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INTERNAL MEDICINE BOARD REVIEW COURSE
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PARATHYROID, CALCIUM METABOLISM, AND OSTEOPOROSIS

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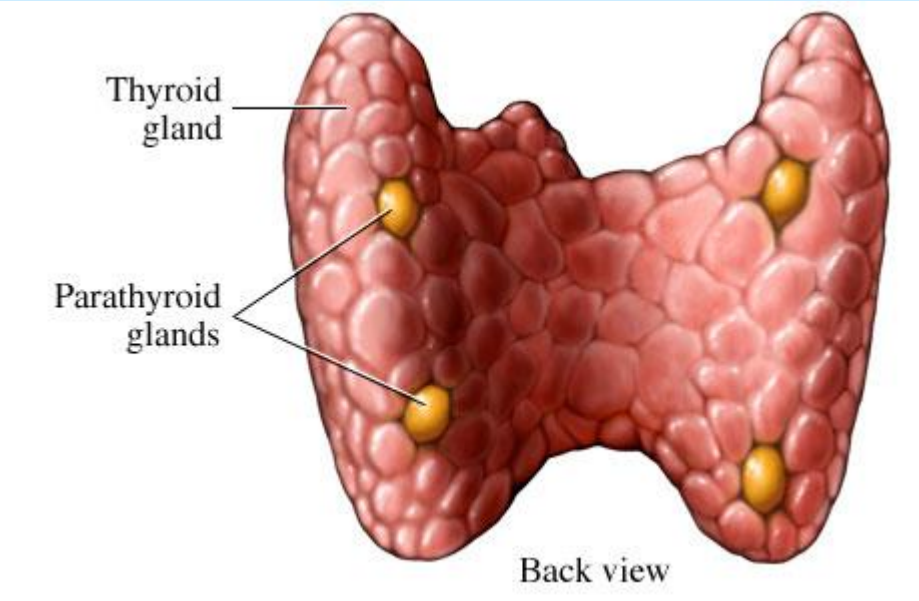
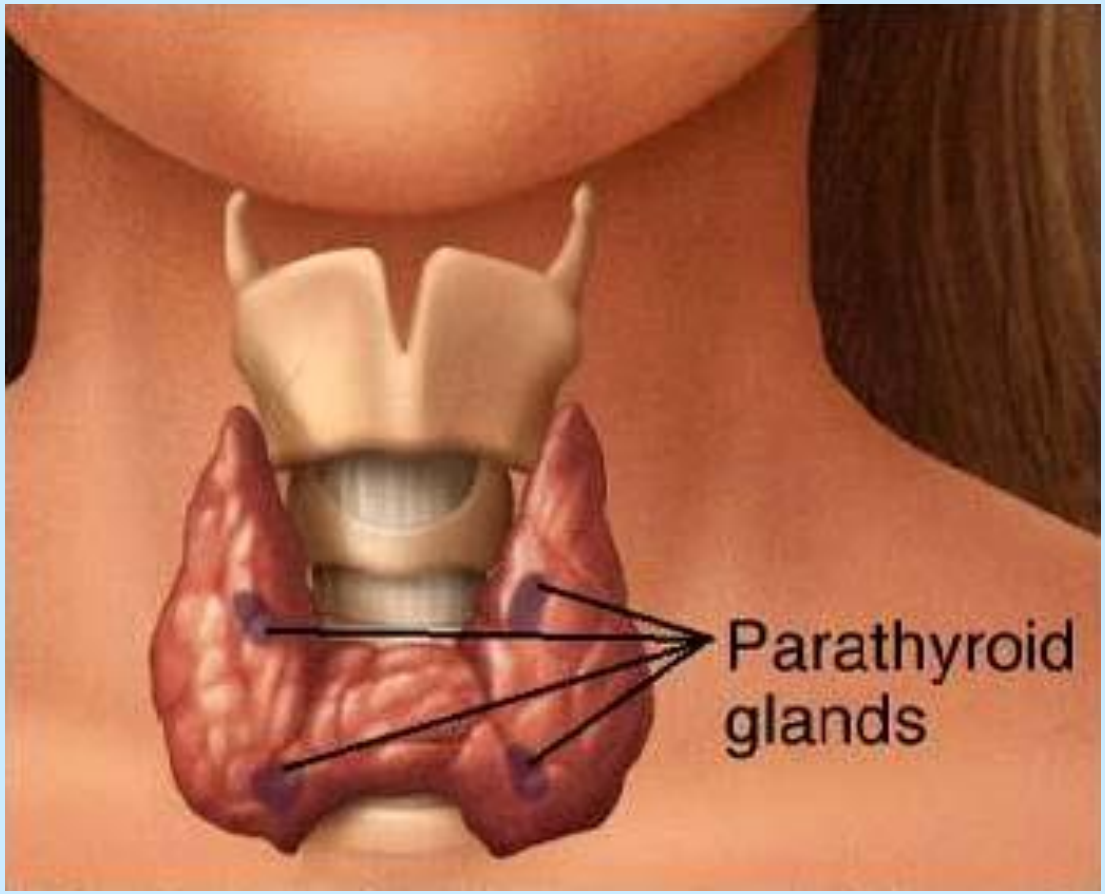
DISCLOSURES

- Speaker bureau for:
  - BI-Lilly
  - Janssen

PARATHYROID GLANDS



PARATHYROID GLANDS



PARATHYROID GLANDS

- Generally 4 glands.
- Generally in or near the thyroid.
- Can have other locations such as anywhere in the neck or mediastinal area.

