/Vitamin D** – The main role of treatment with calcium and vitamin D is to prevent further bone loss, but it also modestly improves gain in bone mass when given with other agents. Since 99% of the body' s calcium is in the bone, calcium is taken out of the bone when dietary intake is inadequate or when calcium is poorly absorbed. The average person needs 1000mg/day, but postmenopausal women and elderly men > age 65 years need more (1200 to 1500mg/day) and some patients need even more. The main dietary source of calcium is dairy (8oz. of mile or yogurt – 300mg calcium; 1oz. cheese – 200mg; 12-18oz. ice cream or frozen yogurt 300mg). Calcium fortified products (orange juice, apple juice, fruit juice, rice) providing 300-450mg/serving are also available. Vitamin D improves intestinal absorption of calcium. It is mainly made after exposure to ultraviolet sunlight and it is present in the diet (fatty

salmon, cod liver oil; 100 units/8oz. of vitamin D milk). The average person needs 600-800 units/day, but some need MUCH more. Vitamin D insufficiency is present in 25% of the United States and worldwide. Key risk factors for inadequate vitamin D include poor skin production (elderly, darker skin, poor sun exposure) and diarrhea (loss of vitamin D into the stool). Most patients are given supplements because their dietary intake of calcium and vitamin D is inadequate to meet their needs. Side effects of calcium treatment include constipation, bloating, and abdominal cramps. Often, additional treatment with magnesium (sometimes present within the same supplement) may prevent the constipation. Rarely, too much treatment with calcium and vitamin D will result in high blood calcium accompanied by symptoms such as fatigue, loss of appetite, nausea, vomiting, or joint pain. It is important to monitor the blood calcium periodically for this reason.

9)**Thiazides/Lozol** – We use these drugs in patients who have high urinary calcium. These diuretics lower urinary calcium and protect both against bone loss and kidney stones. They generally increase bone density slightly (1-2%). There is some data to suggest that they lower fracture risk, but no controlled trial has proven that yet. The drugs are usually well-tolerated but side effects include dizziness, impotence, rash, metabolic changes (high blood calcium, glucose, lipids or uric acid; low blood sodium or potassium).

10) **Combination Therapy** – Studies have shown that the addition of alendronate or risedronate to estrogen or raloxifene raises the bone mass a little more (1-2%) than either one alone. The combination of teriparatide with alendronate increased bone mass less than teriparatide alone but more than alendronate alone. No study has yet demonstrated that combination treatment reduces fractures greater than either drug alone. Due to the increased risk with more drugs without known additional benefit, we generally do not use combination therapy (exception: most patients should take calcium and vitamin with all regimens, some should additionally be given a diuretic as noted above).

11) **Hip Protectors** – May protect against hip fracture by reducing the impact of a fall and spreading the force of impact. One available brand is Safehip (Toll Free 1-877-728-3447; Website: www.safehip.com). Another is the KPH Hip Protector (Phone: ?). There are other websites that have both hip protectors (www.hipprotectors.com) which have been shown to be effective in published studies.

Osteomalacia – When Low Bone Density Does Not Mean Osteoporosis

Center for Mineral Metabolism and Clinical Research

UT Southwestern

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I. Background

A. Bone Composition – Protein (mainly collagen Type I) and mineral (mainly calcium phosphate in the form of hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$

B. Calcium Metabolism

1. PTH – raises serum calcium directly by increasing bone resorption and renal tubular calcium reabsorption and indirectly by stimulating 1,25-D production and, in turn, intestinal calcium absorption. Stimulated by hypocalcemia and hyperphosphatemia; suppressed by hypercalcemia, 1,25-D.

2. Vitamin D –

Pathway of 1,25-D Synthesis

7-dehydrocholesterol → ultraviolet B (290 to 315nm) →→ vitamin D_3 (in the skin) ← (from diet)

↓

Transported in blood bound by vitamin D binding protein (VDBP) to the liver

↓

25-D (hydroxylation by 25-hydroxylase)

↓

Transported in blood bound by vitamin D binding protein (VDBP) and filtered by the kidney

↓

Reabsorbed in the proximal tubule of megalin/cubulin complex

↓

Catabolized ← 1,25-D (hydroxylation by 1-α-hydroxylase)

a. Vitamin D_2 (from plant and yeast soruces; used in the same pathways as D_3), D_3 (mainly from animal sources – fatty fish and cod liver oil, vitamin D fortified milk)- very difficult to directly measure due to rapid fluctuations.

b. 25-D- best test to rule out vitamin D insufficiency (almost all vitamin D is converted to 25-D, long serum half life). 25-D production is not tightly regulated.

c. 1,25-D- most active metabolite of vitamin D. Acts on the vitamin D receptor to directly increase intestinal calcium absorption. 1,25-D may also increase osteoclastogenic bone resorption. Tightly regulated. Stimulated by ↓ SP and PTH; inhibited by ↑ P, ↓ PTH and ↑ 1,25-D.