PARATHYROID AND CALCIUM METABOLISM

-Parathyroid hormone
strictly regulates serum ionized calcium via:

1. GI absorption
2. Bone turnover (osteoclasts)
3. Renal excretion
4. 25-vitamin D to 1,25-dihydroxyvitamin D (calcitriol) conversion

PARATHYROID AND CALCIUM METABOLISM

-Vitamin D:

1. Formed in the skin (sunlight)
2. Converted to 25-hydroxyvitamin D in the liver
3. Converted to 1,25-dihydroxyvitamin D (calcitriol) in the kidneys
4. Regulates the absorption of calcium from the diet

-Calcium is mostly bound to albumin

“Inactive” form of Vitamin D (25-hydroxyvitamin D)

- D2: Ergocalciferol.

  Synthesized by plants

- D3: Cholecalciferol.

  Synthesized in the skin when exposed to ultraviolet B rays from sunlight

Foods might be fortified with D2 or D3.

D3 might be a better form for supplementation.

PRIMARY HYPERPARATHYROIDISM

Primary hyperparathyroidism is common. Slowly increasing calcium level. Generally benign, solitary adenoma. Could be more than one adenoma. Hyperplasia is less common (and might be associated with MEN). Also consider MEN in a younger individual.

PRIMARY HYPERPARATHYROIDISM

- Parathyroid malignancy is uncommon and often associated with a higher and fairly rapidly rising calcium level.

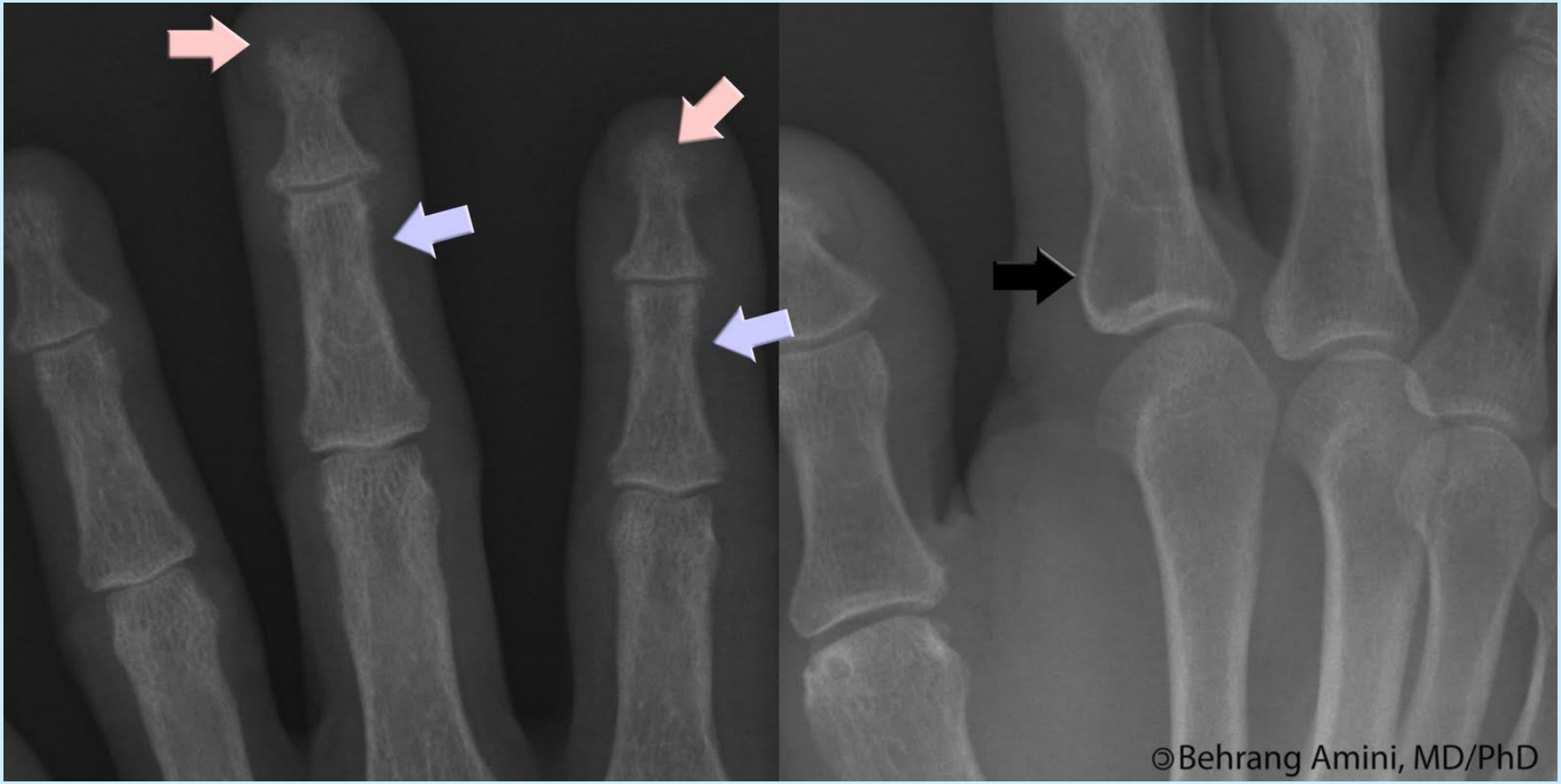
- Ectopic PTH production is rare and generally has a very high calcium level.

PRIMARY HYPERPARATHYROIDISM

-Primary Hyperparathyroidism
"Bones, Groans, Psychic Moans"
Renal calculi, abdominal pain, osteoporotic fractures. Sub-periosteal resorption (distal clavicle and phalanges).

Findings of severe hypercalcemia might include: anorexia, nausea, polyuria, peptic ulcer disease, weakness, shortened Q-T interval.

Sub-periosteal Resorption (left x-ray); Brown tumor (black arrow)



Brown Tumors of bone

- Brown tumors consist of fibrous tissue, woven bone and supporting vasculature, but no matrix. The osteoclasts consume the trabecular bone that osteoblasts lay down and this front of reparative bone deposition followed by additional resorption can expand beyond the usual shape of the bone, involving the periosteum thus causing bone pain. The characteristic brown coloration results from hemosiderin deposition into the osteolytic cysts. Hemosiderin deposition is not a distinctive feature of brown tumors; it may also be seen in giant cell tumors of the bone.
- Brown tumors may be rarely associated with ectopic parathyroid adenomas.
- They are not really tumors.

DIAGNOSIS OF PRIMARY HYPERPARATHYROIDISM

Elevated intact Parathyroid hormone and elevated or high normal calcium. (Ionized calcium better test if done reliably by your lab.)

Elevated calcium with inappropriately normal PTH level.

Elevated or top normal 24 hour urine calcium (with all 24 hour urine samples, include urine creatinine and volume).

PRIMARY HYPERPARTHYROIDISM

- RADIOLOGIC TESTING (generally only obtained if surgery is being considered)

-Sestamibi parathyroid scan: might miss a parathyroid adenoma (false negative rate) 25% of the time; might miss hyperplasia and malignant gland

-Neck ultrasound

PRIMARY HYPERPARATHYROIDISM

- Generally due to a solitary benign parathyroid adenoma.
- Not uncommon is more than one benign adenoma.
- Less common is parathyroid hyperplasia.
- Uncommon is parathyroid cancer.
- Very rare is ectopic PTH production.

PRIMARY HYPERPARATHYROIDISM

- 25-hydroxyvitamin D level is usually low due to increased conversion by PTH of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D.

- It is important to replace the vitamin D with 600-1,000 IU vitamin D3 daily since the PTH might be higher due to a secondary mechanism of vitamin D deficiency stimulating PTH.

PRIMARY HYPERPARATHYROIDISM

-Tx: Observation, Sensipar (cinacalcet), or surgical neck exploration.

-If surgery done:

Watch for post-operative hypocalcemia ("hungry bones"). Intra-operative PTH level should reduce by 50% to indicate operative cure. Surgery should only be done at an institution that has intra-op PTH testing available, and by a surgeon who has good experience with parathyroid surgery.

-Treat bone loss

Sensipar (cinacalcet)

- Can be used for medical management of a patient with primary hyperparathyroidism who is not a candidate for surgery or who refuses surgery.
- 30 mg daily titrated up as needed.
- Might be better at lowering the calcium than at actually reducing the PTH level.

INDICATIONS FOR SURGICAL TREATMENT OF PRIMARY HYPERPARATHYROIDISM

- Serum calcium >1.0 mg/dl above normal
- Creatinine Clearance (calculated) reduced to <60 ml/min/1.73 m^2
- Bone mineral density: T-score worse than -2.5 standard deviations at spine, hip (total or femoral neck), or radius (distal 1/3 site predominantly cortical bone) or presence of fragility fracture
- Patient younger than 50 years old
- Calcium nephrolithiasis

OTHER POSSIBLE REASONS TO CONSIDER SURGERY

- Non-compliant patient
- Bone aches that might be related to primary hyperparathyroidism
- 24 hour urine calcium excretion >400 mg/day

FHH

-Mild hypercalcemia with normal or slightly high PTH:

differentiate primary hyperparathyroidism from Familial Hypocalciuric Hypercalcemia (FHH): no treatment necessary for FHH.

24 hour urine calcium is needed for this (include urine creatinine and volume).Will have low calcium excretion.

SECONDARY HYPERPARATHYROIDISM

-Causes of Secondary Hyperparathyroidism

1. Low calcium
2. Low phosphorus
3. Chronic renal failure (renal osteodystrophy with osteitis fibrosa cystica).
4. Vitamin D deficiency which can cause Osteomalacia (adults)/Rickets (children)

HYPERCALCEMIA with low PTH

-CAUSES OF HYPERCALCEMIA WITH LOW PTH:

Vitamin D excess;
Malignancy (metastatic to bone or PTH-related peptide production);
Granulomatous disease (increased formation of 1,25-dihydroxyvitamin D); TB, Sarcoid, histoplasmosis, etc.
Thyrotoxicosis;
Immobilization;
Adrenal insufficiency;
Thiazides;
Milk-Alkali Syndrome;

HYPERCALCEMIC EMERGENCIES

-Hypercalcemic Emergencies treatment:

1. Saline diuresis, loop diuretic
2. Zoledronic acid (Zometa) 4 mg IV can keep the calcium down for up to 6 weeks. Dose should be adjusted for renal status
3. Pamidronate
4. Glucocorticoids
5. Calcitonin

HYPOCALCEMIA

-Causes of Hypocalcemia

With low PTH level: Hypoparathyroidism (surgical, idiopathic, autoimmune). A few case reports of hypopara being caused by hypomagnesemia due to proton pump inhibitor.