II. Definitions-

A. **Osteomalacia** – defect in bone mineralization of the bone matrix that occurs after the closure of the growth plate. The quantity of bone matrix or osteoid (protein) is normal or even increased. There is no bone deformity

(if fracture has not occurred). Consider Paget's disease of the bone in adults with new bowing of a long bone.

B. **Rickets** – (not discussed further in this lecture) – Defect in bone mineralization of the bone matrix (protein) that occurs before the closure of the growth plate. Deformities which are common, include rachitic rosary (prominence of the costochondral junction), Harrison's groove (indentation at edge of lower ribs), kyphosis, lordosis, limb bowing, swelling of the wrists and ankles, frontal bossing, enamel defects.

Etiology of Osteomalacia

Cause	Details
A. ↓ Vitamin D Effect	Plain D- lack of sunlight, poor dietary intake (need 600-800 IU/day) 25-D- diarrhea, nephritic syndrome 1,25-D- enzyme defect (VDDR I – vitamin D dependent rickets type I), resistance (VDR mutation – VDDRII), most renal phosphate wasting disorders.
B. Hypophosphatemia	Renal Phosphate wasting- XLHP (x-linked hypophosphatemic rickets), TIO (tumor-induced osteomalacia, oncogenic osteomalacia) ADHR (autosomal dominant hypophosphatemic rickets), HHRH (hereditary hypophosphatemic rickets with hypercalciuria) RTA – type II and probably type I Poor GI intake- Almost always requires concomitant phosphate binder.
C. Enzyme Defect	Hypophosphatasia (inactivating mutation in alkaline phosphatase)
D. Drug	Blocking mineralization front – aluminum, Etidronate Enhanced vitamin D catabolism – Dilantin, Phenobarbital, Rifampin Induced RTA – cadmium, lead and mercury Excessive bone formation – toxic doses of fluoride
E. Matrix	Fibrogenesis imperfectum ossium – like Paget's clinically, distinctive bone histomorphometry (abnormal collagen which lacks birefringence with polarized light), poor response to antiresorptives.

III. Clinical Presentation

Osteomalacia presents primarily with progressive diffuse bone and muscle pain. Patients may develop muscular weakness particularly proximally. The first manifestation of weakness is difficulty climbing stairs or standing from a sitting position, but later, patients may develop difficulty combing their hair or ultimately even feeding themselves. They may develop fractures with increased localized pain (most commonly in the ribs, pelvis, hips, and metatarsals). Since osteomalacia is uncommon, patients are often symptomatic > 2 years prior to diagnosis. They may be referred to a Rheumatologist to rule out connective tissue disease, to an Oncologist to rule out malignancy or to an Orthopedist to treat fractures.

IV. Diagnosis

A. **Bloodwork** – In > 90% of cases, serum calcium or phosphate is low, alkaline phosphatase is high and/or serum PTH is high. As noted above, 25-D is often low. 1,25-D is low in VDDRI, certain phosphate wasting disorders and with severe vitamin D deficiency. Non-anion gap metabolic acidosis is present if the underlying cause is renal tubular acidosis.

B. **Urine** – 24hr urine calcium is often low. If hypophosphatemia is due to poor intake and or binders, urine phosphate is also low. If hypophosphatemia is due to phosphate wasting, urine phosphate is inappropriately elevated.

C. **X-rays** – Pseudofractures (or Looser' s zones), which are diagnostic of osteomalacia, are focal accumulations of unmineralized osteoid found in cortical bone perpendicular to the long axis. They are generally bilateral and symmetrical. Common locations include the pelvis, medial aspect of the femur and lateral aspect of the scapulae. Other findings common in osteomalacia include osteopenia (reduction of mineralized bone), trabeculae that are coarsened and indistinct, biconcave vertebral bodies, rib and metatarsal fractures.