With high PTH level: adrenal insufficiency, calcium or vitamin D deficiency (nutritional); Celiac disease, gastric bypass surgery; renal failure; total lack of sun exposure.

MEN

- Multiple Endocrine Neoplasia

  Type 1 (Wermer): Parathyroid hyperplasia, Pancreatic tumor, Pituitary adenoma

  Type 2A (Sipple): Medullary thyroid cancer, Pheochromocytoma, parathyroid hyperplasia

OSTEOPOROSIS

DXA: Osteopenia : T-score worse than –1, up to –2.5.

Osteoporosis: T-score –2.5 or worse.

Use Z-score in young adults under 50 years old and children.

FRAX (Fracture Risk Assessment Algorithm)

10 year probability of major osteoporotic fracture and hip fracture.

OSTEOPOROSIS

- Can be present and diagnosed regardless of bone density measurement if an individual has one or more fragility fractures

T- and Z-scores

- T-score: The standard deviation from the mean bone loss of young adult (25-35 years old).

  Used for interpretation if 50 years old or older.

- Z-score: The standard deviation from the mean bone density of age matched controls.

  Used for interpretation if under 50 years old.

FRAX (WHO Fracture Risk Assessment Tool)

- FRAX (fracture risk):

  meant to be used with patients not on anti-resorptive or anabolic treatment.

Considered to be high risk if:

a. >20% ten year risk of major osteoporotic fracture

b. >3% ten year risk of hip fracture

FRAX

- FRAX developed to try to prevent over-treatment of younger persons and under-treatment of older persons.

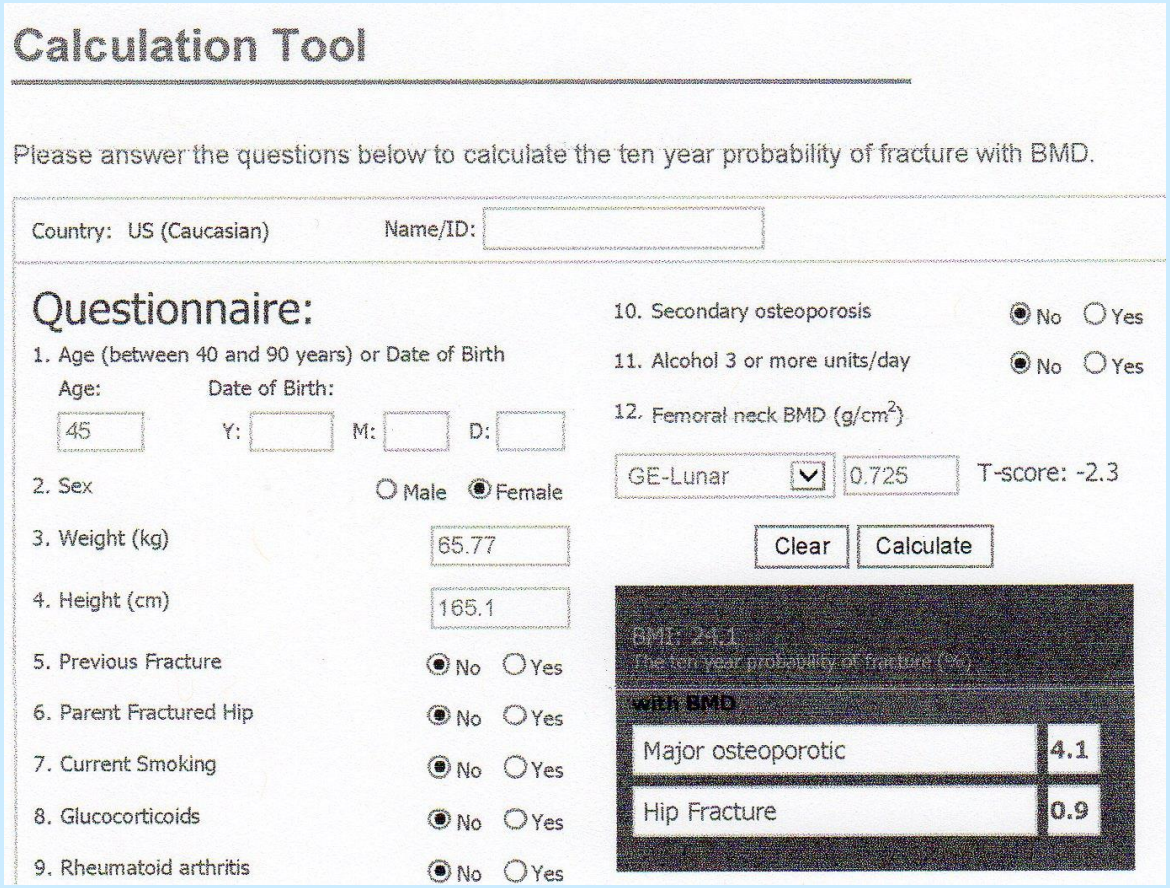
- Treat based on FRAX (fracture risk) and clinical history and Bone Mineral Density (BMD) measurement, not just based on BMD.

FRAX

- FRAX can be calculated by going online to ***www.shef.ac.uk/FRAX***

  or just search for FRAX from the Sheffield, England site

FRAX 45 year old Caucasian female with no risk factors



Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian) Name/ID:

Questionnaire:

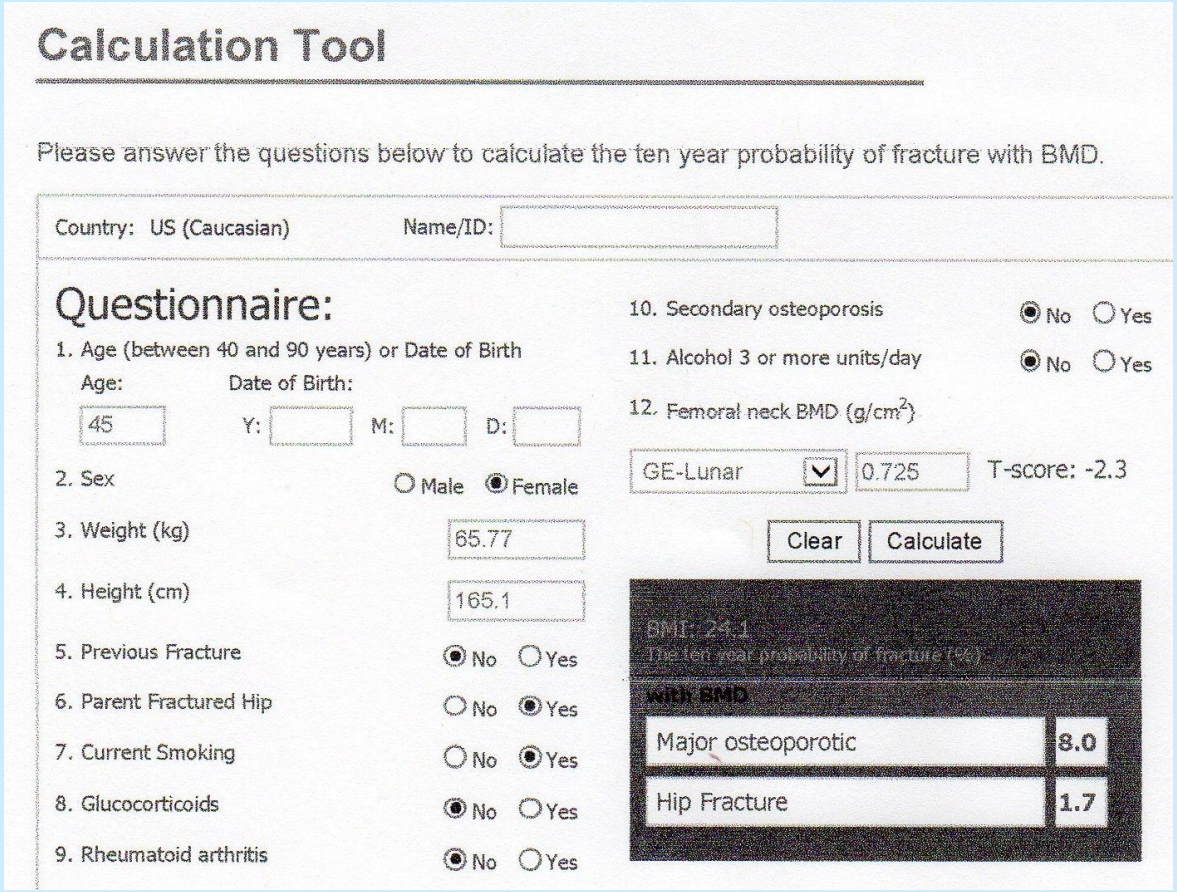
1. Age (between 40 and 90 years) or Date of Birth
   Age: 45 Date of Birth: Y: M: D:
2. Sex — Male / Female
3. Weight (kg) — 65.77
4. Height (cm) — 165.1
5. Previous Fracture — No / Yes
6. Parent Fractured Hip — No / Yes
7. Current Smoking — No / Yes
8. Glucocorticoids — No / Yes
9. Rheumatoid arthritis — No / Yes
10. Secondary osteoporosis — No / Yes
11. Alcohol 3 or more units/day — No / Yes
12. Femoral neck BMD (g/cm^2)
    GE-Lunar 0.725 T-score: -2.3