D. **Bone Mineral Density** – This is poorly studied in osteomalacia. Anecdotally, bone mineral density tends to be low except in x-linked hypophosphatemic rickets, in which it may be above average. Since bone mineral density primarily represents mineral, bone density increases tremendously and rapidly with effective treatment. For example, calcium and vitamin D treatment increase the bone density minimally, if at all, in osteoporosis; in osteomalacia, density may increase 30% in one year with only calcium and vitamin D.

E. **Histomorphometric analysis** of iliac wing bone biopsies – Bone biopsy with tetracycline staining is the only way to absolutely diagnose osteomalacia. Diagnostic criteria are widened unmineralized osteoid seams and prolonged mineralization lag time.

F. **Effect of treatment** – supportive evidence of osteomalacia includes resolution of characteristic symptoms and normalization of lab findings with calcium, vitamin D and/or phosphate treatment.

G. **Summary Diagnosis Table:**

Disorder	SCa	SP	AP	PTH	1,25-D
Vit. D, 25-D	↓	↓	↑	↑	N, ↑ , or ↓
VDDR I	↓	↓	↑	↑	↓
VDDR II	↓	↓	↑	↑	↑ ↑
Most Renal P wasting	N	↓	↑	N or ↑	↓
HHRH	N	↓	↑	N	↑
Hypophosphatasia	N or ↑	N or ↑	↓	N	N

V. **Treatment** – Therapy is based on the underlying findings. Diminished vitamin D effect is treated with calcium and vitamin D (or a potent metabolite). Hypophosphatemic disorders are usually treated with phosphate and 1,25-D. Causative drugs are discontinued.

A. **Calcium** – Since calcium absorption plateaus at about 500mg, it is best to treat with small frequent doses (up to 500mg q 3h if necessary). Calcium should be given separate from food in a hypophosphatemic patient (vitamin D deficiency for example) because it will bind phosphate. In general, calcium citrate is better absorbed than calcium carbonate and calcium carbonate.

B. **Vitamin D** – For deficiency of vitamin D, high doses of vitamin D are needed initially (such as 50,000 units of Ergocalciferol or vitamin D_2 daily). Due to high fat solubility, plain vitamin D treatment requires weeks to reach steady state; with toxicity, weeks to months are required to deplete the stored vitamin as well. More expensive alternatives include 25OHD (20mcg/wk to 40mcg/d) and 1,25-D (0.5 to 1.5mcg/d – higher for VDDRII). 1,25-D directly suppresses PTH production. This property is utilized to prevent secondary hyperparathyroidism requiring phosphate treatment. The $T_{1/2}$ of 25OHD is about 3 weeks and that of 1,25-D is days.

C. **Phosphate** – Treatment usually requires 1 to 3 grams/day in divided doses (usually three to five times daily). Phosphate must be given separate from calcium and dairy to avoid binding. Common side effects of phosphate treatment include bloating, abdominal cramping and diarrhea.

D. **Follow-up** – Symptoms improve over weeks, but generally take months to completely resolve. Serum alkaline phosphatase, a marker of bone formation, initially increases with treatment. As osteomalacia resolves, serum alkaline phosphatase and other abnormalities (serum calcium, phosphate, PTH), correct to normal. Serum calcium should be monitored for hypocalcemia (undertreatment) or hypercalcemia (overtreatment). 24hr urinary calcium is very useful to document adequate calcium and vitamin D treatment (100 to 200mg/day). High urinary calcium (>200mg/d) is an early signal to decrease vitamin D and/or calcium intake.

VI. Comparison of Osteomalacia to Osteoporosis

Category	Osteomalacia	Osteoporosis
Prevalence	Uncommon	Common
Distribution	Men = Women	Women > Men
Symptoms	Severe pain and weakness	Asymptomatic prior to fracture
Fractures	Hips and in unusual locations – ribs, scapula, pelvis and metatarsals. Also, pseudofractures	Fractures tend to occur at the lower spine, hip, proximal humerus and distal radius
Blood and Urine Tests	Multiple lab abnormalities - ↓ serum Ca, P and urine calcium; ↑ serum alkaline phosphatase and PTH	Labs are usually normal
Bone Density	Low, normal or high. Treatment may result in huge increase (> 20%)	Low density. Improvement is generally < 10% with effective therapy

VII. Summary

Osteomalacia is an uncommon disorder characterized by progressive musculoskeletal pain and weakness, lab abnormalities (low serum calcium and/or phosphate, elevated serum alkaline phosphatase, and/or elevated serum PTH), pseudofractures and fractures in unusual locations. It is important to differentiate osteomalacia from osteoporosis because potent antiresorptive agents may potentially lead to tetany.

Suggested Readings:

1. Francis RM, Selby PL. Osteomalacia. Baillier' s Clin Endocrinol Metab 1997; 11 (1): 145-63.

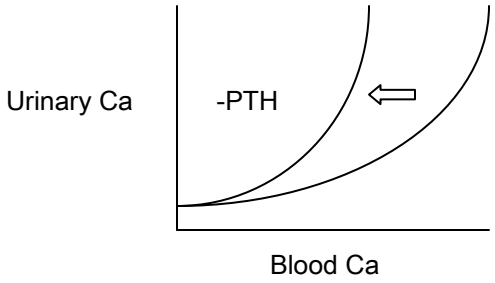
2. Primer on the metabolic bone diseases and disorders of mineral metabolism. MJ Favus, ed. 4th edition. (excellent concise book, available in library).
3. Nykjaer A, et al. Cubilin dysfunction causes abnormal metabolism of the steroid hormone 25(OH) vitamin D (3). Proc Natl Acad Sci USA 2001: 98: 13895
4. Bowe AE, et al. FGF-23 inhibits renal tubular phosphate transport and is a PHEX substrate. Biochem Biophys Res Commun 2001; 284 (4): 977-81.

Ca, MG, P interactions –

Ca

High serum Ca: Suppresses PTH and, in turn, 1,25-D; Low serum Ca: opposite.

Goal serum calcium in hypoparathyroid patients is lower (about 8.0-8.5 mg/dl) due to risk of stones. Remember, PTH improves renal calcium reabsorption, so lack of the hormone shifts the curve below to the left.



Ionized calcium is more sensitive than total calcium.

Oral dose: binds phosphate (so give apart from food if low serum P). Best to give small doses (max 500 mg) frequently.

IV: reduces renal reabsorption of Ca and Mg, but increases that of P (by suppressing PTH)

Avoid giving IV if serum P is high (risk of precipitation including lungs; may cause renal failure and ARDS!)

Indications include hypocalcemic symptoms particularly if < 7.0 mg/ml.

P

K deficiency may cause P wasting.

High Serum P: Stimulates PTH, suppresses 1,25 D; Low Serum P: opposite

Oral dose: binds calcium. Best way to give phosphate is in divided doses. Usually better tolerated if given with food.

IV: Avoid giving IV especially if serum Ca is high (risk of precipitation as noted above)

Consider IV for P < 1.0 mg/dl.

Causes of hypophosphatemia:

1. Poor intake: especially with aluminum binding
2. Increased renal P excretion: hyperparathyroidism, Fanconi' s hypophosphatemic rickets, oncogenic osteomalacia

Causes of hyperphosphatemia:

1. High intake: especially IV or rectal
2. Decreased renal P excretion: renal failure, hypoparathyroidism and PTH resistance, Acromegaly, etidronate, tumoral calcinosis
3. Shift: Rhabdo, tumor lysis, hemolytic anemia, leukemia, acidosis, fulminant hepatitis, hyperthermia

Mg

Mg deficiency causes PTH resistance and then decreased secretion. Also, renal K wasting
P deficiency may cause Mg wasting.
High Mg occurs with renal failure and familial hypocalciuric hypercalcemia (FHH)
High serum Mg may also cause PTH resistance

Oral dose: binds phosphate (so give apart from food if low serum P). Best to give small doses frequently. Very difficult in patients with baseline diarrhea.
IV: reduces renal reabsorption of Ca and Mg. Best to give slowly (example 2 grams over 8 hours). Push the dose for repletion because levels will fall within hours of stopping the infusion (intracellular movement and urinary excretion).

Causes of Mg deficiency:
1. GI: Diarrhea > emesis
2. Renal Loss: DM, hypercalcemia, low PTH, drugs (diuretics, aminoglycosides, alcohol, Cisplatin, Cyclosporin, Amphotericin)
3. Other: Hungry bone, hyperaldo, low serum P