Clear Calculate

BMI: 24.1
The ten year probability of fracture (%)
with BMD

Major osteoporotic	4.1
Hip Fracture	0.9

FRAX 45 year old Caucasian female with risk factors



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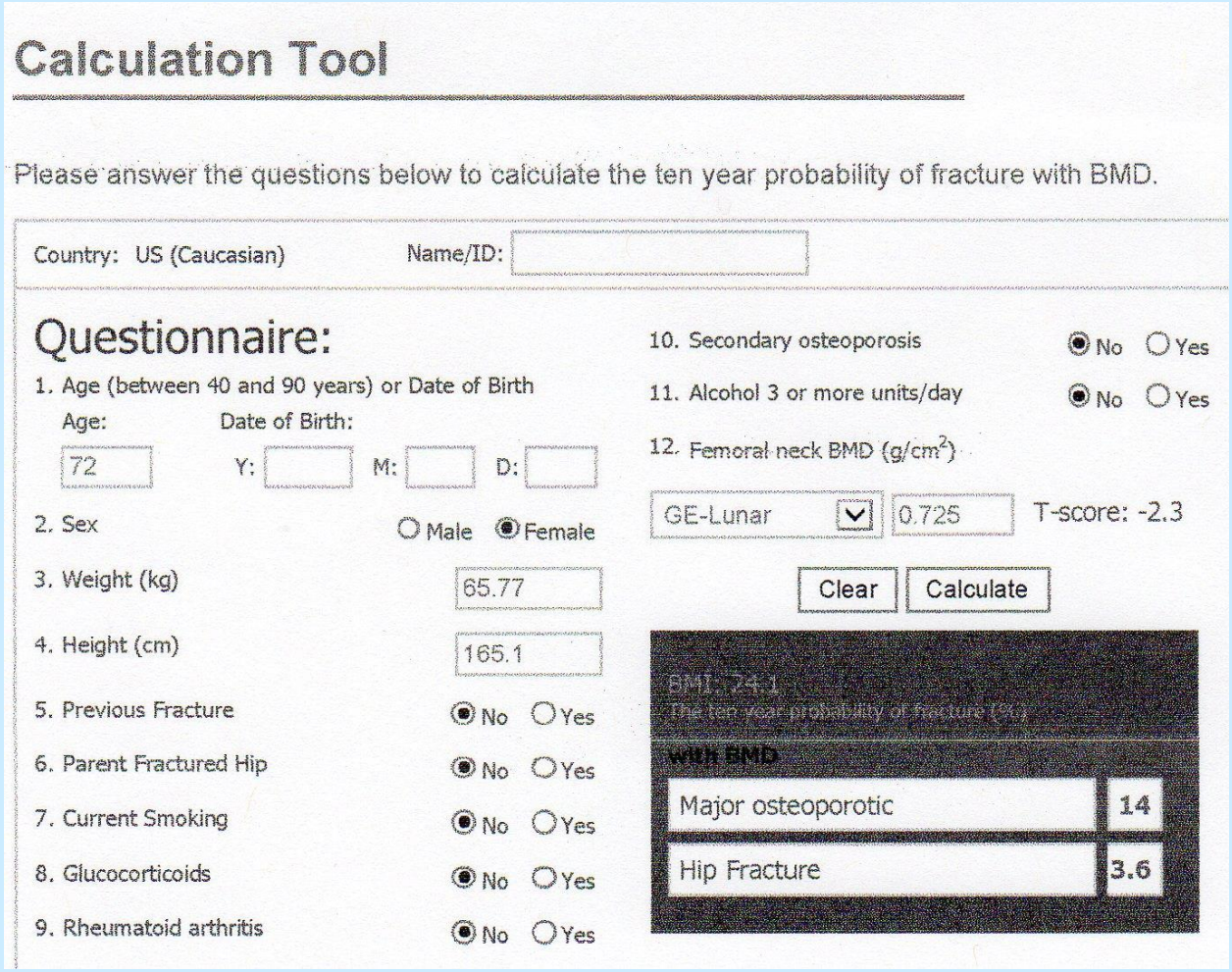
    GE-Lunar 0.725 T-score: -2.3

Clear Calculate

BMI: 24.1
The ten year probability of fracture (%)
with BMD

Major osteoporotic	8.0
Hip Fracture	1.7

FRAX: 72 year old Caucasian female with osteopenia and no other risk factors



Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian) Name/ID:

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 72 Date of Birth: Y: M: D:
2. Sex — Male / Female
3. Weight (kg) 65.77
4. Height (cm) 165.1
5. Previous Fracture — No / Yes
6. Parent Fractured Hip — No / Yes
7. Current Smoking — No / Yes
8. Glucocorticoids — No / Yes
9. Rheumatoid arthritis — No / Yes
10. Secondary osteoporosis — No / Yes
11. Alcohol 3 or more units/day — No / Yes
12. Femoral neck BMD (g/cm^2)

GE-Lunar 0.725 T-score: -2.3

Clear Calculate

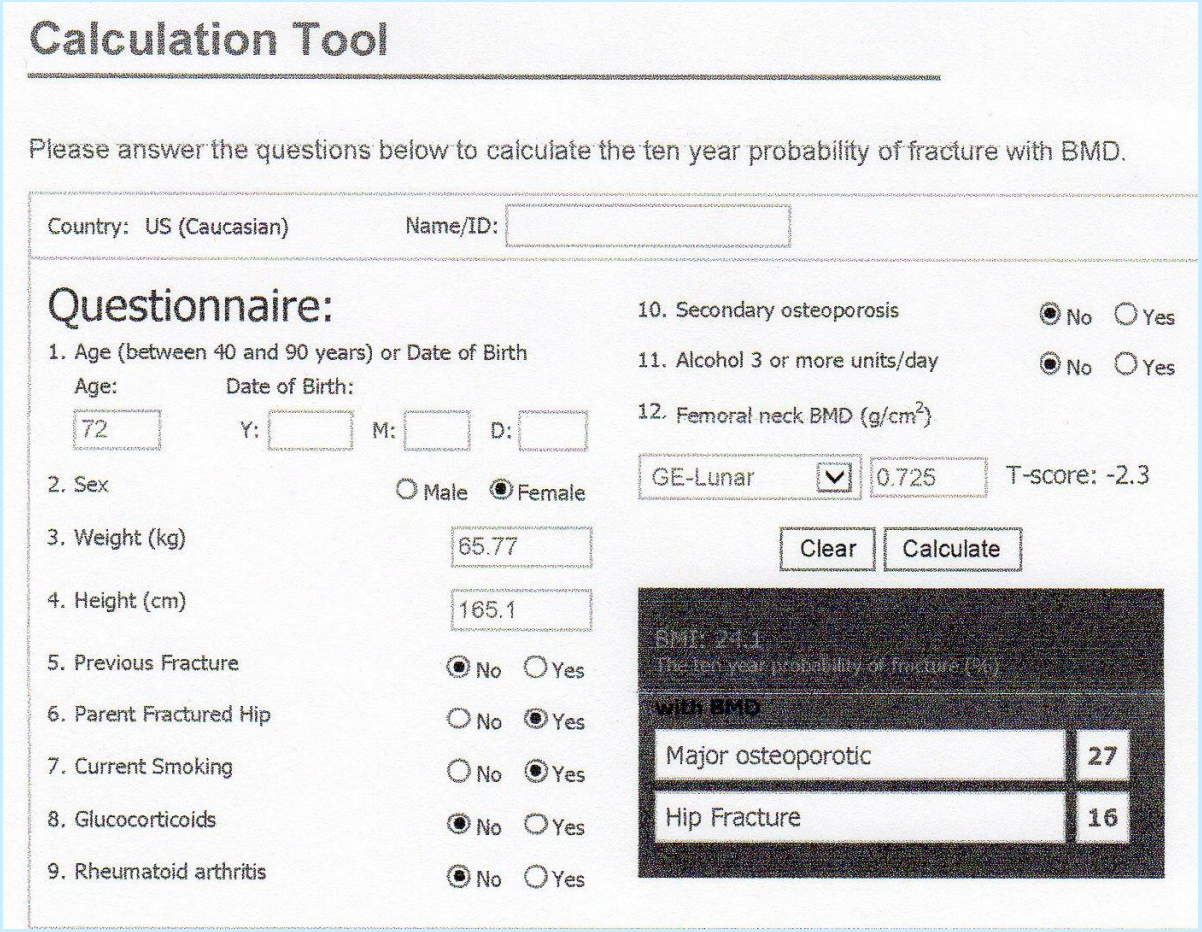
BMI: 24.1

The ten year probability of fracture (%)

with BMD

Major osteoporotic	14
Hip Fracture	3.6

FRAX: 72 year old Caucasian female with osteopenia and other risk factors



Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian) Name/ID:

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1. Age (between 40 and 90 years) or Date of Birth
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11. Alcohol 3 or more units/day — No / Yes
12. Femoral neck BMD (g/cm^2) GE-Lunar 0.725 T-score: -2.3

Clear Calculate

BMI: 24.1

The ten year probability of fracture (%)

with BMD	
Major osteoporotic	27
Hip Fracture	16

BONE DENSITY (DXA) CAVEATS

- If there are significant degenerative changes of the lumbar spine, these cause false elevation of the BMD of this region, so the lumbar spine BMD results might be very inaccurate (higher BMD than actual).

Suspect this if the spine has significantly better BMD than the hips.

Look at the pictures! See if there are degenerative changes of the spine.

A good densitometry report should make note of this.

OSTEOPOROSIS: when to order DXA study

Screening with DXA study:

Women: start at 65 y/o or younger if risk factors.

Men: start at 70 y/o or younger if risk factors.

Adults with a fragility fracture.

Adults with a disease or condition associated with low bone mass or bone loss.

Adults taking medications associated with bone loss.

Anyone being considered for pharmacologic treatment.

Anyone being treated, to monitor treatment effect.

Anyone not being treated, in whom evidence of bone loss would lead to treatment.

OSTEOPOROSIS: when to order DXA study

- Height loss of >1.5 inches.

DXA study in patient with primary hyperparathyroidism

- Order spine, hips, and wrist (non-dominant wrist).
  Hyperparathyroidism might preferentially worsen cortical bone, and the wrist is often more affected than other areas.

- In patients without primary hyperparathyroidism, order DXA of the hips and spine.

Osteoporosis risk factors

- Low body weight.
- Prior fracture.
- High risk medication use.
- Disease or condition associated with bone loss.
- Late menarche/early menopause.

Osteoporosis risk factors

- RISK FACTORS (more detail)

  family history of osteoporosis or fractures; thin Caucasian; late menarche; early menopause; fractures; frequent falls; eating disorder; malabsorption; smoking; renal failure; medications (excessive thyroxine, glucocorticoids, chemotherapy, anti-estrogen therapy [Aromatase inhibitors, (letrozole or anastrozole) but not SERM's (tamoxifen or raloxifene)], anti-seizure meds); hyperparathyroidism: primary or secondary.

PEAK BONE MASS

- Women: about 25 years of age
- Men: about 30 years of age

Calcium recommendations

WOMEN:

Under 50 years old: 1,000 mg daily.

51 + years old: 1,200 mg daily.

MEN:

Under 70: 1,000 mg daily.

71 + years old: 1,200 mg daily.

Vitamin D recommendations

- Under 50 years old: 400-800 IU daily.
- 51 + years old: 800-1,000 IU daily.

OSTEOPOROSIS prevention and treatment

- Resistance and weight-bearing exercises targeting the various bone areas
- Avoid smoking
- Limit alcohol to 2-3 drinks or less daily
- Adequate dairy intake and calcium pill supplementation based on dietary deficits: recommend trying to get most calcium intake from food, and supplement with one calcium pill daily if needed

Osteoporosis prevention and treatment

- Fall avoidance

OSTEOPOROSIS medications

Bisphosphonates:

- inhibit osteoclastic resorption

(poorly absorbed orally)

Alendronate (Fosamax) 70 mg orally weekly;

Residronate (Actonel) 35 mg orally weekly or 150 mg monthly;

Ibandronate (Boniva) 150 mg orally monthly or given IV every 3 months;

Zoledronic acid (Reclast) 5 mg IV yearly;

BISPHOSPHONATE side effects

- Esophageal erosions and ulcers (oral route), aches
- ?Loss of efficacy after 5 or more years
- Hypocalcemia, especially if vitamin D level is low
- Atypical Femoral Fractures: occurs with any bisphosphonate; relative risk is low and rises with duration of therapy; 5 additional cases per 10,000 patient-years of use; often preceded by pain in the upper leg area prior to fracture

BISPHOSPHONATE side effects

- Osteonecrosis of the Jaw (ONJ): more commonly associated with high dose IV therapy but can be associated with oral therapy; generally relative risk low (4.1 cases per 100,000 patient years compared to 0.63 cases in placebo controls)
- Note: make sure vitamin D level is corrected, if low, in all patients being treated with bisphosphonates (to avoid hypocalcemia and to improve efficacy and possibly reduce side effects)

OSTEOPOROSIS medications

Other anti-resorptive agents:

-Prolia (denosumab)

-Estrogen: no longer recommend as primary treatment of low bone density unless on it for another reason

-Evista (Raloxifene)

-Calcitonin: no longer recommended

-Calcium: uncertain effectiveness alone and questionably contributes to increased cardiovascular events

-Vitamin D

OSTEOPOROSIS medications: PROLIA

- Denosumab: RANK-ligand inhibitor

  60 mg SC q 6 months;

  anti-resorptive effect.

Side effects: same as bisphosphonates (but no issue with esophageal erosions or ulcers)

Note: make sure vitamin D level is corrected, if low, in all patients being treated with bisphosphonates (to avoid hypocalcemia and to improve efficacy and possibly reduce side effects)

OSTEOPOROSIS medications: FORTEO

- The only Anabolic agent available:

Forteo (related to parathyroid hormone):

1-34 teriparatide: shot with a pen given once daily subcutaneously for two years; Promotes osteoblastic bone formation. Not indicated past 2 years.

Side effects: nausea, bone aches, flu-like symptoms; ?osteosarcoma

SECONDARY CAUSES OF OSTEOPOROSIS

- Hypogonadism
- Vitamin D deficiency
- Parathyroid disease
- Myeloma
- Malnutrition; calcium or phosphorus deficiency
- Elevated prolactin
- Urinary calcium hyperexcretion
- Malabsorption

SECONDARY CAUSES OF OSTEOPOROSIS

- Prolonged bedrest
- Cortisol excess
- Meds: glucocorticoids, seizure meds, anti-estrogens (aromatase inhibitors), chemotherapy, etc.
- Excessive thyroxine replacement, hyperthyroidism
- Etc.

VITAMIN D DEFICIENCY

- Vitamin D deficiency is thought to be more common than previously recognized and might also have an effect on immune diseases, cancer, etc. (no hard data on these other conditions).
- 25-hydroxyvitamin D level should be

  at least 30.
- Vitamin D supplementation should probably be at least 1,000-2,000 IU daily (vitamin D3)
- Other vitamin D regimens include 50,000 IU vitamin D2 every 2-4 weeks

CASE 1

74 year old thin female with hip fracture and calcium level of 11.0 with normal albumin. Smoker. Calcium was 10.6 one year ago and 10.6 two years ago.

CASE 1

- Likely primary hyperparathyroidism since the calcium has increased minimally in two years.
- Check PTH, 24 hour urine, 25-vitamin D level.
- If PTH high, likely primary hyperparathyroidism
- If PTH is low, rule out cancer (to bone or producing PTH-related peptide), granulomatous disease.
- Stay hydrated: dehydration can acutely elevate the calcium level.

CASE 2

- 56 year old Caucasian female with a T-Score of -2.0 at the femoral neck and T-score of -1.3 at the lumbar spine (osteopenia). No family history of osteoporosis.

CASE 2

- FRAX risk is probably low due to her young age (if she was elderly, FRAX risk would probably be high)
- Since the hip BMD is worse than the spine BMD, rule out hyperparathyroidism: check calcium, parathyroid hormone and 25-vitamin D
- Make sure she doesn’t have degenerative changes of the lumbar spine causing false elevation of the BMD of the spine
- Treatment: vitamin D, calcium. Probably does not need pharmacologic treatment of the osteopenia; needs resistance and weight-bearing exercises